

TAU BINDING COMPOUNDS

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date of U.S. Provisional Patent Application Nos. 63/010261, filed on April 15, 2020, and 63/162976, filed on March 18, 2021, the entire contents of the above-referenced applications, including any sequences in the listings and drawings, are incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been filed electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on December 16, 2025, is named V2071-1308USCON1_SL.txt and is 1,371,717 bytes in size.

FIELD OF THE DISCLOSURE

[0003] The present disclosure presents tau binding compounds and adeno-associated virus (AAV) particles comprising the same.

BACKGROUND OF THE INVENTION

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

[0005] A genetically defined tauopathy was described when mutations in the tau gene were shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). This provided evidence that changes in tau could lead to neurodegenerative changes in the brain. These molecules are considered to be more amyloidogenic, meaning they are more likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. *et al.*, 1998, Nature 393(6686):702-5).

[0006] Several approaches have been proposed for therapeutically interfering with progression of tau pathology and preventing the subsequent molecular and cellular consequences. Given that NFT are composed of hyperphosphorylated, misfolded and aggregated forms of tau, interference at each of these stages provides targets that can be pursued. Introducing agents that limit phosphorylation, block

misfolding or prevent aggregation are promising strategies. It has also been suggested that introduction of anti-tau antibodies can prevent the trans-neuronal spread of tau pathology.

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

SUMMARY OF THE INVENTION

[0008] The present disclosure pertains at least in part to compositions and methods for modulating the level of tau, *e.g.*, aggregation and or distribution of tau, and/or delivery, *e.g.*, vectorized delivery of an antibody that binds to tau, *e.g.*, an anti-tau antibody, *e.g.*, an anti-tau antibody described herein. In some embodiments, the level of tau, *e.g.*, aggregation or distribution, is reduced or inhibited using an anti-tau antibody described herein or an isolated, *e.g.*, recombinant, AAV particle comprising a viral genome encoding an anti-tau antibody, *e.g.*, an anti-tau antibody described herein. In some embodiments, the degradation of tau is increased using an anti-tau antibody described herein or an isolated, *e.g.*, recombinant, AAV particle comprising a viral genome encoding an anti-tau antibody, *e.g.*, an anti-tau antibody described herein. Such inhibition and/or degradation can be useful in treating disorders related to expression of tau and/or neurological disorders, such as tauopathies.

[0009] Accordingly, in one aspect, the present disclosure provides an isolated, *e.g.*, recombinant antibody that binds to tau, comprising a heavy chain variable region (VH) comprising one, two, or three of a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and/or a heavy chain complementary determining region 3 (HC CDR3) of any of the HC CDR sequences of Table 1, 6, 2A-2C, 4, or 5; and/or a light chain variable region (VL) comprising one, two, or three of a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and/or a light chain complementary determining region 3 (LC CDR3) of any of the LC CDR sequences of Table 1, 6, 2A-2B, 4, or 5.

[0010] In another aspect, the present disclosure provides an isolated, *e.g.*, recombinant antibody that binds to human tau, wherein the antibody binds the same or substantially the same epitope as a reference antibody, the reference antibody comprises a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 and a VL comprising a light LC CDR1, a LC CDR2, and a LC CDR3, wherein: the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 315, 341, 410, 474, 529, and 571, respectively; the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 314, 341, 410, 1154, 529, and 571, respectively; or the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 316, 341, 410, 475, 530, and 571, respectively.

[0011] In another aspect, the present disclosure provides an isolated, *e.g.*, recombinant, antibody that binds to human tau, wherein the antibody competes for binding with a reference antibody, wherein the reference antibody comprises a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 and a VL comprising a light LC CDR1, a LC CDR2, and a LC CDR3, wherein: the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 315, 341, 410, 474, 529, and 571, respectively; the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 314, 341, 410, 1154, 529, and 571, respectively; or the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 316, 341, 410, 475, 530, and 571, respectively.

[0012] In yet another aspect, the present disclosure provides an isolated, *e.g.*, recombinant, antibody that binds to a region of a human tau protein comprising residues 409-436, numbered according to SEQ ID NO: 920. In some embodiments, the antibody comprises a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 wherein: the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1180, 341, and 410, respectively; the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of X₁X₂WMH wherein X₁ is R or I and X₂ is Y or F, SEQ ID NO: 1184, and SEQ ID NO: 410, respectively; or the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1186, 1187, and 1167, respectively. In some embodiments, the antibody comprises a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3 wherein: the LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1181, 1182, and 571, respectively; the LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1185, 1182, and 571, respectively; or the LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 1188, RVS, and SEQ ID NO: 571, respectively.

[0013] In yet another aspect, the present disclosure provides an antibody that binds, *e.g.*, directly or indirectly, to a region of a human tau protein comprising residues 32-49, 55-76, 159-194, 185-200, 219-247, 381-426, and/or 409-436, numbered according to SEQ ID NO: 920.

[0014] In yet another aspect, the present disclosure provides an isolated, *e.g.*, recombinant, nucleic acid that encodes an antibody described herein, *e.g.*, an antibody comprising VH comprising one, two, or three of an HC CDR1, an HC CDR2, and/or an HC CDR3 of any of the HC CDR sequences of Table 1, 6, 2A-2C, 4, or 5; and/or a VL comprising one, two, or three of an LC CDR1, an LC CDR2, and/or an LC CDR3 of any of the LC CDR sequences of Table 1, 6, 2A-2C, 4, or 5.

[0015] In yet another aspect, the present disclosure provides a viral genome comprising a promoter operably linked to a nucleic acid encoding an antibody that binds to tau (*e.g.*, an anti-tau antibody described herein). In some embodiments, the viral genome further comprises an internal terminal repeat (ITR) sequence (*e.g.*, an ITR region described herein), an enhancer (*e.g.*, an enhancer

described herein), an intron region (*e.g.*, an intron region described herein) and/or an exon region (*e.g.*, an exon region described herein), a poly A signal region (*e.g.*, a poly A signal sequence described herein), and/or an encoded miR binding site.

[0016] In yet another aspect, the present disclosure provides an isolated, *e.g.*, recombinant, AAV particle comprising a capsid protein and a viral genome comprising nucleic acid encoding an antibody that binds to tau (*e.g.*, an anti-tau antibody described herein). In some embodiments, the capsid protein comprises an AAV capsid protein, *e.g.*, a wild-type AAV capsid protein or a functional variant thereof. In some embodiments, the capsid protein comprises, or is chosen from, an AAV9 capsid protein (*e.g.*, a wild-type AAV9 capsid protein), a VOY101 capsid protein, a PHP.N capsid protein, or a PHP.B capsid protein, or a functional variant thereof.

[0017] In yet another aspect, the present disclosure provides method of delivering an exogenous antibody molecule that binds to tau (*e.g.*, an anti-tau antibody molecule described herein), to a subject. The method comprising administering an effective amount of an AAV particle or a plurality of AAV particles, described herein, said AAV particle comprising a viral genome described herein.

[0018] In yet another aspect, the present disclosure provides a method of treating a subject having or being diagnosed as having a neurological disorder, a tauopathy, and/or a disease associated with expression of tau. The method comprising administering to the subject an effective amount of an AAV particle or a plurality of AAV particles, described herein, comprising a viral genome described herein.

[0019] In some embodiments, the present disclosure provides an antibody that includes (1) a heavy chain variable domain (VH), wherein the VH includes: a complementarity determining region (CDR)H1 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 296-339, or a fragment thereof; a CDRH2 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 340-391, or a fragment thereof; and a CDRH3 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 392-456, or a fragment thereof; and (2) a light chain variable domain (VL), wherein the VL includes: a CDRL1 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 457-514, or a fragment thereof; a CDRL2 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 515-553, or a fragment thereof; and a CDRL3 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 554-600, or a fragment thereof. The antibody may include a set of variable domain CDR amino acid sequences, wherein the variable domain CDR amino acid sequence set is selected from Table 6.

[0020] The VH may include: a framework region (FR)H1 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 601-643, or a fragment thereof; a FRH2 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 644-696, or a fragment thereof; a FRH3 that includes an amino acid sequence selected from the group consisting of

SEQ ID NOs: 697-766, or a fragment thereof; and a FRH4 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 767-775, or a fragment thereof.

[0021] The VL may include: a FRL1 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 776-822, or a fragment thereof; a FRL2 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 823-857, or a fragment thereof; a FRL3 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 858-904, or a fragment thereof; and a FRL4 that includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 905-919, or a fragment thereof.

[0022] The VH may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-74; and/or an amino acid sequence that is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 147-220.

[0023] The VL may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 75-146; and/or an amino acid sequence that is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 221-295.

[0024] The antibody may include a variable domain pair selected from Table 3.

[0025] The CDRH1 may include an amino acid sequence selected from the group consisting of GFTFTRY (SEQ ID NO: 314), GYTFTIF (SEQ ID NO: 315), and GYTFTRF (SEQ ID NO: 316). The CDRH2 may include the amino acid sequence of NPNNGG (SEQ ID NO: 341). The CDRH3 may include the amino acid sequence of GTGTGAMDY (SEQ ID NO: 410).

[0026] The CDRL1 may include an amino acid sequence selected from the group consisting of RSSQSLVHNNGITYLY (SEQ ID NO: 1154), RSSQSLVHSNGITHLY (SEQ ID NO: 474), and RSSQSLVHSNGNTHLY (SEQ ID NO: 475). The CDRL2 may include an amino acid sequence selected from the group consisting of RVSNRFS (SEQ ID NO: 529), and RVSSRFS (SEQ ID NO: 530). The CDRL3 may include the amino acid sequence of FQGTHVPRT (SEQ ID NO: 571).

[0027] The CDRH1 may include an amino acid sequence selected from the group consisting of GFSLSSTAM (SEQ ID NO: 325), GFSLNTSGM (SEQ ID NO: 326), GFSLSSTGM (SEQ ID NO: 321), and GFSLSSTFGM (SEQ ID NO: 327). The CDRH2 may include the amino acid sequence of YWDDD (SEQ ID NO: 362). The CDRH3 may include an amino acid sequence selected from the group consisting of RRRGYGMDY (SEQ ID NO: 435), RVRGYGMDY (SEQ ID NO: 437), RVRYYAMDY (SEQ ID NO: 438), RKRSYGMDY (SEQ ID NO: 440), RSRRGNYYDY (SEQ ID NO: 421), and RGYYSNGNYFDY (SEQ ID NO: 432).

[0028] The CDRL1 may include an amino acid sequence selected from the group consisting of KASQSVSNDVA (SEQ ID NO: 495), KSSQSLLNSGNQKNYLA (SEQ ID NO: 496), KSSQSLLSSGNQKNYLA (SEQ ID NO: 497), KSSQSLLDSDGKTYLN (SEQ ID NO: 484), and SASSSISSTYLH (SEQ ID NO: 493). The CDRL2 may include an amino acid sequence selected from the group consisting of YASNRCT (SEQ ID NO: 540), GTSTRES (SEQ ID NO: 542), GASTRES

(SEQ ID NO: 543), LVSKLDS (SEQ ID NO: 532), and RTSNLAS (SEQ ID NO: 538). The CDRL3 may include an amino acid sequence selected from the group consisting of QQDYRSPLT (SEQ ID NO: 587), QNDHSHPYT (SEQ ID NO: 588), WQGTHFPQT (SEQ ID NO: 576), and QQGSSIPRYT (SEQ ID NO: 585).

[0029] Antibodies of the present disclosure may include a format selected from the group consisting of a monoclonal antibody, a multispecific antibody, a chimeric antibody, an antibody mimetic, a single chain Fv (scFv) format, and an antibody fragment. The antibody may include an antibody class selected from the group consisting of IgA, IgD, IgE, IgG, and IgM. The antibody may include a mouse IgG, wherein the mouse IgG includes an isotype selected from the group consisting of IgG1, IgG2a, IgG2b, IgG2c, and IgG3. The antibody may include a human IgG, wherein the human IgG includes an isotype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4. The antibody may include one or more human constant domain. The one or more human constant domain may include a human IgG constant domain. The antibody may include a humanized antibody.

[0030] Antibodies of the present disclosure may bind to a tau protein epitope. The tau protein epitope may include or may be included within an amino acid sequence selected from the group consisting of SEQ ID NOs: 920-926. The antibody may compete for binding to the tau protein epitope with an antibody selected from one or more of AT100, AT120, PT3, C10.2, PT76, IPN002, 6C5, and UCB D. The tau protein epitope may include residues 409-436 of human tau (SEQ ID NO: 920). The tau protein epitope may include residues 413-430 of human tau (SEQ ID NO: 920). Antibody binding to the tau protein epitope may exhibit a K_D of from about 0.1 nM to about 0.5 nM. The tau protein epitope may include residues 55-76, 159-194, 219-247, and/or 381-426 of human tau (SEQ ID NO: 920). The tau protein epitope may include residues 57-72, 175-191, 223-238, and/or 383-400 of human tau (SEQ ID NO: 920). The tau protein epitope may include residues 223-238 of human tau (SEQ ID NO: 920). Antibody binding to the tau protein epitope may exhibit a K_D of from about 0.5 nM to about 5 nM. The tau protein epitope may include a region formed by a complex of at least two tau proteins. The antibody may bind to enriched paired helical filament tau protein (ePHF) with a half maximal effective concentration (EC50) of from about 0.01 nM to about 100 nM. The antibody may not bind to non-pathological tau. The antibody may bind to pathological tau. The antibody may inhibit tau aggregation with a half maximal inhibitory concentration (IC50) of from about 1 nM to about 30 nM as determined by immunodepletion assay. The immunodepletion assay may be carried out with tau RD Biosensor cells.

[0031] In some embodiments, the present disclosure provides an antibody that competes for binding with a second antibody to a tau protein epitope, wherein the tau protein epitope includes one or more of residues 32-49, 55-76, 57-72, 159-194, 175-191, 185-200, 219-247, 223-238, 381-426, 383-400, 409-436, and 413-430 of human tau (SEQ ID NO: 920). The tau protein epitope may include one or more of residues 409-436 and 413-430 of human tau (SEQ ID NO: 920). The second antibody

may include a variable domain pair selected from the group consisting of: a VH with the amino acid sequence of SEQ ID NO: 21 and a VL with the amino acid sequence of SEQ ID NO: 93; a VH with the amino acid sequence of SEQ ID NO: 22 and a VL with the amino acid sequence of SEQ ID NO: 94; and a VH with the amino acid sequence of SEQ ID NO: 23 and a VL with the amino acid sequence of SEQ ID NO: 95.

[0032] Antibodies of the present disclosure may include a conjugate. The conjugate may include a therapeutic agent. The conjugate may include a detectable label.

[0033] In some embodiments, the present disclosure provides a construct encoding an antibody disclosed herein.

[0034] In some embodiments, the present disclosure provides a method of treating a therapeutic indication in a subject by administering an antibody disclosed herein to the subject. The therapeutic indication may be a neurological indication. The neurological indication may be a neurodegenerative disease, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, or progressive subcortical gliosis.

[0035] In some embodiments, the present disclosure provides a method of diagnosing a therapeutic indication in a subject through the use of an antibody disclosed herein. The therapeutic indication may include a neurological indication. The neurological indication may be a neurodegenerative disease, AD, FTDP-17, FTLD, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, corticobasal syndrome, ALS, a prion disease, CJD, multiple system atrophy, tangle-only dementia, stroke, or progressive subcortical gliosis. The antibody may be used to detect pathological tau in a subject tissue. The subject tissue may include CNS tissue. The subject tissue may be a thin tissue section. The thin tissue section may be a cryopreserved tissue section.

[0036] In some embodiments, the tau binding compounds or antibodies of the present disclosure may be encoded in an adeno-associated virus (AAV) viral genome. In some embodiments, the AAV viral genome may comprise one or more nucleic acid sequences encoding an antibody described herein, or a fragment thereof.

[0037] In some embodiments, the viral genome may comprise a 5' inverted terminal repeat (ITR) sequence region selected from SEQ ID NO: 1035 and 1036, a promoter sequence region selected from 1039-1050, a polyadenylation (polyA) sequence region selected from 1134-1136, and a 3' ITR selected from SEQ ID NO: 1037 and 1038.

[0038] In some embodiments, the viral genome may comprise one or more exon sequence regions selected from SEQ ID NO: 1051-1055, one or more intron sequence regions selected from SEQ ID

NO: 1056-1070, one or more signal sequence regions selected from SEQ ID NO: 1071-1089, one or more tag sequence regions selected from SEQ ID NO: 1127-1133, and/or one or more filler sequence regions selected from SEQ ID NO: 1137 and 1138.

[0039] In some embodiments, the viral genome may have a first nucleic acid sequence and a second nucleic acid sequence wherein the first nucleic acid sequence encodes a VH and the second nucleic acid sequence encodes a VL. In some embodiments, the viral genome encodes a VH having an amino acid sequence selected from SEQ ID NO: 1-74. In some embodiments, the viral genome encodes a VL having an amino acid sequence selected from SEQ ID NO: 75-146. In some embodiments, the viral genome encodes a VH and VL pair selected from the pairings shown in Table 3.

[0040] In some embodiments, the first and second nucleic acid sequences of the viral genome are separated by one or more linker sequences, wherein the linker sequence(s) may be selected from SEQ ID NO: 1090-1126.

[0041] In some embodiments, the viral genome comprises a VH nucleic acid sequence selected from SEQ ID NO: 147-220. In some embodiments, the viral genome comprises a VL nucleic acid sequence selected from SEQ ID NO: 221-295.

[0042] In some embodiments, the viral genome may encode one or more CDR sequences having an amino acid sequence selected from SEQ ID NO: 296-600. In some embodiments, the viral genome may encode a set of CDRs selected from the CDR sets outlined in Table 6. In some embodiments, the viral genome may encode a CDR set pair selected from those outlined in Table 6.

[0043] In some embodiments, the viral genome may encode one or more FR amino acid sequence selected from SEQ ID NO: 601-919.

[0044] In some embodiments, the viral genome encodes from 5' to 3', an antibody heavy chain, one or more linker sequences, and an antibody light chain. In other embodiments, the viral genome encodes from 5' to 3', an antibody light chain, one or more linker sequences and an antibody heavy chain.

[0045] In some embodiments, an AAV viral genome described herein may be incorporated into an AAV particles.

[0046] In some embodiments, the AAV particle comprises an AAV capsid protein chosen from 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, AAV2.BR1, or AAV2G9 capsid protein, or a functional variant thereof.

[0047] In certain embodiments, the AAV particle comprises a VOY101 capsid. In some embodiments, the VOY101 capsid amino acid sequence is given by SEQ ID NO: 1023.

[0048] In some embodiments, the viral genome of an AAV particle described herein may further comprise 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.

[0049] In some embodiments, the viral genome of an AAV particle may further comprise at least 1-5 copies of an encoded miR binding site, *e.g.*, at least 1, 2, 3, 4, or 5 copies. In some embodiments, the viral genome may comprise at least 3 copies of an encoded miR binding site, optionally wherein all three copies are for the same miR binding site or at least one, two, or all of the copies are for different miR binding sites.

[0050] In some embodiments, the viral genome may further comprise a nucleotide sequence encoding a miR122 binding site, a miR183 binding site, a miR-142-3p, or a combination thereof.

[0051] In some embodiments, the viral genome comprises an encoded miR122 binding site having the nucleotide sequence of SEQ ID NO: 1029, or a nucleotide sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleic acid sequence having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of SEQ ID NO: 1029.

[0052] In some embodiments, the viral genome comprises an encoded miR183 binding site having the nucleotide sequence of SEQ ID NO: 1032, or a nucleotide sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleic acid sequence having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of SEQ ID NO: 1032.

[0053] In some embodiments, the viral genome comprises an encoded miR-142-3p binding site having the nucleotide sequence of SEQ ID NO: 1031, or a nucleotide sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleic acid sequence having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications of SEQ ID NO: 1031.

[0054] In some embodiments, the viral genome comprises at least 4 copies of an encoded miR binding site, optionally wherein all four copies comprise the same miR binding site or at least one, two, three, or all of the copies comprise a different miR binding site.

[0055] In some embodiments, the AAV particles disclosed herein may be formulated into a pharmaceutical composition.

[0056] The present disclosure provides a method of producing an antibody in a subject by administering a pharmaceutical composition to the subject.

[0057] The present disclosure also provides methods for preventing or treating a tauopathy in a subject by administering a therapeutically effective amount of a pharmaceutical composition described herein to a subject. The pharmaceutical composition may be administered by any route of administration including, but not limited to, intravenous, intramuscular, intraparenchymal, intracerebroventricular, intracisterna magna (ICM), intrathecal, or a combination thereof.

[0058] The tauopathy that may be treated by the methods and/or compositions of the present disclosure include, but are not limited to, AD, FTDP-17, FTLD, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, Corticobasal syndrome, ALS, Prion diseases, CJD, Multiple system atrophy, Tangle-only dementia, and Progressive subcortical gliosis.

[0059] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

Enumerated Embodiments

- E1. An isolated, *e.g.*, recombinant, antibody that binds to human tau, wherein the antibody binds the same or substantially the same epitope as a reference antibody, the reference antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (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 NO: 315, 341, 410, 474, 529, 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 NO: 314, 341, 410, 1154, 529, 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 NO: 316, 341, 410, 475, 530, and 571, respectively.

- E2. An isolated, *e.g.*, recombinant, antibody that binds to human tau, wherein the antibody competes for binding with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (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 NO: 315, 341, 410, 474, 529, 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 NO: 314, 341, 410, 1154, 529, 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 NO: 316, 341, 410, 475, 530, and 571, respectively.
- E3. The antibody of embodiment E1 or E2, wherein the reference antibody comprises:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 22 and a VL comprising the amino acid sequence of SEQ ID NO: 94;
 - (ii) a VH comprising the amino acid sequence of SEQ ID NO: 21 and a VL comprising the amino acid sequence of SEQ ID NO: 93; or,
 - (iii) a VH comprising the amino acid sequence of SEQ ID NO: 23 and a VL comprising the amino acid sequence of SEQ ID NO: 95.
- E4. The antibody of any one of embodiments E1-E3, wherein the antibody binds an epitope that overlaps the epitope recognized by the reference antibody.
- E5. The antibody of any one of embodiments E1-E4, wherein the antibody binds to a region of a human tau protein comprising residues 409-436, numbered according to SEQ ID NO: 920.
- E6. The antibody of any one of embodiments E1-E5, wherein the antibody binds to a region of a human tau protein comprising residues 413-430, numbered according to SEQ ID NO: 920.
- E7. The antibody of any one of embodiments E1-E6, which binds to a tau protein with a dissociation constant (K_D) of about 0.1 to about 10 nM, or about 0.2-5 nM.
- E8. The antibody of any one of embodiments E1-E7, wherein the antibody comprises a heavy chain variable region comprising at least one, two, or three of an HC CDR1, an HC CDR2,

- and an HC CDR3 comprising the amino acid sequences of:
- (i) SEQ ID NOs: 1180, 341, and 410, respectively;
 - (ii) X₁X₂WMH wherein X₁ is R or I and X₂ is Y or F, SEQ ID NO: 1184, and SEQ ID NO: 410, respectively; or
 - (iii) SEQ ID NOs: 1186, 1187, and 1167, respectively.
- E9. The antibody of any one of embodiments E1-E8, wherein the antibody comprises a light chain variable region (VL) comprising one, two, or three of an LC CDR1, an LC CDR2, and/or an LC CDR3 of:
- (i) SEQ ID NOs: 1181, 1182, and 571, respectively;
 - (ii) SEQ ID NOs: 1185, 1182, and 571, respectively; or,
 - (iii) SEQ ID NO: 1188, RVS, and SEQ ID NO: 571, respectively.
- E10. The antibody of any one of embodiments E1-E9, wherein the antibody comprises:
- (i) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 315, 341, 410, 474, 529, 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 NO: 1147, 1148, 410, 474, 529, 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 NO: 1168, SEQ ID NO: 1169, SEQ ID NO: 1167, SEQ ID NO: 1170, RVS, and SEQ ID NO: 571, respectively.
- E11. The antibody of any one of embodiments E1-E9, wherein the antibody comprises:
- (i) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 314, 341, 410, 1154, 529, 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 NO: 1144, 1145, 410, 1146, 529, 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 NO: 1165, SEQ ID NO: 1166, SEQ ID NO: 1167, SEQ ID NO: 473, RVS, and SEQ ID NO: 571, respectively.
- E12. The antibody of any one of embodiments E1-E9, wherein the antibody comprises:
- (i) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 316, 341, 410, 475, 530, 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 NO: 1149, 1150, 410, 475, 530, 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 NO: 1171, SEQ ID NO: 1166, SEQ ID NO: 1167, SEQ ID NO: 1172, RVS, and SEQ ID NO: 571, respectively.
- E13. The antibody of any one of embodiments E1-E12, wherein the antibody comprises:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 21-23, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 93-95, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E14. An isolated, *e.g.*, recombinant, antibody that binds to a region of a human tau protein comprising residues 409-436, numbered according to SEQ ID NO: 920, and wherein the antibody comprises:
- (i) a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 wherein:
 - (a) the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of of SEQ ID NOs: 1180, 341, and 410, respectively;
 - (b) the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of X₁X₂WMH wherein X₁ is R or I and X₂ is Y or F, SEQ ID NO: 1184, and SEQ ID NO: 410, respectively; or
 - (c) the HC CDR1, HC CDR2, HC CDR3 comprise the amino acid sequence of of SEQ ID NOs: 1186, 1187, and 1167, respectively; and
 - (ii) a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3 wherein:
 - (a) the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1181, 1182, and 571, respectively;
 - (b) the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1185, 1182, and 571, respectively; or,
 - (c) the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NO: 1188, RVS, and SEQ ID NO: 571, respectively.
- E15. An antibody that binds, *e.g.*, directly or indirectly, to a region of a human tau protein comprising residues 32-49, 55-76, 159-194, 185-200, 219-247, 381-426, and/or 409-436, numbered according to SEQ ID NO: 920.
- E16. The antibody of embodiment E14 or E15, which binds a region of a human tau protein

- comprising residues 55-76, 159-194, 219-247, and/or 381-426, numbered according to SEQ ID NO: 920.
- E17. The antibody of embodiment E14 or E15, which binds a region of a human tau protein comprising residues 57-72, 175-191, 223-238, and/or 383-400, numbered according to SEQ ID NO: 920.
- E18. The antibody of embodiment E14 or E15, which binds a region of a human tau protein comprising residues 223-238, numbered according to SEQ ID NO: 920.
- E19. The antibody of any one of embodiments E14-E17, which binds a conformational epitope comprising residues 55-76, 159-194, 219-247, and 381-426, numbered according to SEQ ID NO: 920.
- E20. The antibody of any one of embodiments E15-E19, comprising:
- (i) a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 325, 362, and 435, respectively; and/or a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively;
 - (ii) a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1152, 1153, and 435, respectively; and/or a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively
 - (iii) a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1173, 1174, and 1175, respectively; and/or a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1176, YAS, and SEQ ID NO: 587, respectively.
- E21. The antibody of any one of embodiments E14-E20, which binds to a tau protein with a dissociation constant (K_D) of about 0.1 to about 1 nM.
- E22. An isolated, *e.g.*, recombinant, antibody that binds to tau, comprising:
- (i) a heavy chain variable region (VH) comprising one, two, or three of an HC CDR1, an HC CDR2, and/or an HC CDR3 of any of the HC CDR sequences of Table 1, 6, 2A-2C, 4, or 5; and/or
 - (ii) a light chain variable region (VL) comprising one, two, or three of an LC CDR1, an LC CDR2, and/or an LC CDR3 of any of the LC CDR sequences of Table 1, 6, 2A-2C, 4, or 5.
- E23. The antibody of embodiment E22, comprising a VH comprising the HC CDR1, the HC CDR2, and the HC CDR3 of any one of the antibodies in Table 1, 6, 2A-2C, 4, or 5.

- E24. The antibody of embodiment E22 or E23, comprising a VL comprising the LC CDR1, the LC CDR2, and the LC CDR3 of any one of the antibodies in Table 1, 6, 2A-2C, 4, or 5.
- E25. The antibody of any one of embodiments E22-E24, comprising a VH comprising the HC CDR1, the HC CDR2, and the HC CDR3 of any one of the antibodies in Table 1, 6, 2A-2C, 4, or 5; and a VL comprising the LC CDR1, the LC CDR2, and the LC CDR3 of said any one of the antibodies in Table 1, 6, 2A-2C, 4, or 5.
- E26. The antibody of any one of embodiments E22-E25, comprising:
- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NO: 931 or 932, 341, and 410, respectively; and/or
 - (ii) an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 933 or 934, 935 or 936, and 571, respectively.
- E27. The antibody of any one of embodiments E22-E26, comprising:
- (i) an HC DR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1180, 341, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1181, 1182, and 571, respectively;
 - (ii) an HC DR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of X₁X₂WMH wherein X₁ is R or I and X₂ is Y or F, SEQ ID NO: 1184, and SEQ ID NO: 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1185, 1182, and 571, respectively; or
 - (iii) an HC DR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1186, 1187, and 1167, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1188, RVS, and SEQ ID NO: 571, respectively.
- E28. The antibody of any one of embodiments E22-E27, comprising:
- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 315, 341, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 474, 529, and 571, respectively;
 - (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1147, 1148, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 474, 529, and 571, respectively; or
 - (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence

of SEQ ID NOs: 1168, 1169, and 1167, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1170, RVS, and SEQ ID NO: 571, respectively.

E29. The antibody of any one of embodiments E22-E27, comprising:

- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 314, 341, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1154, 529, and 571, respectively;
- (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NO: 1144, 1145, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1146, 529, and 571, respectively; or
- (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1165, 1166, and 1167, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 473, RVS, and SEQ ID NO: 571, respectively.

E30. The antibody of any one of embodiments E22-E27, comprising:

- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 316, 341, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 475, 530, and 571, respectively;
- (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NO: 1149, 1150, and 410, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 475, 1151, and 571, respectively; or
- (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1171, 1166, and 1167, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1172, RVS, and SEQ ID NO: 571, respectively.

E31. The antibody of any one of embodiments E22-E27, comprising:

- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 325, 362, and 435, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively;
- (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence

- of SEQ ID NO: 1152, 1153, and 435, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 495, 540, and 587, respectively; or
- (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1173, 1174, and 1175, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1176, YAS, and SEQ ID NO: 587, respectively.
- E32. The antibody of any one of embodiments E22-E27, comprising:
- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 304, 347, and 400, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 464, 523, and 562, respectively;
- (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NO: 1142, 1143, and 400, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 464, 523, and 562, respectively; or
- (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1160, 1161, and 1162, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1163, WAS, and SEQ ID NO: 562, respectively.
- E33. The antibody of any one of embodiments E22-E27, comprising:
- (i) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 299, 343, and 395, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NOs: 460, 518, and 557, respectively;
- (ii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NO: 1140, 1141, and 395, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 460, 518, and 557, respectively; or
- (iii) an HC CDR1, an HC CDR2, and an HC CDR3 comprising the amino acid sequence of SEQ ID NOs: 1155, 1156, and 1157, respectively; and/or an LC CDR1, an LC CDR2, and an LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1158, NAK, and SEQ ID NO: 557, respectively.
- E34. The antibody of any one of the preceding embodiments, comprising:
- (i) one, two, three, or all of a heavy chain framework region 1 (FRH1), a heavy chain

- framework region 2 (FRH2), a heavy chain framework region 3 (FRH3), and/or a heavy chain framework region 4 (FRH4) comprising the amino sequence of any of the heavy chain framework regions of the antibodies provided in Table 7 or 4; or
- (ii) one, two, three, or all of a heavy chain framework region 1 (FRH1), a heavy chain framework region 2 (FRH2), a heavy chain framework region 3 (FRH3), and/or a heavy chain framework region 4 (FRH4) comprising an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to the amino acid sequence of any of the heavy chain framework regions of the antibodies provided in Table 7 or 4.
- E35. The antibody of any one of the preceding embodiments, comprising:
- (i) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 603, an FRH2 comprising the amino acid sequence of SEQ ID NO: 664, an FRH3 comprising the amino acid sequence of SEQ ID NO: 718, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 771; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 603, 664, 718, and/or 771;
- (ii) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 619, an FRH2 comprising the amino acid sequence of SEQ ID NO: 663, an FRH3 comprising the amino acid sequence of SEQ ID NO: 717, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 771; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 619, 663, 717, and/or 771;
- (iii) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 603, an FRH2 comprising the amino acid sequence of SEQ ID NO: 665, an FRH3 comprising the amino acid sequence of SEQ ID NO: 719, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 771; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 603, 665, 719, and/or 771;
- (iv) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 633, an FRH2 comprising the amino acid sequence of SEQ ID NO: 682, an FRH3 comprising the amino acid sequence of SEQ ID NO: 745, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 771; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*,

substitutions, relative to each of the amino acid sequences of SEQ ID NO: 663, 682, 745, and/or 771.

- (v) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 608, an FRH2 comprising the amino acid sequence of SEQ ID NO: 652, an FRH3 comprising the amino acid sequence of SEQ ID NO: 705, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 767; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 608, 652, 705, and/or 767; or,
- (vi) one, two, three, or all of an FRH1 comprising the amino acid sequence of SEQ ID NO: 604, an FRH2 comprising the amino acid sequence of SEQ ID NO: 647, an FRH3 comprising the amino acid sequence of SEQ ID NO: 700, and/or an FRH4 comprising the amino acid sequence of SEQ ID NO: 770; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 604, 647, 700, and/or 770.

E36. The antibody of any one of the preceding embodiments, comprising:

- (i) one, two, three, or all of a light chain framework region 1 (FRL1), a light chain framework region 2 (FRL2), a light chain framework region 3 (FRL3), and/or a light chain framework region 4 (FRL4) comprising the amino sequence of any of the light chain framework regions of the antibodies provided in Table 7 or 4; or
- (ii) one, two, three, or all of a light chain framework region 1 (FRL1), a light chain framework region 2 (FRL2), a light chain framework region 3 (FRL3), and/or a light chain framework region 4 (FRL4) comprising an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to the amino acid sequence of any of the light chain framework regions of the antibodies provided in Table 7 or 4.

E37. The antibody of any one of the preceding embodiments, comprising:

- (i) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID NO: 793, an FRL2 comprising the amino acid sequence of SEQ ID NO: 836, an FRL3 comprising the amino acid sequence of SEQ ID NO: 874, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 910; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 793, 836, 874, and/or 910;
- (ii) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID

NO: 1178, an FRL2 comprising the amino acid sequence of SEQ ID NO: 831, an FRL3 comprising the amino acid sequence of SEQ ID NO: 1179, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 906; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 1178, 831, 1179, and/or 906;

- (iii) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID NO: 787, an FRL2 comprising the amino acid sequence of SEQ ID NO: 831, an FRL3 comprising the amino acid sequence of SEQ ID NO: 870, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 906, or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 787, 831, 870, and/or 906; or
- (iv) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID NO: 807, an FRL2 comprising the amino acid sequence of SEQ ID NO: 830, an FRL3 comprising the amino acid sequence of SEQ ID NO: 888, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 908; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 807, 830, 888, and/or 908.
- (v) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID NO: 783, an FRL2 comprising the amino acid sequence of SEQ ID NO: 830, an FRL3 comprising the amino acid sequence of SEQ ID NO: 866, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 906; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 783, 830, 866, and/or 906; or,
- (vi) one, two, three, or all of an FRL1 comprising the amino acid sequence of SEQ ID NO: 779, an FRL2 comprising the amino acid sequence of SEQ ID NO: 825, an FRL3 comprising the amino acid sequence of SEQ ID NO: 861, and/or an FRL4 comprising the amino acid sequence of SEQ ID NO: 908; or an amino acid sequence having at least one, two, or three but no more than four modifications, *e.g.*, substitutions, relative to each of the amino acid sequences of SEQ ID NO: 779, 825, 861, and/or 908.

E38. The antibody of any one of embodiments E22-E37, comprising a VH comprising:

- (i) the amino acid sequence of any VH provided in Table 3 or 4, or an amino acid

- sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
- (ii) an amino acid sequence 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; or
 - (iii) an amino acid sequence encoded by a nucleotide sequence of any VH provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E39. The antibody of any one of embodiments E22-E38, comprising a VH comprising:
- (i) the amino acid sequence of SEQ ID NO: 4, 9, 21-23, or 51, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (ii) an amino acid sequence 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: 4, 9, 21-23, or 51; or,
 - (iii) an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 150, 155, 167-169, or 197, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E40. The isolated antibody of any of the preceding embodiments, comprising a VH comprising, from N-terminus to C-terminus:
- (i) an FRH1 comprising the amino acid sequence of any FRH1 of an antibody in Table 7;
 - (ii) an HC CDR1 comprising the amino acid sequence of the HC CDR1 of the antibody in Table 6 or 5;
 - (iii) an FRH2 comprising the amino acid sequence of the FRH2 of the antibody in Table 7 or 4;
 - (iv) an HC CDR2 comprising the amino acid sequence of the HC CDR2 of the antibody in Table 6 or 5;
 - (v) an FRH3 comprising the amino acid sequence of the FRH3 of the antibody in Table 7 or 4;
 - (vi) an HC CDR3 comprising the amino acid sequence of the HC CDR3 of the antibody in Table 6, or 5; and
 - (vii) an FRH4 comprising the amino acid sequence of the FRH4 of the antibody in Table 7 or 4.
- E41. The antibody of any one of the preceding embodiments comprising a VH comprising, from

N-terminus to C-terminus, an FRH1, an HC CDR1, an FRH2, an HC CDR2, an FRH3, an HC CDR3, and an FRH4, wherein:

- (i) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HC CDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 603, 315, 664, 341, 718, 410, and 771, respectively;
- (ii) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HC CDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 619, 314, 663, 341, 717, 410, and 771, respectively;
- (iii) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HC CDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 603, 316, 665, 341, 719, 410, and 771, respectively;
- (vi) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HC CDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 663, 325, 682, 362, 745, 435, and 771, respectively.
- (v) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HCDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 608, 304, 652, 347, 705, 400, and 767, respectively;
or,
- (vi) the FRH1, HC CDR1, FRH2, HC CDR2, FRH3, HC CDR3, FRH4 comprise the amino acid sequences of SEQ ID NO: 604, 299, 647, 343, 700, 395, and 770, respectively.

E42. The antibody of any one of embodiments E22-E41, wherein the nucleotide sequence encoding the VH comprises a nucleotide sequence of any VH provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E43. The antibody of any one of embodiments E22-E42, wherein the nucleotide sequence encoding the VH comprises the nucleotide sequence of SEQ ID NO: 150, 155, 167-169, or 197, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E44. The antibody of any one of embodiments E22-E43, comprising a VL comprising:

- (i) the amino acid sequence of any VL provided in Table 3 or 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
- (ii) an amino acid sequence 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; or

- (iii) an amino acid sequence encoded by a nucleotide sequence of any VL provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E45. The antibody of any one of embodiments E22-E44, comprising a VL comprising:
- (i) the amino acid sequence of SEQ ID NO: 78, 83, 93-95, or 122, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (ii) an amino acid sequence 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: 78, 83, 93-95, or 122; or
 - (iii) an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 224, 229, 241-243, or 270, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E46. The antibody of any of the preceding embodiments, comprising a VL comprising from N-terminus to C-terminus:
- (i) an FRL1 comprising the amino acid sequence of any FRL1 of an antibody in Table 7 or 4;
 - (ii) an LC CDR1 comprising the amino acid sequence of the LC CDR1 of the antibody in Table 6 or 5;
 - (iii) an FRL2 comprising the amino acid sequence of the FRL2 of the antibody in Table 7 or 4;
 - (iv) an LC CDR2 comprising the amino acid sequence of the LC CDR2 of the antibody in Table 6 or 5;
 - (v) an FRL3 comprising the amino acid sequence of the FRL3 of the antibody in Table 7 or 4;
 - (vi) an LC CDR3 comprising the amino acid sequence of the LC CDR3 of the antibody in Table 6 or 5; and
 - (vii) an FRL4 comprising the amino acid sequence of the FRL4 of the antibody in Table 7 or 4.
- E47. The antibody of any one of the preceding embodiments comprising a VL comprising, from N-terminus to C-terminus, an FRL1, an LC CDR1, an FRL2, an LC CDR2, an FRL3, an LC CDR3, and an FRL4, wherein:
- (i) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino acid sequences of SEQ ID NO: 793, 474, 836, 529, 874, 571, and 910, respectively;
 - (ii) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino

- acid sequences of SEQ ID NO: 1178, 1154, 831, 529, 1179, 571, and 906, respectively;
- (iii) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino acid sequences of SEQ ID NO: 787, 475, 831, 530, 870, 571, and 906, respectively;
 - (iv) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino acid sequences of SEQ ID NO: 807, 495, 830, 540, 888, 587, and 908, respectively.
 - (v) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino acid sequences of SEQ ID NO: 783, 464, 830, 523, 866, 562, and 906, respectively; or,
 - (vi) the FRL1, LC CDR1, FRL2, LC CDR2, FRL3, LC CDR3, FRL4 comprise the amino acid sequences of SEQ ID NO: 779, 460, 825, 518, 861, 557, and 908, respectively.
- E48. The antibody of any one of embodiments E22-E47, wherein the nucleotide sequence encoding the VL comprises a nucleotide sequence of any VL provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E49. The antibody of any one of embodiments E22-E48, wherein the nucleotide sequence encoding the VL comprises the nucleotide sequence of SEQ ID NO: 224, 229, 241-243, or 270, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E50. The antibody of any one of the preceding embodiments, comprising:
- (i) a VH comprising:
 - (a) the amino acid sequence of any VH provided in Table 3 or 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (b) an amino acid sequence 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; or
 - (c) an amino acid sequence encoded by a nucleotide sequence of any VH provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising:
 - (a) the amino acid sequence of any VL provided in Table 3 or 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

- (b) an amino acid sequence 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; or
 - (c) an amino acid sequence encoded by a nucleotide sequence of any VL provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E51. The antibody of any one of the preceding embodiments, comprising the amino acid sequence of any VH of an antibody provided in Table 3 and 4, and the amino acid sequence of the VL of the antibody provided in Table 3 or 4.
- E52. The antibody of any one of embodiments E22-E28 and E34-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 94, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E53. The antibody of any one of embodiments E22-E27, E29, and E34-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 21, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 93, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E54. The antibody of any one of embodiments E22-E27, E30, and E34-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 23, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 95, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E55. The antibody of any one of embodiments E22-E27, E31, and E44-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 51, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and

- (ii) a VL comprising the amino acid sequence of SEQ ID NO: 122, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E56. The antibody of any one of embodiments E22-E27, E32, and E44-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 83, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E57. The antibody of any one of embodiments E22-E27, and E33-E51, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 78, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E58. The antibody of any one of the preceding embodiments, wherein the nucleotide sequence encoding the antibody comprises:
- (i) the nucleotide sequence of SEQ ID NO: 150, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 224, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (ii) the nucleotide sequence of SEQ ID NO: 155, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 229, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (iii) the nucleotide sequence of SEQ ID NO: 167, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 241, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (iv) the nucleotide sequence of SEQ ID NO: 168, or a nucleotide sequence having at least

- 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 242, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
- (v) the nucleotide sequence of SEQ ID NO: 169, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 243, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or
 - (vi) the nucleotide sequence of SEQ ID NO: 197, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence of SEQ ID NO: 270, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E59. The antibody of any one of the preceding embodiments, which is a full length antibody, a bispecific antibody, an Fab, an F(ab')₂, an Fv, or a single chain Fv fragment (scFv).
- E60. The antibody of any one of the preceding embodiments, comprising 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 chosen from the light chain constant regions of kappa or lambda.
- E61. The antibody of any one of the preceding embodiments, 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 70%, 75%, 80%, 85%, 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 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E62. The antibody of any one of the preceding embodiments, wherein the nucleotide sequence encoding the heavy chain constant region comprises the nucleotide sequence of a heavy chain constant region provided in Table X, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or the nucleotide sequence encoding the light chain constant region comprises the nucleotide sequence of a light chain constant region provided in Table X, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

- E63. The antibody of any one of the preceding embodiments, comprising:
- (i) a VH comprising the amino acid sequence of any VH provided in Table 3 or 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and a heavy chain constant region comprising the amino acid sequence of an amino acid of a heavy chain constant region provided in Table X, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
 - (ii) a VL comprising the amino acid sequence of any VL provided in Table 3 or 4, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and a light chain constant region comprising the amino acid sequence of an amino acid of a light chain constant region provided in Table X, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E64. The antibody of any one of the preceding embodiments, comprising:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 4, 9, 21-23, or 51, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and a heavy chain constant region comprising the amino acid sequence of an amino acid of a heavy chain constant region provided in Table X, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or;
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 78, 83, 93-95, or 122, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and a light chain constant region comprising the amino acid sequence of an amino acid of a light chain constant region provided in Table X, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E65. The antibody of any one of the preceding embodiments, which antibody binds the C-terminus of a tau protein, *e.g.*, residues 409-436 numbered according to SEQ ID NO: 920.
- E66. The antibody of any one of the preceding embodiments, which antibody binds a microtubule binding domain of a tau protein.
- E67. The antibody of any one of the preceding embodiments, which antibody binds a proline rich domain of a tau protein.
- E68. The antibody of any one of the preceding embodiments, which antibody binds to a tau protein

with a dissociation constant (K_D) of less than about 120 nM, *e.g.*, measured by Octet, *e.g.*, as described in Example 8.

- E69. The antibody of any one of the preceding embodiments, which antibody binds to a tau protein with a K_D of about 0.1 nM to about 0.5 nM.
- E70. The antibody of any one of the preceding embodiments, which antibody is capable of binding to a tau protein with a K_D of about 0.5 nM to about 5 nM.
- E71. The antibody of any one of the preceding embodiments, which antibody is capable of binding to a tau protein with a K_D of about 5 nM to about 30 nM.
- E72. The antibody of any one of the preceding embodiments, which antibody binds 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.
- E73. The antibody of any one of the preceding embodiments, which antibody binds enriched paired helical filament tau protein (ePHF), *e.g.*, at a half maximal effective concentration (EC_{50}) of from about 0.01 nM to about 100 nM.
- E74. The antibody of any one of the preceding embodiments, which antibody reduces, *e.g.*, inhibits, aggregation of tau.
- E75. The antibody of any one of the preceding embodiments, which antibody inhibits aggregation of tau at a half maximal inhibitory concentration (IC_{50}) 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.
- E76. The antibody of any one of the preceding embodiments, which binds an epitope comprising a region formed by a complex of at least two tau proteins, *e.g.*, a tau dimer.
- E77. An antibody that competes for binding to tau with the antibody of any one of the preceding embodiments.
- E78. An 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 embodiments.
- E79. An isolated, *e.g.*, recombinant, nucleic acid encoding the antibody of any one of the preceding embodiments.
- E80. An isolated, *e.g.*, recombinant, nucleic acid encoding an antibody that binds to tau, wherein the antibody comprises:
 - (i) a heavy chain variable region (VH) comprising at least one, two, or three of an HC CDR1, an HC CDR2, and/or an HC CDR3 of an antibody in Table 1, 6, 2A-2C, 4, or 5; and/or

- (ii) a light chain variable region (VL) comprising at least one, two, or three of an LC CDR1, an LC CDR2, and/or an LC CDR3 of the antibody in Table 1, 6, 2A-2C, 4, or 5.
- E81. The nucleic acid of embodiment E80, wherein:
- (i) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 315, 341, 410, 474, 529, 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 NO: 314, 341, 410, 1154, 529, and 571, respectively;
 - (iii) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 316, 341, 410, 475, 530, and 571, respectively;
 - (iv) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 325, 362, 435, 495, 540, and 587, respectively;
 - (v) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 304, 347, 400, 464, 523, and 562, respectively; or,
 - (vi) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NO: 299, 343, 395, 460, 518, and 557, respectively.
- E82. The nucleic acid of embodiment E80, wherein the antibody comprises:
- (i) a VH comprising the amino acid sequence of any VH provided in Table 3 or 4, an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to any VH provided in Table 3 or 4, 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; and/or
 - (ii) a VL comprising the amino acid sequence of any VL provided in Table 3 or 4; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to any VL provided in Table 3 or 4; 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.

- E83. The nucleic acid of any one of embodiments E80-E82, wherein the antibody comprises:
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 4, 9, 21-23, or 51, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 4, 9, 21-23, or 51; and/or
 - (ii) a VL comprising the amino acid sequence of SEQ ID NO: 78, 83, 93-95, or 122, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 78, 83, 93-95, or 122.
- E84. The nucleic acid of any one embodiment E80-E83, 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 70%, 75%, 80%, 85%, 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 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E85. The nucleic acid of any one of embodiments E80-E84, comprising:
- (i) the nucleotide sequence of any VH provided in Table 3 or 4, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 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 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E86. The nucleic acid of any one of embodiments E80-E85, comprising:
- (i) the nucleotide sequence of SEQ ID NO: 150, 155, 167-169, or 197, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
 - (ii) the nucleotide sequence of SEQ ID NO: 224, 229, 241-243, or 270, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
- E87. The isolated nucleic acid sequence of any one of embodiments E79-E86, wherein the nucleic acid sequence encoding the heavy chain variable region and/or the light chain variable region

is codon-optimized.

- E88. An isolated, *e.g.*, recombinant, antibody encoded by the nucleic acid of any one of embodiments E79-E87.
- E89. A vector comprising the nucleic acid of any one of embodiments E79-E87, or a nucleic acid encoding the antibody of any one of embodiments E1-E78 and E88.
- E90. A host cell comprising the nucleic acid of any one of embodiments E79-E87, a nucleic acid encoding the antibody of any one of embodiments E1-E78 and E88, or the vector (*e.g.*, expression vector) of embodiment E89.
- E91. The host cell of embodiment E90, wherein the host cell is an insect cell, bacterial cell, or a mammalian cell.
- E92. A method of producing an antibody, the method comprising culturing the host cell of embodiment E90 or E91, under conditions suitable for gene expression.
- E93. An isolated nucleic acid encoding a payload, wherein the encoded payload comprises the antibody of any one of embodiments E1-E78 and E88.
- E94. The nucleic acid of embodiment E93, further encoding a signal sequence, optionally wherein the nucleotide sequence encoding the signal sequence 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.
- E95. The nucleic acid of any one of embodiments E93-E94, further encoding a second signal sequence, optionally wherein the nucleotide sequence encoding the signal sequence 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.
- E96. The nucleic acid of any one of embodiments E93-E95, 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.
- E97. The nucleic acid of any one of embodiments E93-E96, wherein the sequences of the encoded VH and VL are connected directly, *e.g.*, without a linker.
- E98. The nucleic acid of any one of embodiments E93-E97, wherein the sequences of the encoded VH and VL are connected via a linker.
- E99. The nucleic acid of embodiment E98, wherein 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.

- E100. The nucleic acid of any one of embodiments E93-E99, 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.
- E101. A viral genome comprising a promoter operably linked to the nucleic acid encoding a payload comprising the antibody of any one of embodiments E1-E78 and E88.
- E102. The viral genome of embodiment E101, 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.
- E103. The viral genome of any one of embodiments E101-E102, which further comprises an enhancer, optionally wherein the enhancer is a CMV immediate-early (CMVie) enhancer.
- E104. The viral genome of any one of embodiments E101-E103, which further comprises a polyadenylation (polyA) signal region.
- E105. The viral genome of embodiment E104, 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.
- E106. The viral genome of any one of embodiments E101-E105, further comprising an inverted terminal repeat (ITR) sequence.
- E107. The viral genome of embodiment E106, wherein:
- (i) the ITR sequence is positioned 5' relative to the encoded payload; and/or
 - (ii) the ITR sequence is positioned 3' relative to the encoded payload.
- E108. The viral genome of any one of embodiments E101-E107, which comprises an ITR sequence

positioned 5' relative to the encoded payload and an ITR sequence positioned 3' relative to the encoded payload.

- E109. The viral genome of any one of embodiments E101-E108, wherein 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.
- E110. The viral genome of any one of embodiments E101-E109, further comprising an intron region.
- E111. The viral genome of embodiment E110, wherein the intron region comprises a nucleotide sequence of any of the intron regions listed in Table 13, or a nucleotide sequence with at least 95% identity thereto.
- E112. The viral genome of any one of embodiments E101-E111, comprising at least one, two, or three intron regions.
- E113. The viral genome of any one of embodiments E101-E112, further comprising an exon region.
- E114. The viral genome of embodiment E113, wherein the exon region comprises the nucleotide sequence of any of the exon sequences in Table 12, or a nucleotide sequence with at least 95% identity thereto.
- E115. The viral genome of any one of embodiments E101-E114, comprising at least one, two, or three exon regions.
- E116. The viral genome of any one of embodiments E101-E115, which further comprises a Kozak sequence, optionally wherein the Kozak sequence comprises the nucleotide sequence of GCCGCCACCATG (SEQ ID NO: 1079) or GAGGAGCCACC (SEQ ID NO: 1089).
- E117. The viral genome of any one of embodiments E101-E116, 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.
- E118. The viral genome of embodiment E117, which comprises at least 1-5 copies of an encoded miR binding site, *e.g.*, at least 1, 2, 3, 4, or 5 copies.
- E119. The viral genome of any one of embodiments E117-E118, which comprises at least 3 copies of an encoded miR binding sites, optionally wherein all three copies comprise the same miR binding site, or at least one, two, or all of the copies comprise a different miR binding site.
- E120. The viral genome of any one of embodiments E117-E119, which comprises at least 4 copies of an encoded miR binding site, optionally wherein all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding

site.

- E121. The viral genome of any one of embodiments E117-E120, 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 70%, 75%, 80%, 85%, 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 70%, 75%, 80%, 85%, 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 70%, 75%, 80%, 85%, 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.
- E122. The viral genome of any one of embodiments E101-E121, which is single stranded.
- E123. The viral genome of any one of embodiments E101-E122, which further comprises 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.
- E124. The viral genome of embodiment E123, wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.
- E125. The viral genome of any one of embodiments E101-E124, which further comprises a nucleic acid sequence encodes a capsid protein, *e.g.*, a structural protein, wherein the capsid protein comprises a VP1 polypeptide, a VP2 polypeptide, and/or a VP3 polypeptide.
- E126. The viral genome of embodiment E125, wherein the VP1 polypeptide, the VP2 polypeptide, and/or the VP3 polypeptide are encoded by at least one Cap gene.
- E127. A vector comprising the viral genome of any one embodiments E101-E126.
- E128. An isolated, *e.g.*, recombinant AAV particle comprising:
- (i) a capsid protein, and,
 - (ii) the nucleic acid of any one of embodiments E79-E87 and E93-E100, or the viral

genome of any one of embodiments E101-E126.

E129. The isolated AAV particle of embodiment E128, 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.

E130. The isolated AAV particle of embodiment E128 or E129, 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.

E131. The AAV particle of any one of embodiments E128-E130, wherein the capsid protein comprises (i) the amino acid substitution of K449R numbered according to SEQ ID NO: 1003; and (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 of

SEQ ID NO: 1003.

- E132. The AAV particle of any one of embodiments E128-E130, wherein the capsid protein comprises (i) the amino acid substitution of K449R 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; and (iii) the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.
- E133. The AAV particle of any one of embodiments E128-E130, wherein the capsid protein comprises (i) 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 (ii) the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.
- E134. The AAV particle of any one of embodiments E128-E133, wherein the capsid protein comprises any of the capsid proteins listed in Table 9 or a functional variant thereof.
- E135. The AAV particle of any one of embodiments E128-E134, wherein the capsid protein comprises 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.
- E136. The AAV particle of any of embodiments E128-E135, wherein the capsid protein comprises a VOY101 capsid protein.
- E137. The AAV particle of embodiment E136, wherein the capsid protein comprises:
- (i) the amino acid sequence of SEQ ID NO: 1023, or an amino acid sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;
 - (ii) an amino acid sequence comprising at least one, two, or three modifications but no

- more than 30, 20, or 10 modifications, *e.g.*, substitutions, relative to the amino acid sequence of SEQ ID NO: 1023; or,
- (iii) an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1022 or a nucleotide sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.
- E138. The AAV particle of embodiment E136 or E137, wherein the nucleotide sequence encoding the capsid protein comprises the nucleotide sequence of SEQ ID NO: 1022, or a nucleotide sequence substantially identical (*e.g.*, having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.
- E139. The AAV particle of any one of embodiments E128-E138, wherein the capsid protein comprises:
- (i) a VP1 polypeptide, VP2 polypeptide, VP3 polypeptide, or a combination thereof;
 - (ii) the amino acid sequence corresponding to positions 138-743, *e.g.*, a VP2, of SEQ ID NO: 1023, or a sequence with at least 80% (*e.g.*, at least about 85, 90, 92, 95, 96, 97, 98, or 99%) sequence identity thereto;
 - (iii) the amino acid sequence corresponding to positions 203-743, *e.g.*, a VP3, of SEQ ID NO: 1023, or a sequence with at least 80% (*e.g.*, at least about 85, 90, 92, 95, 96, 97, 98, or 99%) sequence identity thereto; and/or
 - (iv) the amino acid sequence corresponding to positions 1-743, *e.g.*, a VP1, of SEQ ID NO: 1023, or a sequence with at least 80% (*e.g.*, at least about 85, 90, 92, 95, 96, 97, 98, or 99%) sequence identity thereto.
- E140. A host cell comprising the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, or the AAV particle of any one of embodiments E128-E139, optionally wherein the host cell is an insect cell, a bacterial cell or a mammalian cell.
- E141. A nucleic acid encoding the viral genome of any one of embodiments E101-E126, and a backbone region suitable for replication of the viral genome in a cell, *e.g.*, a bacterial cell (*e.g.*, wherein the backbone region comprises one or both of a bacterial origin of replication and a selectable marker).
- E142. A method of making a viral genome, the method comprising:
- (i) providing the nucleic acid molecule comprising the viral genome of any one of embodiments E101-E126; and
 - (ii) excising the viral genome from the backbone region, *e.g.*, by cleaving the nucleic acid molecule at upstream and downstream of the viral genome.
- E143. A method of making an isolated, *e.g.*, recombinant, AAV particle, the method comprising

- (i) providing a host cell comprising the viral genome of embodiment E140; and
 - (ii) incubating the host cell under conditions suitable to enclose the viral genome in a capsid protein, *e.g.*, a VOY101 capsid protein;
- thereby making the isolated AAV particle.
- E144. The method of embodiment E143, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the host cell.
- E145. The method of embodiment E143 or E144, wherein the host cell comprises a second nucleic acid encoding a capsid protein, *e.g.*, a VOY101 capsid protein.
- E146. The method of any one of embodiments E143-E144, wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.
- E147. A pharmaceutical composition comprising the antibody of any one of embodiments E1-E78 and E88, an AAV particle of any one of embodiments E128-E139, or an AAV particle comprising the viral genome of any one of embodiments E101-E126, or the isolated nucleic acid of any one of embodiments E79-E87 and E93-E100, and a pharmaceutically acceptable excipient.
- E148. A method of delivering an exogenous antibody that binds to tau, to a subject, comprising administering an effective amount of the pharmaceutical composition of embodiment S1, the antibody of any one of embodiments E1-E78 and E88, an AAV particle, *e.g.*, a plurality of AAV particles, of any one of embodiments E128-E139, or an AAV particle, *e.g.*, a plurality of AAV particles, comprising the viral genome of any one of embodiments E101-E126, or the isolated nucleic acid of any one of embodiments E79-E87 and E93-E100.
- E149. The method of embodiment E148, wherein the subject has, has been diagnosed with having, or is at risk of having a disease associated with expression of tau.
- E150. The method of embodiment E148 or E149, wherein the subject has, has been diagnosed with having, or is at risk of having a neurological, *e.g.*, neurodegenerative disorder.
- E151. The method of embodiment E148, E149, or E150, wherein the subject has, has been diagnosed with having, or is at risk of having a tauopathy.
- E152. A method of treating a subject having or diagnosed with having a disease associated with expression of tau comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment E147, the antibody of any one of embodiments E1-E78 and E88, an AAV particle, *e.g.*, a plurality of AAV particles, of any one of embodiments E128-E139, or an AAV particle, *e.g.*, a plurality of AAV particles, comprising

the viral genome of any one of embodiments E101-E126, or the isolated nucleic acid of any one of embodiments E79-E87 and E93-E100.

- E153. A method of treating a subject having or diagnosed with having a neurological, *e.g.*, neurodegenerative disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment E147, the antibody of any one of embodiments E1-E78 and E88, an AAV particle, *e.g.*, a plurality of AAV particles, of any one of embodiments E128-E139, or an AAV particle, *e.g.*, a plurality of AAV particles, comprising the viral genome of any one of embodiments E101-E126, or the isolated nucleic acid of any one of embodiments E79-E87 and E93-E100.
- E154. A method of treating a subject having or diagnosed with having a tauopathy comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment E147, the antibody of any one of embodiments E1-E78 and E88, an AAV particle, *e.g.*, a plurality of AAV particles, of any one of embodiments E128-E139, or an AAV particle, *e.g.*, a plurality of AAV particles, comprising the viral genome of any one of embodiments E101-E126, or the isolated nucleic acid of any one of embodiments E79-E87 and E93-E100.
- E155. The method of any one of embodiments E152-E154, wherein the disease associated with Tau expression, the neurological disorder, or the tauopathy comprises AD, FTDP-17, FTLD, 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.
- E156. The method of any one of embodiments E152-E155, where treating comprises prevention of progression of the disease in the subject.
- E157. The method of any one of embodiments E152-E156, wherein the subject is a human.
- E158. The method of any one of embodiments E152-E157, 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.
- E159. The method of any one of embodiments E152-E158, wherein the AAV particle is administered to the subject intravenously.
- E160. The method of any one of embodiments E152-E158, wherein the AAV particle is administered to the subject via intra-cisterna magna injection (ICM).

- E161. The method of any one of embodiments E152-E160, further comprising evaluating, *e.g.*, measuring, the level of antibodies generated in a subject, *e.g.*, in a cell or tissue of the subject.
- E162. The method of any one of embodiments E152-E161, wherein the administration results in the generation of 0.001 ug/mL to 100 mg/mL of antibodies in the subject, *e.g.*, in a cell or tissue of the subject.
- E163. The method of embodiment E162, wherein the cell is a neuronal cell.
- E164. The method of embodiment E162, wherein the tissue is a central nervous system tissue, *e.g.*, a brain tissue.
- E165. The method of any one of embodiments E152-E164, further comprising performing a blood test, an imaging test, a CNS biopsy sample, or an aqueous cerebral spinal fluid biopsy.
- E166. The method of any one of embodiments E161-E165, wherein measuring the level of antibodies is performed prior to, during, or subsequent to treatment with the AAV particle, *e.g.*, plurality of AAV particles.
- E167. The method of any one of embodiments E152-E166, wherein the subject has a level of antibodies that is a greater than a reference level, *e.g.*, a subject that has not received treatment, *e.g.*, has not been administered the AAV particle or plurality of AAV particles.
- E168. The method of any one of embodiments E152-E167, wherein the plurality of AAV particles are administered at a dose of about 1×10^6 VG/mL to about 1×10^{16} VG/mL or about 0.0001 mg/kg to about 100 mg/kg.
- E169. The method of any one of embodiments E152-E168, further comprising administration of an additional therapeutic agent and/or therapy suitable for treatment or prevention of a disorder associated with tau expression, a neurological, *e.g.*, neurodegenerative, disorder.
- E170. The method of embodiment E169, 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.
- E171. The antibody of any one of embodiments E1-E78 and E88, the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, the pharmaceutical composition of embodiment E147, or the AAV particle of any one

of embodiments E128-E139, for use in the manufacture of a medicament.

- E172. The antibody of any one of embodiments E1-E78 and E88, the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, the pharmaceutical composition of embodiment E147, or the AAV particle of any one of embodiments E128-E139, for use in the treatment of a disease associated with tau expression.
- E173. The antibody of any one of embodiments E1-E78 and E88, the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, the pharmaceutical composition of embodiment E147, or the AAV particle of any one of embodiments E128-E139, for use in the treatment of a neurological, *e.g.*, neurodegenerative, disorder.
- E174. The antibody of any one of embodiments E1-E78 and E88, the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, the pharmaceutical composition of embodiment E147, or the AAV particle of any one of embodiments E128-E139, for use in the treatment of a tauopathy.
- E175. Use of an effective amount of the antibody of any one of embodiments E1-E78 and E88, the nucleic acid of any one of embodiments E79-E87 and E93-E100, the viral genome of any one of embodiments E101-E126, the pharmaceutical composition of embodiment E147, or the AAV particle of any one of embodiments E128-E139, in the manufacture of a medicament for the treatment of a disease associated with tau expression, a neurological, *e.g.*, neurodegenerative, disorder, or a tauopathy in a subject.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0060] FIGs. 1A-1B show alignment of variable light chain or VL (FIG. 1A) and variable heavy chain or VH (FIG. 1B) regions of selected antibodies V0004, V0009, V0022, V0023, V0024 and V0052, with the CDR sequences highlighted according to the Kabat numbering system. The corresponding framework region sequences under the Kabat numbering system, including FRH1-FRH4 and FRL1-FRL4, are defined by the boundaries of the CDR regions.

[0061] FIGs. 2A-2B show alignment of variable light chain (FIG. 2A) and variable heavy chain (FIG. 2B) regions of selected antibodies V0004, V0009, V0022, V0023, V0024 and V0052, with CDR sequences highlighted according to the Chothia numbering system. The corresponding framework region sequences under the Chothia numbering system, including FRH1-FRH4 and FRL1-FRL4, are defined by the boundaries of the CDR regions.

[0062] FIGs. 3A-3B show alignment of variable light chain (FIG. 3A) and variable heavy chain (FIG. 3B) regions of selected antibodies V0004, V0009, V0022, V0023, V0024 and V0052, with CDR sequences highlighted according to IMGT numbering system. The corresponding framework region sequences under the IMGT numbering system, including FRH1-FRH4 and FRL1-FRL4, are defined by the boundaries of the CDR regions.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOSITIONS

[0063] In some embodiments, the present disclosure provides compositions that interact with human microtubule associated protein tau. Such compositions may be antibodies that bind tau protein epitopes, referred to herein as “anti-tau antibodies.” Dysfunction and/or aggregation of tau is found in a class of neurodegenerative diseases referred to as tauopathies. Tau hyperphosphorylation leads to aggregation and depressed tau-dependent microtubule assembly. In tauopathies, the tau aggregates form paired helical filaments (PHF) found in neurofibrillary tangles (NFTs). These aggregates lead to neuronal loss and cognitive decline. Anti-tau antibodies of the present disclosure may be useful for treating and/or diagnosing tauopathies, as well as other applications described herein.

Antibodies

[0064] In some embodiments, compounds (*e.g.*, anti-tau antibodies) and compositions of the present disclosure include antibodies or fragments thereof. In some embodiments, the antibody described herein bind tau. For example, the antibody binds to an epitope, *e.g.*, a confirmation epitope, phosphorylated epitope, or a linear epitope, on tau, *e.g.*, as described herein.

[0065] As used herein, the term “antibody” is referred to in the broadest sense and specifically covers various embodiments including, but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies formed from at least two intact

antibodies), single chain Fv (scFv) formats, and antibody fragments (such as Fab, F(ab'), F(ab')₂, Fv, *etc.*), so long as they exhibit a desired functional or biological activity. Antibodies are primarily amino acid-based molecules but may also include one or more modifications (including, but not limited to the addition of sugar moieties, fluorescent moieties, chemical tags, *etc.*).

[0066] Antibodies (including antigen-binding fragments thereof) of the present disclosure may include, but are not limited to, polyclonal, monoclonal antibodies, multispecific antibodies, bispecific antibodies, trispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, single chain antibodies, diabodies, linear antibodies, Fab fragments, F(ab') fragments, F(ab')₂ fragments, Fv fragments, fragments produced by a Fab expression library, variable domains, anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), intracellularly made antibodies (*i.e.*, intrabodies), codon-optimized antibodies, scFv fragments, tandem scFv antibodies, bispecific T-cell engagers, mAb2 antibodies, chimeric antigen receptors (CAR), tetravalent bispecific antibodies, biosynthetic antibodies, native antibodies, miniaturized antibodies, unibodies, maxibodies, and epitope-binding fragments of any of the above.

[0067] In some embodiments, the antibody comprises at least one immunoglobulin variable domain sequence. An antibody may include, for example, full-length, mature antibodies and antigen-binding fragments of an antibody. For example, an antibody can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In another example, an antibody includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')₂, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (*e.g.*, humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments retain the ability to selectively bind with their respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (*e.g.*, human IgG1, IgG2, IgG3, and IgG4, and murine IgG1, IgG2a, IgG2b, IgG2c, and IgG3) of antibodies. The antibodies of the present disclosure can be monoclonal or polyclonal. The antibody can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. The antibody can have a heavy chain constant region chosen from, *e.g.*, IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, *e.g.*, kappa or lambda.

[0068] In some embodiments, an antibody of the present disclosure comprises a functional fragment or variant thereof. Constant regions of the antibodies can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

[0069] As used herein, the term “antibody fragment” refers to a portion of an intact antibody or fusion-protein thereof, in some cases including at least one antigen binding region. Examples of antigen-binding fragments include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), see *e.g.*, Bird *et al.* (1988) Science 242:423-426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883; and (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, for example, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005).''In some embodiments, papain digestion of antibodies produces two identical antigen-binding fragments, called “Fab” fragments, each with a single antigen-binding site. Also produced is a residual “Fc” fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-binding sites and is still capable of cross-linking antigen. Antibodies of the present disclosure may include one or more of these fragments and may, for example, be generated through enzymatic digestion of whole antibodies or through recombinant expression.

[0070] In some embodiments, the antibody can be single domain antibody. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to another aspect of the invention, a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 9404678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain; such VHHs are within the scope of the invention.

[0071] “Native antibodies” are usually heterotetrameric glycoproteins of about 150,000 Daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda, F. *et al.*, 1998. The Journal of Experimental Medicine. 188(11); 2151-62 and Li, A. *et al.*, 2004. Blood. 103(12: 4602-9, the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0072] As used herein, the term “variable domain” refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. In some embodiments, the V_H and V_L regions of the antibody described herein can be subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR).

[0073] As used herein, the term “hypervariable region” refers to a region within a variable domain that includes amino acid residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody.

[0074] As used herein, the term “CDR” refers to a region of an antibody that includes a structure that is complementary to its target antigen or epitope. CDR regions generally confer antigen specificity and binding affinity. Other portions of the variable domain, not interacting with the antigen, are each referred to as a “framework region” (FR). The antigen-binding site (also known as the antigen combining site or paratope) includes the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site may be determined by CDR analysis.

[0075] As used herein, the term “CDR analysis” refers to any process used to determine which antibody variable domain residues make up the CDRs. The extent of the framework region and CDRs has been precisely defined by a number of methods (see, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.* (1987) J. Mol. Biol. 196:901-917; and the AbM definition used by Oxford Molecular’s AbM antibody modeling software. See, generally, *e.g.*, Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab

Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). CDR analysis may be conducted by co-crystallography with bound antigen. In some embodiments, CDR analysis may include computational assessments based on comparisons with other antibodies (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety). CDR analysis and/or the precise amino acid sequence boundaries may include the use of numbering schemes including, but not limited to, those taught by Kabat [Wu, T.T. *et al.*, 1970, JEM, 132(2):211-50 and Johnson, G. *et al.*, 2000, Nucleic Acids Res. 28(1): 214-8, the contents of each of which are herein incorporated by reference in their entirety], Chothia [Chothia and Lesk, J. Mol. Biol. 196, 901 (1987), Chothia *et al.*, Nature 342, 877 (1989), and Al-Lazikani, B. *et al.*, 1997, J. Mol. Biol. 273(4):927-48, the contents of each of which are herein incorporated by reference in their entirety], Lefranc (Lefranc, M.P. *et al.*, 2005, Immunome Res. 1:3), and Honegger (Honegger, A. and Pluckthun, A. 2001. J. Mol. Biol. 309(3):657-70, the contents of which are herein incorporated by reference in their entirety). In some embodiments, the CDRs defined according the Chothia number scheme are also sometimes referred to as hypervariable loops.

[0076] For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3).

[0077] Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3).

[0078] By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL.

[0079] For certain antibodies of the invention, equivalent CDR sequences and framework region sequences, based on the Kabat, Chothia, and IMGT numbering systems, can be readily obtained based at least on Tables and sequences described herein, which provide SEQ ID NOs: for the equivalent CDR regions based on the Kabat, Chothia, and IMGT numbering systems, respectively. Also see FIGs. 1A-3B.

[0080] In general, the VH and VL domains have three CDRs each. VL CDRs are referred to herein as CDRL1, CDRL2 and CDRL3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. VH CDRs are referred to herein as CDRH1, CDRH2 and CDRH3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. Each of the CDRs have favored canonical structures with the exception of the CDRH3, which includes amino acid sequences that may be highly variable in sequence and length between

antibodies resulting in a variety of three-dimensional structures in antigen-binding domains (Nikoloudis, D. *et al.*, 2014. PeerJ. 2:e456). In some cases, CDRH3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[0081] In some embodiments, the VH and VL domains each have four framework regions (FRs) located before, after, and between CDR regions. VH framework regions are referred to herein as FRH1, FRH2, FRH3, and FRH4 and VL framework regions are referred to herein as FRL1, FRL2, FRL3, and FRL4. In some embodiments, on VH domains, FRs and CDRs are in the order of FRH1-CDRH1-FRH2-CDRH2-FRH3-CDRH3-FRH4, from N-terminus to C-terminus. In some embodiments, on VL domains, FRs and CDRs are in the order of FRL1-CDRL1-FRL2-CDRL2-FRL3-CDRL3-FRL4, from N-terminus to C-terminus.

[0082] In some embodiments, the antigen binding domain of the antibodies of the present disclosure is the part of the antibody that comprises determinants that form an interface that binds to the tau polypeptide or an epitope thereof. With respect to proteins (or protein mimetics), the antigen-binding site typically includes one or more loops (of at least four amino acids or amino acid mimics) that form an interface that binds to the tau polypeptide. Typically, the antigen-binding site of an antibody includes at least one or two CDRs and/or hypervariable loops, or more typically at least three, four, five or six CDRs and/or hypervariable loops.

[0083] In yet other embodiments, the antibody has a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the human heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4, or the murine heavy chain constant regions of IgG1, IgG2a, IgG2b, IgG2c, and IgG3. In another embodiment, the antibody has a light chain constant region chosen from, *e.g.*, the (*e.g.*, murine or human) light chain constant regions of kappa or lambda.

[0084] The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In some embodiments the antibody has: effector function; and can fix complement. In other embodiments the antibody does not recruit effector cells; or fix complement. In other embodiments, the antibody has reduced or no ability to bind an Fc receptor. For example, it is an isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

[0085] Methods for altering an antibody constant region are known in the art. Antibodies with altered function, *e.g.* altered affinity for an effector ligand, such as FcR on a cell, or the C1 component

of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see *e.g.*, EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648,260, the contents of all of which are hereby incorporated by reference). Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

[0086] As used herein, the term “Fv” refers to an antibody fragment that includes the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable domain and the heavy chain variable domain (to form a single chain Fv (scFv)) or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl, W.R. *Therapeutic Antibody Engineering*. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[0087] Antibody “light chains” from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes.

[0088] As used herein, the term “single chain Fv” or “scFv” refers to a fusion protein of VH and VL antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding. In some embodiments, scFvs are utilized in conjunction with phage display, yeast display or other display methods where they may be expressed in association with a surface member (*e.g.* phage coat protein) and used in the identification of high affinity peptides for a given antigen. In some embodiments, antibodies of the present disclosure are prepared as scFvFc antibodies. The term “scFvFc” refers to an antibody format which includes the fusion of one or more scFv with an antibody Fc domain.

[0089] The term “chimeric antibody” refers to an antibody with portions derived from two or more sources. Chimeric antibodies may include portions derived from different species. For example, chimeric antibodies may include antibodies with mouse variable domains and human constant domains. Further examples of chimeric antibodies and methods for producing them include any of those described in Morrison, S.L., *Transfectomas provide novel chimeric antibodies*. Science. 1985 Sep 20;229(4719):1202-7; Gillies, S.D. *et al.*, *High-level expression of chimeric antibodies using adapted cDNA variable region cassettes*. J Immunol Methods. 1989 Dec 20;125(1-2):191-202.; and U.S. Pat. Nos. 5,807, 715; 4,816,567; and 4,816,397, the contents of each of which are incorporated herein by reference in their entirety.

[0090] The term “diabodies” refers to small antibody fragments with two antigen-binding sites, which fragments include a heavy chain variable domain V_H connected to a light chain variable domain V_L in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993), the contents of each of which are incorporated herein by reference in their entirety.

[0091] The term “intrabody” refers to a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular protein(s). Intrabodies may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods of the present invention may include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein may be incorporated into one or more constructs for intrabody-based therapy. In some cases, intrabodies of the invention may target one or more glycosylated intracellular proteins or may modulate the interaction between one or more glycosylated intracellular protein and an alternative protein.

[0092] The term “chimeric antigen receptor” or “CAR” as used herein, refers to artificial receptors that are engineered to be expressed on the surface of immune effector cells resulting in specific targeting of such immune effector cells to cells expressing entities that bind with high affinity to the artificial receptors. CARs may be designed to include one or more segments of an antibody, antibody variable domain and/or antibody CDR, such that when such CARs are expressed on immune effector cells, the immune effector cells bind and clear any cells that are recognized by the antibody portions of the CARs. In some cases, CARs are designed to specifically bind cancer cells, leading to immune-regulated clearance of the cancer cells.

[0093] The antibody of the invention can be a monoclonal antibody or a polyclonal antibody. The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous cells (or clones), *i.e.g.*, the individual antibodies making up the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen

[0094] The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

[0095] In some embodiments, the antibody comprises an amino acid sequence of an antibody in which the variable region, or a portion thereof, *e.g.*, the CDRs, are generated in a non-human organism, *e.g.*, a rat or mouse. Antibodies comprising chimeric, CDR-grafted, and humanized antibodies are within the invention. Antibodies comprising the sequences of antibodies generated in a non-human organism, *e.g.*, a rat or mouse, and then modified, *e.g.*, in the variable framework or constant region, to decrease antigenicity in a human are within the invention.

[0096] The monoclonal antibodies herein include “chimeric” antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[0097] Antibodies of the present disclosure may be from any animal origin including mammals, birds, reptiles, and insects. Mammalian antibodies may be, for example, of human, murine (*e.g.*, mouse or rat), donkey, sheep, rabbit, goat, guinea pig, camel, bovine, or horse origin.

[0098] In some embodiments, antibodies of the present disclosure may be antibody mimetics. The term “antibody mimetic” refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US 6,673,901; US 6,348,584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, DARPins, Fynomers and Kunitz and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide region.

[0099] As used herein, the term “antibody variant” refers to a biomolecule resembling an antibody in structure, sequence and/or function, but including some differences in their amino acid sequence, composition or structure as compared to another antibody or a native antibody.

Multispecific Antibodies

[0100] In some embodiments, the antibody is a multispecific antibody, *e.g.*, it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In some embodiments, a multispecific antibody comprises a third, fourth or

fifth immunoglobulin variable domain. In some embodiments, a multispecific antibody is a bispecific antibody, a trispecific antibody, or tetraspecific antibody. In some embodiments, the anti-tau antibody is a multispecific antibody.

[0101] In some embodiments, a multispecific antibody is a bispecific antibody. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In some embodiments, a bispecific antibody comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In some embodiments, a bispecific antibody comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In some embodiments, a bispecific antibody comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In some embodiments, a bispecific antibody comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope. In some embodiment, the anti-tau antibody is a bispecific antibody.

[0102] In some embodiments, the sequences of the antibody of the present disclosure can be generated from bispecific or heterodimeric antibody produced using protocols known in the art; including but not limited to, for example, the “knob in a hole” approach described in, *e.g.*, US5731168; the electrostatic steering Fc pairing as described in, *e.g.*, WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US4433059; bispecific antibody determinants generated by recombining half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab’ fragments cross-linked through sulfhydryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive

chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono- and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also disclosed creating bispecific, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*, US5844094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus further associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, *e.g.*, US5869620.

Antibody development

[0103] Antibodies according to the present disclosure may be developed using methods standard in the art. Two primary antibody preparation technologies are immunization and antibody display technology. In either case, desired antibodies are identified from a larger pool of candidates based on affinity for a specific target or epitope. An immune response is characterized by the reaction of the cells, tissues and/or organs of an organism to the presence of a foreign entity. Such an immune response typically leads to the production by the organism of one or more antibodies against the foreign entity, *e.g.*, antigen or a portion of the antigen.

Antigens

[0104] Antibodies may be developed (*e.g.*, through immunization) or selected (*e.g.*, from pool of candidates), for example, using any naturally occurring or synthetic antigen. As used herein, an “antigen” is an entity which induces or evokes an immune response in an organism and may also refer

to an antibody binding partner. An immune response is characterized by the reaction of the cells, tissues and/or organs of an organism to the presence of a foreign entity. Such an immune response typically leads to the production by the organism of one or more antibodies against the foreign entity. In some embodiments, antigens include tau proteins.

[0105] As used herein, the term “tau protein” refers to proteins or protein complexes that include microtubule-associated protein tau or peptide fragments thereof. Tau proteins may include enriched paired helical filament tau protein (ePHF), also referred to as “sarkosyl insoluble tau,” or fragments thereof. Tau proteins may include one or more phosphorylated residues. Such phosphorylated residues may correspond to tau proteins associated with disease (also referred to herein as “pathological tau”).

Immunization

[0106] In some embodiments, antibodies may be prepared by immunizing a host with an antigen of interest. Host animals (*e.g.*, mice, rabbits, goats, or llamas) may be immunized with an antigenic protein to elicit lymphocytes that specifically bind to the antigen. Lymphocytes may be collected and fused with immortalized cell lines to generate hybridomas which can be cultured in a suitable culture medium to promote growth (*e.g.*, see Kohler, G. *et al.*, Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature*. 1975 Aug 7;256(5517):495-7, the contents of which are herein incorporated by reference in their entirety). Alternatively, lymphocytes may be immunized *in vitro*.

[0107] Lymphocytes may be fused with immortalized cell lines using suitable fusing agents (*e.g.*, polyethylene glycol) to form a hybridoma cell (*e.g.*, see Goding, J.W., *Monoclonal Antibodies: Principles and Practice*. Academic Press. 1986; 59-1031, the contents of which are herein incorporated by reference in their entirety). Immortalized cell lines may be transformed mammalian cells, particularly myeloma cells of rodent, rabbit, bovine, or human origin. In some embodiments, rat or mouse myeloma cell lines are employed. Hybridoma cells may be cultured in suitable culture media, typically including one or more substances that inhibit the growth or survival of unfused cells. For example, parental cells lacking the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT) may be used and culture media for resulting hybridoma cells may be supplemented with hypoxanthine, aminopterin, and thymidine (“HAT medium”) to prevent growth of HGPRT-deficient (unfused) cells.

[0108] Desirable properties for immortalized cell lines may include, but are not limited to, efficient fusing, supportive of high level antibody expression by selected antibody-producing cells, and sensitivity to unfused cell-inhibitory media (*e.g.*, HAT media). In some embodiments, immortalized cell lines are murine myeloma lines. Such cell lines may be obtained, for example, from the Salk Institute Cell Distribution Center (San Diego, CA) or the American Type Culture Collection, (Manassas, VA). Human myeloma and mouse-human heteromyeloma cell lines may also be used for the production of human monoclonal antibodies (*e.g.*, see Kozbor, D. *et al.*, A human hybrid myeloma

for production of human monoclonal antibodies. J Immunol. 1984 Dec;133(6):3001-5 and Brodeur, B. *et al.*, Monoclonal Antibody Production Techniques and Applications. Marcel Dekker, Inc., New York. 1987; 33:51-63, the contents of each of which are herein incorporated by reference in their entirety).

[0109] Hybridoma cell culture media may be assayed for the presence of monoclonal antibodies with desired binding specificity. Assays may include, but are not limited to, immunoprecipitation assay, *in vitro* binding assay, radioimmunoassay (RIA), surface plasmon resonance (SPR) assay, and/or enzyme-linked immunosorbent assay (ELISA). In some embodiments, binding specificity of monoclonal antibodies may be determined by Scatchard analysis (Munson, P.J. *et al.*, Ligand: a versatile computerized approach for characterization of ligand-binding systems. Anal Biochem. 1980 Sep 1;107(1):220-39, the contents of which are herein incorporated by reference in their entirety).

[0110] Antibodies produced by cultured hybridomas may be analyzed to determine binding specificity for target antigens. Once antibodies with desirable characteristics are identified, corresponding hybridomas may be subcloned through limiting dilution procedures and grown by standard methods. Antibodies produced by hybridomas may be isolated and purified using standard immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxyapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. Alternatively, hybridoma cells may be grown *in vivo* as ascites in a mammal. In some embodiments, antibodies may be isolated directly from serum of immunized hosts.

[0111] In some embodiments, recombinant versions of antibodies generated through immunization may be prepared. Such antibodies may be prepared using genomic antibody sequences from selected hybridomas. Hybridoma genomic antibody sequences may be obtained by extracting RNA molecules from antibody-producing hybridoma cells and producing cDNA by reverse transcriptase polymerase chain reaction (PCR). PCR may be used to amplify cDNA using primers specific for antibody heavy and light chains. PCR products may then be subcloned into plasmids for sequence analysis. Antibodies may be produced by insertion of resulting antibody sequences into expression vectors. Some recombinant antibodies may be prepared using synthetic nucleic acid constructs that encode amino acid sequences corresponding to amino acid sequences obtained from isolated hybridoma antibodies.

Antibody display

[0112] In some embodiments, antibodies may be developed using antibody display technologies. “Display technology” refers to systems and methods for expressing amino acid-based candidate compounds in a format where they are linked with nucleic acids encoding them and are accessible to a target or ligand. Candidate compounds are expressed at the surface of a host capsid or cell in most systems, however, some host-free systems (*e.g.*, ribosomal display) exist. Display technologies may be used to generate display “libraries,” which include sets of candidate compound library members.

Display libraries with antibodies (or variants or fragments thereof) as library members are referred to herein as “antibody display libraries.” Antibodies may be designed, selected, or optimized by screening target antigens using antibody display libraries. Antibody display libraries may include millions to billions of members, each expressing unique antibody domains. Antibody fragments displayed may be scFv antibody fragments, which are fusion proteins of V_H and V_L antibody domains joined by a flexible linker. Display libraries may include antibody fragments with differing levels of diversity between variable domain framework regions and CDRs. Display library antibody fragment CDRs may include unique variable loop lengths and/or sequences. Antibody variable domains or CDRs obtained from display library selection may be directly incorporated into antibody sequences for recombinant antibody production or mutated and utilized for further optimization through *in vitro* affinity maturation.

[0113] Antibody display libraries may include antibody phage display libraries. Antibody phage display libraries utilize phage virus particles as hosts with millions to billions of members, each expressing unique antibody domains. Such libraries may provide richly diverse sources that may be used to select potentially hundreds of antibody fragments with diverse levels of affinity for one or more antigens of interest (McCafferty, *et al.*, 1990. *Nature*. 348:552-4; Edwards, B.M. *et al.*, 2003. *JMB*. 334: 103-18; Schofield, D. *et al.*, 2007. *Genome Biol.* 8, R254 and Pershad, K. *et al.*, 2010. *Protein Engineering Design and Selection*. 23:279-88; the contents of each of which are herein incorporated by reference in their entirety). Antibody fragments displayed may be scFv antibody fragments. Phage display library members may be expressed as fusion proteins, linked to viral coat proteins (*e.g.* the N-terminus of the viral pIII coat protein). V_L chains may be expressed separately for assembly with V_H chains in the periplasm prior to complex incorporation into viral coats. Precipitated library members may be sequenced from the bound phage to obtain cDNA encoding desired antibody domains.

[0114] In some embodiments, antibody display libraries may be generated using yeast surface display technology. Antibody yeast display libraries are made up of yeast cells with surface displayed antibodies or antibody fragments. Antibody yeast display libraries may include antibody variable domains expressed on the surface of *Saccharomyces cerevisiae* cells. Yeast display libraries may be developed by displaying antibody fragments of interest as fusion proteins with yeast surface proteins (*e.g.* Aga2p protein). Yeast cells displaying antibodies or antibody fragments with affinity for a specific target may be isolated according to standard methods. Such methods may include, but are not limited to, magnetic separation and flow cytometry.

Recombinant synthesis

[0115] Antibodies of the present disclosure may be prepared using recombinant DNA technology and related processes. Constructs (*e.g.*, DNA expression plasmids) encoding antibodies may be prepared and used to synthesize full antibodies or portions thereof. In some embodiments, DNA

sequences encoding antibody variable domains of the present disclosure may be inserted into expression vectors (*e.g.*, mammalian expression vectors) encoding other antibody domains and used to prepare antibodies with the inserted variable domains. DNA sequences encoding antibody variable domains may be inserted downstream of upstream expression vector regions with promoter/enhancer elements and/or encoding immunoglobulin signal sequences. DNA sequences encoding antibody variable domains may be inserted upstream of downstream expression vector regions encoding immunoglobulin constant domains. Encoded constant domains may be from any class (*e.g.*, IgG, IgA, IgD, IgE, and IgM) or species (*e.g.*, human, mouse, rabbit, rat, and non-human primate). In some embodiments, encoded constant domains encode human IgG (*e.g.*, IgG1, IgG2, IgG3, or IgG4) constant domains. In some embodiments, encoded constant domains encode mouse IgG (*e.g.*, IgG1, IgG2a, IgG2b, IgG2c, or IgG3) constant domains.

[0116] Expression vectors encoding antibodies of the present disclosure may be used to transfect cells for antibody production. Such cells may be mammalian cells. Cell lines with stable transfection of antibody expression vectors may be prepared and used to establish stable cell lines. Cell lines producing antibodies may be expanded for expression of antibodies which may be isolated or purified from cell culture media.

Antibody characterization

[0117] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on different characteristics. Such characteristics may include, but are not limited to, physical and functional characteristics. Physical characteristics may include features of antibody structures [*e.g.*, amino acid sequence or residues; secondary, tertiary, or quaternary protein structure; post-translational modifications (*e.g.*, glycosylations); chemical bonds, and stability]. Functional characteristics may include, but are not limited to, antibody affinity (*i.e.*, for specific epitopes and/or antigens) and antibody activity (*e.g.*, antibody ability to activate or inhibit a target, process, or pathway).

Antibody binding and affinity

[0118] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on binding and/or level of affinity for specific epitopes and/or antigens. Antibody binding and/or affinity level may be assessed with different antigen formats. In some embodiments, antibody affinity for different antigen formats may be tested *in vitro* (*e.g.*, by ELISA). Anti-tau antibody *in vitro* testing may be carried out using brain samples or fractions. Such samples or fractions may be obtained from subjects with AD (*e.g.*, human AD patients). In some embodiments, brain samples or fractions may be obtained from non-human subjects. Such non-human subjects may include non-human animals used in AD disease model studies (*e.g.*, mice, rats, and primates). In some embodiments, brain samples or fractions used for antibody affinity testing may be derived from TG4510/P301S mouse strains. Antibody affinity may be compared against control samples lacking

the particular antigen for which affinity is being analyzed. In some embodiments, control samples used for anti-tau antibody testing may include brain samples or fractions from non-diseased human subjects. In some embodiments, brain samples or fractions from wild type and/or Tau knockout mouse strains may be used as control samples.

[0119] *In vitro* affinity testing may be carried out (*e.g.*, by ELISA) using recombinant or isolated protein antigens. For example, recombinant or isolated ePHF may be used for anti-tau antibody affinity testing. In some embodiments, anti-tau antibodies of the present disclosure may exhibit a half maximal effective concentration (EC50) of from about 0.01 nM to about 100 nM for binding to ePHF when assessed by ELISA. In some embodiments, the exhibited EC50 may be less than about 50 nM, less than about 20 nM, less than about 10 nM, or less than about 1 nM. In some embodiments, anti-tau antibodies of the present disclosure may exhibit an EC50 of from about 0.01 nM to about 100 nM for binding to any of the antigens listed in Table 8, or an epitope that includes or is included within any of the antigens (including, but not limited to conformational epitopes), when assessed by ELISA. In some embodiments, the exhibited EC50 may be less than about 50 nM, less than about 20 nM, less than about 10 nM, or less than about 1 nM.

[0120] In some embodiments, anti-tau antibodies of the present disclosure bind to pathological tau, but do not bind to non-pathological tau. Such antibodies may be referred to herein as being “selective” for pathological forms of tau. In some embodiments, anti-tau antibodies of the present disclosure bind to tau tangles.

[0121] In some embodiments, antibody affinity analysis may be used to identify, select, or exclude polyspecific antibodies. As used herein, the term “polyspecific antibody” refers to an antibody with affinity for more than one epitope or antigen. In some embodiments, polyspecific antibodies may be identified, selected, or excluded based on relative affinity for each epitope or antigen recognized. For example, a polyspecific antibody may be selected for use or further development based on higher affinity for one epitope or antigen over a second epitope or antigen for which the polyspecific antibody demonstrates affinity.

[0122] In some embodiments, anti-tau antibodies may be tested for competition with other anti-tau antibodies. Such testing may be carried out to provide information on the specific epitope recognized by an antibody and may yield information related to level of epitope affinity in comparison to the competing antibody. In some embodiments, anti-tau antibodies used in antibody binding and/or affinity analysis may include anti-tau antibody PT3, as described in United States Patent Number 9,371,376; anti-tau antibody C10.2, as described in United States Patent Number 10,196,439 (referred to as antibody “C10-2,” therein); anti-tau antibody IPN002, as described in US Patent Number 10,040,847; anti-tau antibody AT8 (ThermoFisher, Waltham, MA); anti-tau antibody AT100 (ThermoFisher, Waltham, MA); anti-tau antibody AT120 as described in United States Patent

Number 5,843,779; or anti-tau antibody PT76, as described in Vandermeeren, M. *et al.*, J Alzheimers Dis. 2018;65(1):265-281.

Antibody activity

[0123] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on their ability to promote or reduce a certain activity. Antibody activity may be assessed using analytical assays. Such assays may be selected or designed to detect, screen, measure, and/or rank antibodies based on such antibody activity.

[0124] Anti-tau antibodies may be characterized by ability to inhibit tau aggregation. Inhibition may be based on physical disruption of tau aggregation or may be based on anti-tau antibody-dependent depletion (immunodepletion) of tau protein. Characterization based on tau aggregation inhibition may be assessed using one or more assays of tau aggregation. In some embodiments, anti-tau antibodies may be characterized by tau seeding assay. Tau seeding assays typically involve *in vitro* initiation of tau aggregation and assessment of aggregation inhibition by candidate compounds being tested. Tau seeding assays may be carried out using tau aggregation biosensor cells. Tau aggregation biosensor cells yield a detectable signal (*e.g.*, a fluorescent signal) in response to tau aggregation. Tau aggregation biosensor cells may be cultured with recombinant or isolated tau or with samples from high tau brain tissues or fluids (to promote tau aggregation) and treated with or without candidate compounds to assess tau aggregation inhibition. In some embodiments, anti-tau antibodies may be used to deplete tau from media prior to incubation with biosensor cells. Aggregation levels with depleted media may be compared to aggregation levels with non-depleted media to assess anti-tau antibody inhibitory function. Tau aggregation biosensor cells may include, but are not limited to, tau RD Biosensor cells. In some embodiments, neurons expressing human tau may be used.

[0125] In some embodiments, anti-tau antibodies of the present disclosure may inhibit tau aggregation with a half maximal inhibitory concentration (IC₅₀) of from about 1 nM to about 30 nM as determined by immunodepletion assay (*e.g.*, using tau RD Biosensor cells).

Antibody structure and variations

[0126] Antibodies of the present disclosure may exist as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, a plurality of nucleic acids, fragments of nucleic acids or variants of any of the aforementioned.

[0127] As used herein, “polypeptide” means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. Polypeptides smaller than about 50 amino acids may be referred to using the term “peptide.” Peptides may be at least about 2, 3, 4, or at least 5 amino acid residues long. Polypeptides of the present disclosure may include gene products,

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

[0128] The term “polypeptide variant” refers to molecules which differ in their amino acid sequence from a native or reference sequence. Amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[0129] In some embodiments “variant mimics” are provided. As used herein, the term “variant mimic” is one which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphorylated threonine and/or phosphorylated serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, *e.g.*, phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

[0130] The term “amino acid sequence variant” refers to molecules with some differences in their amino acid sequences as compared to a native or starting sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence. “Native” or “starting” sequence should not be confused with a wild type sequence. As used herein, a native or starting sequence is a relative term referring to an original molecule against which a comparison may be made. “Native” or “starting” sequences or molecules may represent the wild-type (that sequence found in nature) but do not have to be the wild-type sequence.

[0131] Ordinarily, variants will possess at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5% at least 99.8%, or at least 99.9% sequence identity as compared to a native sequence.

[0132] By “homologs” as it applies to amino acid sequences is meant the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[0133] “Analog” is meant to include polypeptide variants which differ by one or more amino acid alterations, *e.g.*, substitutions, additions or deletions of amino acid residues that still maintain the properties of the parent polypeptide.

[0134] The present disclosure contemplates variants and derivatives of antibodies presented herein. These include substitutional, insertional, deletion and covalent variants and derivatives. For example, sequence tags or amino acids, such as one or more lysines, may be added to antibody

peptide sequences (*e.g.*, at the N-terminal or C-terminal ends). Sequence tags may be used for peptide purification or localization. Lysines may be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or polypeptide may optionally be deleted providing for truncated sequences. Certain amino acids (*e.g.*, C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[0135] “Substitutional variants” when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[0136] As used herein the term “conservative amino acid substitution” refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[0137] “Insertional variants” when referring to polypeptides are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. “Immediately adjacent” to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[0138] “Deletional variants” when referring to polypeptides, are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[0139] As used herein, the term “derivative” is used synonymously with the term “variant” and refers to a molecule that has been modified or changed in any way relative to a reference molecule or starting molecule. In some embodiments, derivatives include native or starting polypeptides that have been modified with an organic proteinaceous or non-proteinaceous derivatizing agent, and post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted

amino acid residues of a polypeptide with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of antibodies for immunoaffinity purification.

[0140] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in polypeptides used in accordance with the present disclosure.

[0141] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[0142] Covalent derivatives specifically include fusion molecules in which polypeptides are covalently bonded to non-proteinaceous polymers. Non-proteinaceous polymers may include hydrophilic synthetic polymers, *i.e.*, polymers not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or *in vitro* methods are useful, as are polymers which are isolated from nature. Hydrophilic polyvinyl polymers may include polyvinylalcohol and/or polyvinylpyrrolidone. Particularly useful are polyvinylalkylene ethers such as polyethylene glycol and polypropylene glycol. Polypeptides may be linked to various non-proteinaceous polymers, such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337, the contents of each of which are herein incorporated by reference in their entirety.

[0143] As used herein when referring to polypeptides the term “loop” refers to a structural feature of a peptide or polypeptide which reverses the direction of the backbone of a peptide or polypeptide and includes four or more amino acid residues. Oliva *et al.* have identified at least 5 classes of polypeptide loops (J. Mol Biol 266 (4): 814-830; 1997, the contents of which are herein incorporated by reference in their entirety).

[0144] As used herein when referring to polypeptides the term “half-loop” refers to a portion of an identified loop having at least half the number of amino acid residues as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to include an odd number of amino acids, a half-loop of the odd-numbered loop will include the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a

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

[0145] As used herein when referring to polypeptides the term “domain” refers to a motif of a polypeptide having one or more identifiable structural and/or functional characteristics or properties (e.g., binding capacity), e.g., serving as a site for protein-protein interactions.

[0146] As used herein when referring to polypeptides, the term “site” is synonymous with “amino acid residue” and “amino acid side chain.” A site represents a position on a polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide.

[0147] As used herein the terms “termini or terminus” when referring to polypeptides refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. Polypeptide based molecules of the present disclosure may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group) and a C-terminus (terminated by an amino acid with a free carboxyl group). Proteins of the present disclosure are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

Antibody modification

[0148] Antibodies may be modified to obtain variants with one or more altered properties. Such properties may include or relate to antibody structure, function, affinity, specificity, protein folding, stability, manufacturing, expression, and/or immunogenicity (i.e., immune reactions in subjects being treated with such antibodies). In some embodiments, antibody fragments or variants may be used to modify another antibody or may be incorporated into a synthetic antibody.

[0149] Antibody modification may include amino acid sequence modifications. Such modifications may include, but are not limited to, amino acid deletions, additions, and/or substitutions. Modifications may be informed by amino acid sequence analysis. Such analysis may include alignment of amino acid sequences between different antibodies or antibody variants. Two or more antibodies may be compared to identify residues or regions suitable for modification. Compared antibodies may include those binding to the same epitope. Compared antibodies may bind to different epitopes (separate or overlapping) of the same protein or target (e.g., to identify residues or regions conferring specificity to specific epitopes). Comparisons may include light and/or heavy chain sequence variation analysis, CDR sequence variation analysis, germline sequence analysis, and/or framework sequence analysis. Information obtained from such analysis may be used to identify amino acid residues, segments of amino acids, amino acid side chains, CDR lengths, and/or other features or properties that are conserved or variable among antibodies binding to the same or different epitopes.

[0150] In some embodiments, modified versions of anti-tau antibodies described above may be prepared by adding, deleting, or substituting one or more CDR amino acid residues.

[0151] In some embodiments, anti-tau antibodies may be modified by amino acid sequence alignment of antibodies binding to similar targets and preparing modified antibodies with one or more amino acid deletions, substitutions, or insertions based on analysis of the aligned sequences.

[0152] The present disclosure includes amino acid consensus sequences for CDR region sequences, showing specific amino acids (shown in square brackets) that may be modified or amino acid residue positions that may be more generally deleted or substituted (shown using variable “X”) in antibody amino acid sequences, *e.g.* as described in Table 1A or Z.

[0153] Related CDR sequences that can appear in the same VH and/or VL sequences of an antibody are grouped together in the same row. For example, an antibody of the invention may comprise one each of CDRH1-CDRH3 and CDRL1-CDRL3, wherein said CDRH1-CDRH3 and CDRL1-CDRL3 are represented by SEQ ID NOs: 928, 930, 409, 472, 525, and 570, respectively.

[0154] In addition, in Table 5, for example, each odd numbered rows below the table heading, and the even numbered rows immediately therebelow, are related (if not identical) consensus sequences (*e.g.*, SEQ ID NOs: 927 and 928 are related, SEQ ID NOs: 933 and 934 are related). It is contemplated that an antibody of the invention may comprise one each of CDRH1-CDRH3 and CDRL1-CDRL3, wherein each of said CDRH1-CDRH3 and CDRL1-CDRL3 can be independently represented by one of the two related consensus sequences. For example, an antibody of the invention may comprise one each of CDRH1-CDRH3 and CDRL1-CDRL3, wherein said CDRH1-CDRH3 and CDRL1-CDRL3 are represented by SEQ ID NOs: 931, 341, 410, 934, 935, and 571, respectively.

[0155] Furthermore, amino acid at each X position or Xi position (where $i = 1, 2, 3, \dots$) may be any naturally occurring amino acids, or may be a selected subset of amino acids as specified in each consensus sequence X / Xi position. It is contemplated that any one or more of the enumerated specific amino acids at each X or Xi positions can be eliminated as a permissible value for the X or Xi position. For example, in SEQ ID NO: 947, X4 may be any residues, such as T, S, A, V, I, or L. In some embodiments, X4 is T, L, or V; or S, A, or V, *etc.*

Table 5 CDR Consensus Sequences

CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
GYTFTS [Y/N] (SEQ ID NO: 927)	NPNNS [D/E] (SEQ ID NO: 929)	ANYYGGSQFAY (SEQ ID NO: 409)	RSSQSLVHSNGKTYLH (SEQ ID NO: 472)	KVSNRFS (SEQ ID NO: 525)	SQSTHVPFT (SEQ ID NO: 570)
GYTFTSX (SEQ ID NO: 928), X = any; <i>e.g.</i> , Y, F, N, Q	NPNNSX (SEQ ID NO: 930) X = any, <i>e.g.</i> , negatively charged	ANYYGGSQFAY (SEQ ID NO: 409)	RSSQSLVHSNGKTYLH (SEQ ID NO: 472)	KVSNRFS (SEQ ID NO: 525)	SQSTHVPFT (SEQ ID NO: 570)
G [F/Y] TFT [R/I] [Y/F] (SEQ ID NO: 931)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)	RSSQSLVH [N/S] NG [I/N] T [H/Y] LY (SEQ ID NO: 933)	RVS [N/S] RFS (SEQ ID NO: 935)	FQGTHVPRT (SEQ ID NO: 571)
G-X1-TFT-X2-X3 (SEQ ID NO: 932), X1 = any; <i>e.g.</i> , F, Y X2 = any; <i>e.g.</i> , R, K, H, A, V, I, L X3 = any; <i>e.g.</i> , Y, F	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)	RSSQSLVH-X1-NG-X2-T-X3-LY (SEQ ID NO: 934), X1 = any; <i>e.g.</i> , N, Q, S, T X2 = any; <i>e.g.</i> , A, V, I, L, N, Q X3 = any; <i>e.g.</i> , H, R, K, Y, F	RVSXRFS (SEQ ID NO: 936), X = any; <i>e.g.</i> , N, Q, S, T	FQGTHVPRT (SEQ ID NO: 571)
G [F/Y] TFT [R/I/D] [Y/F] (SEQ ID NO: 937)	NPNNG [G/E] (SEQ ID NO: 939)	G [T/R] G [T/M] G [-/Y] [-/Y] A [M/L] DY (SEQ ID NO: 941)	[R/G] [S/A] S [Q/E] [S/N] [L/V] [V/Y] [H/G] [S/A/N] [N/T/L] [G/N] [I/N/absent] [T/absent]	[R/G] [V/A] [S/T] [N/T/S] [R/L] [F/A] [S/D]	[F/Q] [G/N] [G/V] [T/L] [H/T] [V/I] P [R/W] T (SEQ ID NO: 947)

			[H/Y/absent] [L/absent] [Y/absent]		
G-X1-TFT-X2-X3 (SEQ ID NO: 938), X1 = any; <i>e.g.</i> , F, Y X2 = any; <i>e.g.</i> , R, K, H, G, A, V, I, L, D, E X3 = any; <i>e.g.</i> , Y, F	NPNNGX (SEQ ID NO: 940) X = any; <i>e.g.</i> , G, A, V, I, L, E, D	G-X1-G-X2-G-X3- X4-A-X5-DY (SEQ ID NO: 942), X1 = any; <i>e.g.</i> , T, S, R, K, H X2 = any; <i>e.g.</i> , T, S, M, A, V, I, L X3 = any or absent; <i>e.g.</i> , Y, F, - X4 = any or absent; <i>e.g.</i> , Y, F, - X5 = any; <i>e.g.</i> , M, A, I, L, V	X1-X2-S-X3-X4-X5-X6- X7-X8-X9-X10-X11- X12-X13-X14-X15, X1 = any; <i>e.g.</i> , R, K, H, G, A, V, I, L X2 = any; <i>e.g.</i> , S, T, A, V, I, L X3 = any; <i>e.g.</i> , Q, N, E, D X4 = any; <i>e.g.</i> , S, T, N, Q X5 = any; <i>e.g.</i> , A, V, I, L X6 = any; <i>e.g.</i> , A, V, I, L, Y, F X7 = any; <i>e.g.</i> , H, R, K, G, A X8 = any; <i>e.g.</i> , S, T, A, V, I, L, N, Q X9 = any; <i>e.g.</i> , N, Q, T, S, A, V, I, L, M X10 = any; <i>e.g.</i> , G, A, N, Q	X1-X2-X3-X4-X5- X6-X7, X1 = any; <i>e.g.</i> , R, K, H, G, A X2 = any; <i>e.g.</i> , A, V, I, L X3 = any; <i>e.g.</i> , S, T X4 = any; <i>e.g.</i> , N, Q, T, S X5 = any; <i>e.g.</i> , R, K, H, A, V, I, L X6 = any; <i>e.g.</i> , F, Y, A, V, I, L, G X7 = any; <i>e.g.</i> , S, T, D, E	X1-X2-X3-X4-X5-X6- P-X7-T (SEQ ID NO: 948), X1 = any; <i>e.g.</i> , F, Y, Q, N X2 = any; <i>e.g.</i> , G, A, N, Q X3 = any; <i>e.g.</i> , G, A, V, I, L X4 = any; <i>e.g.</i> , T, S, A, V, I, L X5 = any; <i>e.g.</i> , H, K, R, T, S X6 = any; <i>e.g.</i> , A, V, I, L X7 = any; <i>e.g.</i> , R, K, H, W, F, Y

			X11 = any or absent; <i>e.g.</i> , A, V, I, L, N, Q, - X12 = any or absent; <i>e.g.</i> , T, S, - X13 = any or absent; <i>e.g.</i> , R, K, H, Y, F, - X14 = any or absent; <i>e.g.</i> , A, V, I, L, - X15 = any or absent; <i>e.g.</i> , Y, F, -		
GY [S/T] FT [D/E] Y (SEQ ID NO: 949)	[F/Y] PG [S/R] [D/G] [S/N]	P [T/A] [V/I/Y] [V/Y] [A/S] [R/K] DYAM [D/E] Y (SEQ ID NO: 953)	RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955)	KVSNRFS (SEQ ID NO: 525)	FQGSHVP [Y/F] T (SEQ ID NO: 957)
GY-X1-FT-X2-Y (SEQ ID NO: 950), X1 = any; <i>e.g.</i> , S, T X2 = any; <i>e.g.</i> , D, E, S, T	X1-PG-X2-X3-X4, X1 = any; <i>e.g.</i> , F, Y X2 = any; <i>e.g.</i> , S, T, R, K, H X3 = any; <i>e.g.</i> , D, E, G, A X4 = any; <i>e.g.</i> , S, T, N, Q	P-X1-X2-X3-X4-X5- DYAM-X6-Y (SEQ ID NO: 954), X1 = any; <i>e.g.</i> , T, S, A, V, I, L X2 = any; <i>e.g.</i> , A, V, I, L, Y, F X3 = any; <i>e.g.</i> , A, V, I, L, Y, F	RSSQSIV-X1-X2- NGNTYLE (SEQ ID NO: 956), X1 = any; <i>e.g.</i> , Y, F, H, R, K X2 = any; <i>e.g.</i> , S, T, R, K, H	KVSNRFS (SEQ ID NO: 525)	FQGSHVPXT (SEQ ID NO: 958), X = any; <i>e.g.</i> , Y, F

		X4 = any; <i>e.g.</i> , A, V, I, L, S, T X5 = any; <i>e.g.</i> , R, K, H X6 = any; <i>e.g.</i> , D, E			
GY [S/T] FT [D/E/S] Y (SEQ ID NO: 959)	[F/Y] P [G/S] [S/R/N] [D/G] [S/G/N]	[P/S] [T/A/S] [V/I/Y] [V/Y] [A/S/G] [R/K] DYAM [D/E] Y (SEQ ID NO: 962)	RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955)	KVSNRFS (SEQ ID NO: 525)	FQGSHVP [Y/F] T (SEQ ID NO: 957)
GY-X1-FT-X2-Y (SEQ ID NO: 950), X1 = any; <i>e.g.</i> , S, T X = any; <i>e.g.</i> , D, E, S, T	X1-P-X2-X3-X4-X5, X1 = any; <i>e.g.</i> , F, Y X2 = any; <i>e.g.</i> , S, T, G, A, V, I, L X3 = any; <i>e.g.</i> , S, T, R, K, H, N, Q X4 = any; <i>e.g.</i> , D, E, G, A X5 = any; <i>e.g.</i> , S, T, G, A, N, Q	X1-X2-X3-X4-X5- X6-DYAM-X7-Y (SEQ ID NO: 963), X1 = any; <i>e.g.</i> , P, S, T, A, V, I, L X2 = any; <i>e.g.</i> , T, S, A, V, I, L X3 = any; <i>e.g.</i> , A, V, I, L, Y, F X4 = any; <i>e.g.</i> , A, V, I, L, Y, F X5 = any; <i>e.g.</i> , A, V, I, L, S, T, G	RSSQSIV-X1-X2- NGNTYLE (SEQ ID NO: 956), X1 = any; <i>e.g.</i> , Y, F, H, R, K X2 = any; <i>e.g.</i> , S, T, R, K, H	KVSNRFS (SEQ ID NO: 525)	FQGSHVPXT (SEQ ID NO: 958), X = any; <i>e.g.</i> , F, Y

		X6 = any; <i>e.g.</i> , R, K, H X7 = any; <i>e.g.</i> , E, D			
GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964)	YWDDD (SEQ ID NO: 362)	R [R/V/K] R [G/Y/S] Y [G/A] MDY (SEQ ID NO: 966)	K [A/S] SQS [V/L] [S/L] [N/S] [-/S] [-/G] [-/N] [-/Q] [-/K] [-/N] [D/Y] [V/L] A (SEQ ID NO: 968)	[Y/G] [A/T] S [N/T] R [C/E] [T/S]	Q [Q/N] D [Y/H] [R/S] [S/H] P [L/Y] T (SEQ ID NO: 972)
GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), X1 = any; <i>e.g.</i> , S, T, N, Q X2 = any; <i>e.g.</i> , S, T, F, Y X3 = any; <i>e.g.</i> , A, V, I, L, G	YWDDD (SEQ ID NO: 362)	R-X1-R-X2-Y-X3-MDY (SEQ ID NO: 967), X1 = any; <i>e.g.</i> , R, K, H, A, V, I, L X2 = any; <i>e.g.</i> , A, V, I, L, G, S, T, Y, F X3 = any; <i>e.g.</i> , A, V, I, L, G	K-X1-SQS-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-A (SEQ ID NO: 969), X1 = any; <i>e.g.</i> , A, V, I, L, S, T X2 = any; <i>e.g.</i> , A, V, I, L X3 = any; <i>e.g.</i> , S, T, A, V, I, L X4 = any; <i>e.g.</i> , S, T, N, Q X5 = any or absent; <i>e.g.</i> , S, T, - X6 = any or absent; <i>e.g.</i> , G, A, V, I, L, -	X1-X2-S-X3-R-X4-X5, X1 = any; <i>e.g.</i> , Y, F, G, A, V, I, L X2 = any; <i>e.g.</i> , A, V, I, L, T, S X3 = any; <i>e.g.</i> , N, Q, T, S X4 = any; <i>e.g.</i> , C, E, D, S X5 = any; <i>e.g.</i> , T, S	Q-X1-D-X3-X4-X5-P-X6-T (SEQ ID NO: 973), X1 = any; <i>e.g.</i> , Q, N X2 = any; <i>e.g.</i> , Y, F, H, K, R X3 = any; <i>e.g.</i> , R, K, H, S, T X4 = any; <i>e.g.</i> , S, T, H, K, R X5 = any; <i>e.g.</i> , A, V, I, L, Y, F

			X7 = any or absent; <i>e.g.</i> , N, Q, - X8 = any or absent; <i>e.g.</i> , N, Q, - X9 = any or absent; <i>e.g.</i> , K, R, H, - X10 = any or absent; <i>e.g.</i> , N, Q, - X11 = any; <i>e.g.</i> , D, E, Y, F X12 = any; <i>e.g.</i> , A, V, I, L		
GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964)	YWDDD (SEQ ID NO: 362)	R [R/V/K/S/G] [Y/R] [Y/-] [S/-] [-/N] [G/S/Y/R] [Y/N/G] [G/A/Y/N] [M/F/Y] DY	[K/S] [S/A] S [Q/S] S [L/I/V] [L/S] [N/S/D] [D/S/T] [V/G/D/Y] [N/G/-] [Q/-] [K/-] [N/T/-] [Y/-] [L/-] [A/H/N]	[Y/G/L/R] [A/T/V] S [N/T/K] [R/L] [C/E/D/A] [T/S]	[W/Q] [Q/N] [G/D] [T/S/Y/H] [H/S/R] [F/I/S/H] P [Q/R/L/Y] [-/Y] T
GFSL-X1-T-X2- X3-M (SEQ ID NO: 965), X1 = any; <i>e.g.</i> , S, T, N, Q	YWDDD (SEQ ID NO: 362)	R-X1-X2-X3-X4- X5-X6-X7-X8-X9- DY, X1 = any; <i>e.g.</i> , R, K, H, A, V, I, L, S, T, G	X1-X2-S-X3-S-X4-X5- X6-X7-X8-X9-X10-X11- X12-X13-X14-X15, X1 = any; <i>e.g.</i> , K, R, H, S, T	X1-X2-S-X3-X4-X5- X6, X1 = any; <i>e.g.</i> , Y, F, G, A, V, I, L, R, K, H	X1-X2-X3-X4-X5-X6- P-X7-X8-T, X1 = any; <i>e.g.</i> , Q, N, W, F, Y X2 = any; <i>e.g.</i> , Q, N

X2 = any; <i>e.g.</i> , S, T, F, Y X3 = any; <i>e.g.</i> , A, V, I, L, G		X2 = any; <i>e.g.</i> , Y, F, R, K, H X3 = any or absent; <i>e.g.</i> , Y, F, - X4 = any or absent; <i>e.g.</i> , S, T, - X5 = any or absent; <i>e.g.</i> , N, Q, - X6 = any; <i>e.g.</i> , G, A, V, I, L, S, T, Y, F, R, K, H X7 = any; <i>e.g.</i> , Y, F, N, Q, G, A, V, I, L X8 = any; <i>e.g.</i> , G, A, V, I, L, N, Q, Y, F X9 = any; <i>e.g.</i> , M, Y, F	X2 = any; <i>e.g.</i> , S, T, A, V, I, L X3 = any; <i>e.g.</i> , Q, N, S, T X4 = any; <i>e.g.</i> , A, V, I, L X5 = any; <i>e.g.</i> , A, V, I, L, S, T X6 = any; <i>e.g.</i> , N, Q, S, T, D, E X7 = any; <i>e.g.</i> , D, E, S, T X8 = any; <i>e.g.</i> , A, V, I, L, G, D, E, Y, F X9 = any or absent; <i>e.g.</i> , N, Q, G, A, - X10 = any or absent; <i>e.g.</i> , Q, N, - X11 = any or absent; <i>e.g.</i> , K, R, H, - X12 = any or absent; <i>e.g.</i> , N, Q, T, S, - X13 = any or absent; <i>e.g.</i> , Y, F, - X14 = any or absent; <i>e.g.</i> , A, V, I, L, -	X2 = any; <i>e.g.</i> , A, V, I, L, S, T X3 = any; <i>e.g.</i> , N, Q, T, S, K, R, H X4 = any; <i>e.g.</i> , R, K, H, A, V, I, L X5 = any; <i>e.g.</i> , C, S, E, D, A, V, I, L X6 = any; <i>e.g.</i> , T, S	X3 = any; <i>e.g.</i> , D, E, G, A, V, I, L X4 = any; <i>e.g.</i> , T, S, Y, F, H, K, R X5 = any; <i>e.g.</i> , H, R, K, S, T X6 = any; <i>e.g.</i> , F, Y, A, V, I, L, S, T, H, K, R X7 = any; <i>e.g.</i> , Q, N, R, K, H, L, V, A, I, Y, F X8 = any or absent; <i>e.g.</i> , Y, F, -
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			X15 = any; <i>e.g.</i> , A, V, I, L, H, R, K, N, Q		
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* In the table above, “-” in the bracket means the residue can be absent.

Table 1: Consensus CDRs for exemplary anti-tau antibodies V0022, V0023 and V0024

SEQ ID NO	Description	Sequence
SEQ ID NO: 1180 (Chothia)	HCDR1	GX ₁ TFTX ₂ X ₃ , wherein X ₁ is F or Y; X ₂ is R or I; and X ₃ is Y or F
SEQ ID NO: 341 (Chothia)	HCDR2	NPNNGG
SEQ ID NO: 410 (Chothia)	HCDR3	GTGTGAMDY
SEQ ID NO: 1181 (Chothia)	LCDR1	RSSQSLVHX ₁ NGX ₂ TX ₃ LY, wherein X ₁ is N or S; X ₂ is I or N; and X ₃ is Y or H
SEQ ID NO: 1182 (Chothia)	LCDR2	RVSX ₁ RFS, wherein X ₁ is N or S
SEQ ID NO: 571 (Chothia)	LCDR3	FQGTHVPRT
(Kabat)	HCDR1	X ₁ X ₂ WMH, wherein X ₁ is R or I; and X ₂ is Y or F
SEQ ID NO: 1184 (Kabat)	HCDR2	X ₁ INPNNGGX ₂ DX ₃ NEX ₄ FKX ₅ , wherein X ₁ is N or K; X ₂ is T or G; X ₃ is F, Y, or N; X ₄ is K or R; and X ₅ is N or S;
SEQ ID NO: 410 (Kabat)	HCDR3	GTGTGAMDY
SEQ ID NO: 1185 (Kabat)	LCDR1	RSSQSLVHX ₁ NGX ₂ TX ₃ LY, wherein X ₁ is N or S; X ₂ is I or N; and X ₃ is Y or H
SEQ ID NO: 1182 (Kabat)	LCDR2	RVSX ₁ RFS, wherein X ₁ is N or S

SEQ ID NO: 571 (Kabat)	LCDR3	FQGTHVPRT
SEQ ID NO: 1186 (IMGT)	HCDR1	GX ₁ TFTX ₂ X ₃ W, wherein X ₁ is F or Y; X ₂ is R or I; and X ₃ is Y or F
SEQ ID NO: 1187 (IMGT)	HCDR2	INPNNGG X ₁ , wherein X ₁ is T or G
SEQ ID NO: 1167 (IMGT)	HCDR3	ARGTGTGAMDY
SEQ ID NO: 1188 (IMGT)	LCDR1	QSLVHX ₁ NGX ₂ TX ₃ , wherein X ₁ is N or S; X ₂ is I or N; and X ₃ is Y or H
(IMGT)	LCDR2	RVS
SEQ ID NO: 571 (IMGT)	LCDR3	FQGTHVPRT

[0156] In some embodiments, anti-tau antibodies of the present disclosure may include a CDRH1 that includes the amino acid sequence GYTFTS [Y/N] (SEQ ID NO: 927), or a CDRH1 that includes the amino acid sequence GYTFTSX (SEQ ID NO: 928), wherein X may be any amino acid, *e.g.*, X is Y/F/N/Q; a CDRH2 that includes the amino acid sequence NPNNS [D/E] (SEQ ID NO: 929), or a CDRH2 that includes the amino acid sequence NPNNSX (SEQ ID NO: 930), wherein X may be any amino acid, *e.g.*, an amino acid with a negatively charged side chain; and a CDRH3 that includes the amino acid sequence ANYYGGSQFAY (SEQ ID NO: 409); a CDRL1 that includes the amino acid sequence RSSQSLVHSNGKTYLH (SEQ ID NO: 472); a CDRL2 that includes the amino acid sequence KVSNRFS (SEQ ID NO: 525); and/or a CDRL3 that includes the amino acid sequence SQSTHVPFT (SEQ ID NO: 570).

[0157] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence G [F/Y] TFT [R/I] [Y/F] (SEQ ID NO: 931), or a CDRH1 that includes the amino acid sequence G-X₁-TFT-X₂-X₃ (SEQ ID NO: 932), wherein each of X₁, X₂, and X₃ may be any amino acid, *e.g.*, X₁ and/or X₃ may be an amino acid with a hydrophobic and/or aromatic side chain, such as F or Y, and/or X₂ may be a positively charged residue (such as R, K, H) or a residue with aliphatic side chain (such as A, V, I, or L); a CDRH2 that includes the amino acid sequence NPNNGG (SEQ ID NO: 341); a CDRH3 that includes the amino acid sequence GTGTGAMDY (SEQ ID NO: 410); a CDRL1 that includes the amino acid sequence RSSQSLVH [N/S] NG [I/N] T [H/Y] LY (SEQ ID

NO: 933), or a CDRL1 that includes the amino acid sequence RSSQSLVH-X1-NG-X2-T-X3-LY (SEQ ID NO: 934), where X1, X2, and X3 may be any amino acid, *e.g.*, X1 is Q/N/S/T and/or X2 is A/V/I/L/Q/N and/or X3 is H/R/K/Y/F; a CDRL2 that includes the amino acid sequence RVS [N/S] RFS (SEQ ID NO: 935), or a CDRL2 that includes the amino acid sequence RVSEXRF (SEQ ID NO: 936), where X may be any amino acid, *e.g.*, X is Q/N/S/T; and/or a CDRL3 that includes the amino acid sequence FQGTHVPRT (SEQ ID NO: 571).

[0158] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence G [F/Y] TFT [R/I/D] [Y/F] (SEQ ID NO: 937), or a CDRH1 that includes the amino acid sequence G-X1-TFT-X2-X3 (SEQ ID NO: 938), where X1, X2 and X3 may be any amino acid, *e.g.*, X1 and X3 are each independently F/Y and/or X2 is any residue (such as R/K/H/D/E/G/A/I/L/V); a CDRH2 that includes the amino acid sequence NPNNG [G/E] (SEQ ID NO: 939), or a CDRH2 that includes the amino acid sequence NPNNGX (SEQ ID NO: 940), where X may be any amino acid, *e.g.*, E/D/G/A/V/I/L; a CDRH3 that includes the amino acid sequence of G [T/R] G [T/M] G [absent/Y] [absent/Y] A [M/L] DY (SEQ ID NO: 941), or a CDRH3 that includes the amino acid sequence G-X1-G-X2-G-X3-X4-A-X5-DY (SEQ ID NO: 942), where each of X1-X5 may be any amino acid and/or where X3 and/or X4 may be absent, *e.g.*, X1 is S/T/R/K/H and/or X2 is S/T/V/L/A/I/M and/or X3 and X4 are each independently Y/F/absent and/or X5 is A/V/I/L/M; a CDRL1 that includes the amino acid sequence [R/G] [S/A] S [Q/E] [S/N] [L/V] [V/Y] [H/G] [S/A/N] [N/T/L] [G/N] [I/N/absent] [T/absent] [H/Y/absent] [L/absent] [Y/absent], or a CDRL1 that includes the amino acid sequence X1-X2-S-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15, where X1-X15 may be any amino acid and/or where X11, X12, X13, X14, and/or X15 may be absent, *e.g.*, X1 is R/K/H/G/A/V/I/L and/or X2 is S/T/A/V/I/L and/or X3 is Q/N/E/D and/or X4 is S/T/N/Q and/or X5 is L/V/A/I and/or X6 is A/V/I/L/Y/F and/or X7 is H/R/K/G/A and/or X8 is S/T/A/V/I/L/N/Q and/or X9 is N/Q/A/I/L/V/M/S/T and/or X10 is G/A/N/Q and/or X11 is Q/N/A/V/I/L/absent and/or X12 is T/S/absent and/or X13 is H/R/K/Y/F/absent and/or X14 is A/V/I/L/absent and/or X15 is Y/F/absent; a CDRL2 consensus sequence with from about 3 to about 7 amino acids with an amino acid sequence of [R/G][V/A][S/T][N/T/S][R/L][F/A][S/D], or a CDRL2 that includes the amino acid sequence X1-X2-X3-X4-X5-X6-X7, where X1, X2, X3, X4, X5, X6, and X7 may be any amino acid, *e.g.*, X1 is R/K/H/G/A and/or X2 is V/A/I/L and/or X3 is S/T and/or X4 is N/Q/T/S and/or X5 is R/K/H/A/V/I/L and/or X6 is F/Y/A/V/I/L/G and/or X7 is S/T/D/E; and/or a CDRL3 that includes the amino acid sequence [F/Q] [G/N] [G/V] [T/L] [H/T] [V/I] P [R/W] T (SEQ ID NO: 947), or a CDRL3 that includes the amino acid sequence X1-X2-X3-X4-X5-X6-P-X7-T (SEQ ID NO: 948), where X1, X2, X3, X4, X5, X6, and X7 may be any amino acid, *e.g.*, X1 is F/Y/Q/N and/or X2 is G/A/Q/N and/or X3 is G/A/V/I/L and/or X4 is T/S/A/V/I/L and/or X5 is H/R/K/T/S and/or X6 is V/I/A/L and/or X7 is R/K/H/W/F/Y.

[0159] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence GY [S/T] FT [D/E] Y (SEQ ID NO: 949), or a CDRH1 that includes the amino acid sequence GY-X1-FT-X2-Y (SEQ ID NO: 950), where X1 and X2 may be any amino acid, *e.g.*, X1 is S/T and/or X2 is D/E/S/T; a CDRH2 that includes the amino acid sequence [F/Y]PG[S/R][D/G][S/N], or a CDRH2 that includes the amino acid sequence X1-PG-X2-X3-X4, where X1-X4 may be any amino acid, *e.g.*, X1 is F/Y and/or X2 is S/T/R/K/H and/or X3 is D/E/G/A and/or X4 is S/T/N/Q; a CDRH3 that includes the amino acid sequence P [T/A] [V/I/Y] [V/Y] [A/S] [R/K] DYAM [D/E] Y (SEQ ID NO: 953), or a CDRH3 that includes the amino acid sequence P-X1-X2-X3-X4-X5-DYAM-X6-Y (SEQ ID NO: 954), where X1-X6 may be any amino acid, *e.g.*, X1 is T/S/A/V/I/L and/or X2 is V/I/A/L/Y/F and/or X3 is V/I/A/L/Y/F and/or X4 is A/V/I/L/S/T and/or X5 is R/K/H and/or X6 is D/E; a CDRL1 that includes the amino acid sequence RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955), or a CDRL1 that includes the amino acid sequence RSSQSIV-X1-X2-NGNTYLE (SEQ ID NO: 956), where X1 and X2 may be any amino acid, *e.g.*, X1 is Y/F/H/R/K and/or X2 is S/T/R/K/H; a CDRL2 that includes the amino acid sequence KVSNRFS (SEQ ID NO: 525); and/or a CDRL3 that includes the amino acid sequence FQGSHVP[Y/F]T (SEQ ID NO: 957), or a CDRL3 that includes the amino acid sequence FQGSHVPXT (SEQ ID NO: 958), wherein X may be any amino acid, *e.g.*, X is Y/F.

[0160] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence GY [S/T] FT [D/E/S] Y (SEQ ID NO: 959), or a CDRH1 that includes the amino acid sequence GY-X1-FT-X2-Y (SEQ ID NO: 950), where X1 and X2 may be any amino acid, *e.g.*, X1 is S/T and/or X2 is E/D/S/T; a CDRH2 that includes the amino acid sequence [F/Y] P [G/S] [S/R/N] [D/G] [S/G/N], or a CDRH2 that includes the amino acid sequence X1-P-X2-X3-X4-X5, where X1-X5 may be any amino acid, *e.g.*, X1 is F/Y and/or X2 is S/T/G/A/V/I/L and/or X3 is S/T/R/K/H/N/Q and/or X4 is D/E/G/A and/or X5 is S/T/N/Q/G/A; a CDRH3 that includes the amino acid sequence [P/S] [T/A/S] [V/I/Y] [V/Y] [A/S/G] [R/K] DYAM [D/E] Y (SEQ ID NO: 962), or a CDRH3 that includes the amino acid sequence X1-X2-X3-X4-X5-X6-DYAM-X7-Y (SEQ ID NO: 963), where X1-X7 may be any amino acid, *e.g.*, X1 is S/T/P/A/I/L/V and/or X2 is T/S/A/V/I/L and/or X3 is A/V/I/L/Y/F and/or X4 is A/V/I/L/Y/F and/or X5 is A/V/I/L/G/S/T and/or X6 is R/K/H and/or X7 is E/D; a CDRL1 that includes the amino acid sequence RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955), or a CDRL1 that includes the amino acid sequence RSSQSIV-X1-X2-NGNTYLE (SEQ ID NO: 956), where X1 and X2 may be any amino acid, *e.g.*, X1 is Y/F/H/R/K and/or X2 is S/T/R/K/H; a CDRL2 that includes the amino acid sequence KVSNRFS (SEQ ID NO: 525); and/or a CDRL3 that includes the amino acid sequence FQGSHVP[Y/F]T (SEQ ID NO: 957), or a CDRL3 that includes the amino acid sequence FQGSHVPXT (SEQ ID NO: 958), wherein X may be any amino acid, *e.g.*, X is F/Y.

[0161] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964), or a CDRH1 that includes the amino acid sequence GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), where X1-X3 may be any amino acid, *e.g.*, X1 is S/T/N/Q and/or X2 is S/T/F/Y and/or X3 is A/V/I/L/G; a CDRH2 that includes the amino acid sequence YWDDD (SEQ ID NO: 362); a CDRH3 that includes the amino acid sequence R [R/V/K] R [G/Y/S] Y [G/A] MDY (SEQ ID NO: 966), or a CDRH3 that includes the amino acid sequence R-X1-R-X2-Y-X3-MDY (SEQ ID NO: 967), where X1-X3 may be any amino acid, *e.g.*, X1 is R/K/H/A/V/I/L and/or X2 is G/A/V/I/L/S/T/Y/F and/or X3 is A/V/I/L/G; a CDRL1 that includes the amino acid sequence K [A/S] SQS [V/L] [S/L] [N/S] [absent/S] [absent/G] [absent/N] [absent/Q] [absent/K] [absent/N] [D/Y] [V/L] A (SEQ ID NO: 968), or a CDRL1 that includes the amino acid sequence K-X1-SQS-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-A (SEQ ID NO: 969), where X1-X12 may be any amino acid and/or where one or more of X5-X10 may be absent, *e.g.*, X1 is S/T/A/V/I/L and/or X2 is A/V/I/L and/or X3 is S/T/A/V/I/L and/or X4 is N/Q/S/T and/or X5 is S/T/absent and/or X6 is G/A/V/I/L/absent and/or X7 is N/Q/absent and/or X8 is N/Q/absent and/or X9 is K/R/H/absent and/or X10 is N/Q/absent and/or X11 is E/D/Y/F and/or X12 is A/V/I/L; a CDRL2 that includes the amino acid sequence [Y/G] [A/T] S [N/T] R [C/E] [T/S], or a CDRL2 that includes the amino acid sequence X1-X2-S-X3-R-X4-X5, where X1-X5 may be any amino acid, *e.g.*, X1 is Y/F/G/A/V/I/L and/or X2 is A/V/I/L/T/S and/or X3 is N/Q/T/S and/or X4 is C/S/E/D and/or X5 is T/S; and/or a CDRL3 that includes the amino acid sequence Q [Q/N] D [Y/H] [R/S] [S/H] P [L/Y] T (SEQ ID NO: 972), or a CDRL3 that includes the amino acid sequence Q-X1-D-X3-X4-X5-P-X6-T (SEQ ID NO: 973), where X1-X6 may be any amino acid, *e.g.*, X1 is Q/N and/or X2 is Y/F/H/R/K and/or X3 is R/K/H/S/T and/or X4 is S/T/H/K/R and/or A/V/I/L/Y/F.

[0162] In some embodiments, anti-tau antibodies include a CDRH1 that includes the amino acid sequence GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964), or a CDRH1 that includes the amino acid sequence GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), where X1-X3 may be any amino acid, *e.g.*, X1 is S/T/N/Q and/or X2 is S/T/F/Y and/or X3 is G/A/I/L/V; a CDRH2 that includes the amino acid sequence YWDDD (SEQ ID NO: 362); a CDRH3 that includes the amino acid sequence R [R/V/K/S/G] [Y/R] [Y/absent] [S/absent] [absent/N] [G/S/Y/R] [Y/N/G] [G/A/Y/N] [M/F/Y] DY, or a CDRH3 that includes the amino acid sequence R-X1-X2-X3-X4-X5-X6-X7-X8-X9-DY, where each of X1-X9 may be any amino acid and/or where one or more of X3-X5 may be absent, *e.g.*, X1 is R/K/H/A/V/I/L/G/S/T and/or X2 is Y/F/R/K/H and/or X3 is Y/F/absent and/or X4 is S/T/absent and/or X5 is N/Q/absent and/or X6 is G/A/V/I/L/S/T/Y/F/R/K/H and/or X7 is Y/F/N/Q/G/A/V/I/L and/or X8 is G/A/V/I/L/Y/F/N/Q and/or X9 is M/F/Y; a CDRL1 that includes the amino acid sequence [K/S] [S/A] S [Q/S] S [L/I/V] [L/S] [N/S/D] [D/S/T] [V/G/D/Y] [N/G/absent] [Q/absent] [K/absent] [N/T/absent] [Y/absent] [L/absent] [A/H/N], or a CDRL1 that includes the amino acid sequence X1-X2-S-X3-S-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15, where each of X1-

X15 may be any amino acid and/or where one or more of X9-X14 may be absent, *e.g.*, X1 is K/R/H/S/T and/or X2 is S/T/A/V/I/L and/or X3 is Q/N/S/T and/or X4 is L/I/V/A and/or X5 is A/V/I/L/S/T and/or X6 is N/Q/S/T/D/E and/or X7 is D/E/S/T and/or X8 is G/A/V/I/L/D/E/Y/F and/or X9 is N/Q/G/A/absent and/or X10 is Q/N/absent and/or X11 is K/R/H/absent and/or X12 is N/Q/T/S/absent and/or X13 is Y/F/absent and/or X14 is A/V/I/L/absent and/or X15 is A/V/I/L/H/K/R/N/Q; a CDRL2 that includes the amino acid sequence [Y/G/L/R] [A/T/V] S [N/T/K] [R/L] [C/E/D/A] [T/S], or a CDRL2 that includes the amino acid sequence X1-X2-S-X3-X4-X5-X6, where X1-X6 may be any amino acid, *e.g.*, X1 is Y/F/G/A/V/I/L/R/K/H and/or X2 is A/V/I/L/T/S and/or X3 is N/Q/T/S/K/R/H and/or X4 is R/K/H/A/V/I/L and/or X5 is C/S/E/D/A/V/I/L and/or X6 is T/S; and/or a CDRL3 that includes the amino acid sequence [W/Q] [Q/N] [G/D] [T/S/Y/H] [H/S/R] [F/I/S/H] P [Q/R/L/Y] [absent/Y] T, or a CDRL3 that includes the amino acid sequence X1-X2-X3-X4-X5-X6-P-X7-X8-T, where each of X1-X8 may be any amino acid and/or where X8 may be absent, *e.g.*, X1 is Q/N/W/F/Y and/or X2 is Q/N and/or X3 is G/A/V/I/L/D/E and/or X4 is T/S/Y/F/H/K/R and/or X5 is H/K/R/S/T and/or X6 is F/Y/A/V/I/L/S/T/H/K/R and/or X7 is Q/N/R/K/H/A/V/I/L/Y/F and/or X8 is Y/F/absent.

Functional modifications

[0163] In some embodiments, antibodies of the present disclosure may be modified to optimize one or more functional properties (*e.g.*, antibody affinity or activity). Non-limiting examples of antibody functional properties include epitope or antigen affinity, ability to mobilize or immobilize targets, and ability to activate or inhibit a target, process, or pathway. In some embodiments, functional properties include or relate to ability to modulate protein-protein interactions, protein aggregation, enzyme activity, receptor-ligand interactions, cellular signaling pathways, proteolytic cascades, and/or biological or physiological responses.

[0164] Antibody modifications may optimize antibodies by modulating epitope affinity. Such modifications may be carried out by affinity maturation. Affinity maturation technology is used to identify sequences encoding CDRs with highest affinity for target antigens. In some embodiments, antibody display technologies (*e.g.*, phage or yeast) may be used. Such methods may include mutating nucleotide sequences encoding parental antibodies being optimized. Nucleotide sequences may be mutated randomly as a whole or to vary expression at specific amino acid residues to create millions to billions of variants. Sites or residues may be selected for mutation based on sequences or amino acid frequencies observed in natural human antibody repertoires. Variants may be subjected to repeated rounds of affinity screening [*e.g.*, using display library screening technologies, surface plasmon resonance technologies, fluorescence-associated cell sorting (FACS) analysis, enzyme-linked immunosorbent assay (ELISA), *etc.*] for target antigen binding. Repeated rounds of selection, mutation, and expression may be carried out to identify antibody fragment sequences with highest affinity for target antigens. Such sequences may be directly incorporated into antibody sequences for

production. In some cases, the goal of affinity maturation is to increase antibody affinity by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100 fold, at least 500-fold, at least 1,000-fold, or more than 1,000-fold as compared to the affinity of an original or starting antibody. In cases where affinity is less than desired, the process may be repeated.

[0165] In some embodiments, antibody affinity may be assessed with different antigen formats. In some embodiments, antibody affinity for different antigen formats may be tested *in vitro* (e.g., by ELISA). *In vitro* testing may be carried out using brain samples or fractions. Such samples or fractions may be obtained from subjects with AD (e.g., human AD patients). In some embodiments, brain samples or fractions may be obtained from non-human subjects. Such non-human subjects may include non-human animals used in AD disease model studies (e.g., mice, rats, and primates). In some embodiments, brain samples or fractions used for antibody affinity testing may be derived from TG4510/P301S mouse strains. Antibody affinity may be compared against control samples lacking the particular antigen for which affinity is being analyzed. In some embodiments, control samples may include brain samples or fraction from non-diseased human subjects. In some embodiments, brain samples or fractions from wild type and/or Tau knockout mouse strains may be used as control samples. *In vitro* affinity testing may be carried out (e.g., by ELISA) using recombinant or isolated protein antigens. In some embodiments, recombinant or isolated ePHF is used for antibody affinity testing. In some embodiments, antigens listed in Table 8 may be used.

[0166] In some embodiments, antibody affinity analysis may be used to modulate antibody polyspecificity (e.g., to reduce or enhance antibody polyspecificity). Such modulation may include modulating relative affinity for two or more epitopes or antigens. For example, antibodies may be optimized for higher affinity for one epitope or antigen over a second epitope or antigen.

[0167] Antibodies may be modified to optimize antibody functional properties. Such functional properties may be assessed or engineered based on analytical assay results relating to one or more antibody functional properties. Assays may be used to screen multiple antibodies to identify or rank antibodies based on functional criteria. Anti-tau antibodies may be modified to optimize tau aggregation inhibition. Such inhibition may be based on physical disruption of tau aggregation or may be based on the ability of anti-tau antibodies to deplete tau protein from assay samples. Optimization based on tau aggregation inhibition may be assessed using one or more assays of tau aggregation (e.g., by tau seeding assay).

Production modifications

[0168] In some embodiments, modifications may be made to optimize antibody production. Such modifications may include or relate to one or more of protein folding, stability, expression, and/or immunogenicity. Modifications may be carried out to address one or more antibody features negatively impacting production. Such features may include, but are not limited to, unpaired cysteines

or irregular disulfides; glycosylation sites (*e.g.*, N-linked NXS/T sites); acid cleavage sites, amino acid oxidation sites, conformity with mouse germline sequences; asparagine deamidation sites; aspartate isomerization sites; N-terminal pyroglutamate formation sites; and aggregation-prone amino acid sequence regions (*e.g.*, within CDR sequences).

[0169] In some embodiments, antibodies of the present disclosure may be prepared using recombinant DNA technology (*e.g.*, see United States Patent No. 4,816,567, which is hereby incorporated by reference in its entirety). Antibody-encoding DNA may be isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). In some embodiments, hybridoma cells may be used as a preferred source of DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells. Host cells may include, but are not limited to HEK293 cells, HEK293T cells, simian COS cells, Chinese hamster ovary (CHO) cells, and myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Pat. No. 4,816,567) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Antibody humanization

[0170] In some embodiments, anti-tau antibodies of the present disclosure may be prepared as humanized antibodies. “Humanized” antibodies are chimeric antibodies that contain minimal sequences (*e.g.*, variable domains or CDRs) derived from non-human immunoglobulins (*e.g.*, murine immunoglobulins). Humanized antibodies may be prepared from human (recipient) immunoglobulins in which residues from the hypervariable regions are replaced by hypervariable region residues from one or more non-human “donor” antibodies (*e.g.*, mouse, rat, rabbit, or nonhuman primate). Donor antibodies may be selected based on desired specificity, affinity, and/or capacity. Humanized antibodies may include one or more back-mutation that includes the reversion of one or more amino acids back to amino acids found in a donor antibody. Conversely, residues from donor antibodies included in humanized antibodies may be mutated to match residues present in human recipient antibodies. Back-mutations may be introduced to reduce human immune response to the humanized antibodies. In some embodiments, back-mutations are introduced to avoid issues with antibody manufacturing (*e.g.*, protein aggregation or post-translational modification).

[0171] For construction of expression plasmids encoding fully humanized antibodies with human constant regions, DNA sequences encoding antibody variable regions may be inserted into expression vectors (*e.g.*, mammalian expression vectors) between an upstream promoter/enhancer and immunoglobulin signal sequence and a downstream immunoglobulin constant region gene. DNA

samples may then be transfected into mammalian cells for antibody production. Constant domains from any class of human antibody may be used. There are five major classes of intact human antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1 (human and murine), IgG2 (human), IgG2a (murine), IgG2b (murine), IgG2c (murine), IgG3 (human and murine), IgG4 (human), IgA (murine), IgA1 (human), and IgA2 (human).

[0172] Cell lines with stable transfection of DNA encoding humanized antibodies may be prepared and used to establish stable cell lines. Cell lines producing humanized antibodies may be expanded for expression of humanized antibodies that may be harvested and purified from cell culture media.

[0173] In some embodiments, humanized antibodies of the present disclosure may have cross-reactivity with non-human species. Species cross-reactivity may allow antibodies to be used in different animals for various purposes. For example, cross-reactive antibodies may be used in pre-clinical animal studies to provide information about antibody efficacy and/or toxicity. Non-human species may include, but are not limited to, mouse, rat, rabbit, dog, pig, goat, sheep, and nonhuman primates (*e.g.*, *Cynomolgus* monkeys).

Antibody conjugates

[0174] In some embodiments, antibodies of the present disclosure may be or be prepared as antibody conjugates. As used herein, the term “conjugate” refers to any agent, cargo, or chemical moiety that is attached to a recipient entity or the process of attaching such an agent, cargo, or chemical moiety. As used herein, the term “antibody conjugate” refers to any antibody with an attached agent, cargo, or chemical moiety. Conjugates utilized to prepare antibody conjugates may include therapeutic agents. Such therapeutic agents may include drugs. Antibody conjugates that include a conjugated drug are referred to herein as “antibody drug conjugates.” Antibody drug conjugates may be used to direct conjugated drugs to specific targets based on the affinity of associated antibodies for proteins or epitopes associated with such targets. Such antibody drug conjugates may be used to localize biological activity associated with such conjugated drugs to targeted cells, tissues, organs, or other targeted entities. In some embodiments, conjugates utilized to prepare antibody conjugates include detectable labels. Antibodies may be conjugated with detectable labels for purposes of detection. Such detectable labels may include, but are not limited to, radioisotopes, fluorophores, chromophores, chemiluminescent compounds, enzymes, enzyme co-factors, dyes, metal ions, ligands, biotin, avidin, streptavidin, haptens, quantum dots, or any other detectable labels known in the art or described herein.

[0175] Conjugates may be attached to antibodies directly or via a linker. Direct attachment may be by covalent bonding or by non-covalent association (*e.g.*, ionic bonds, hydrostatic bonds, hydrophobic bonds, hydrogen bonds, hybridization, *etc.*). Linkers used for conjugate attachment may include any chemical structure capable of connecting an antibody to a conjugate. In some

embodiments, linkers include polymeric molecules (*e.g.*, nucleic acids, polypeptides, polyethylene glycols, carbohydrates, lipids, or combinations thereof). Antibody conjugate linkers may be cleavable (*e.g.*, through contact with an enzyme, change in pH, or change in temperature).

Exemplary anti-tau antibodies

[0176] In some embodiments, the anti-tau antibody comprises at least one antigen-binding domain, *e.g.*, a variable region or antigen binding fragment thereof, from an antibody described herein, *e.g.*, antibody chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Tables 1, 3, 6, 2A-2C, 4, or 5, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0177] In some embodiments, the anti-tau antibody comprises a heavy chain variable region from an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 3, 6, or 4, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the heavy chain variable region comprises an amino acid sequence having at least one, two, or three modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions), but not more than 30, 20, or 10 modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 3, 6, or 4.

[0178] In some embodiments, the nucleotide sequence encoding the anti-tau antibody comprises the nucleotide sequence of a heavy chain variable region from an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 3 or 4, or a nucleotide sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0179] In some embodiments, the anti-tau antibody comprises a light chain variable region from an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 3, 6, or 4, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the light chain variable region comprises an amino acid sequence having at least one, two, or three modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions), but not more than 30, 20, or 10 modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 3, 6, or 4.

[0180] In some embodiments, the nucleotide sequence encoding the anti-tau antibody comprises the nucleotide sequence of a light chain variable region from an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 3 or 4, or a nucleotide sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0181] In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region from an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 3, 6, or 4, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising an amino acid sequence having at least one, two, or three modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions), but not more than 30, 20, or 10 modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 3, 6, or 4; and a light chain variable region comprising an amino acid sequence having at least one, two, or three modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions), but not more than 30, 20, or 10 modifications (*e.g.*, substitutions, *e.g.*, conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 3, 6, or 4.

[0182] In some embodiments, the anti-tau antibody comprises a heavy chain constant region, *e.g.*, a human IgG1, IgG2, IgG3, or IgG4 constant regions, or a murine IgG1, IgG2A, IgG2B, IgG2C, or IgG3 constant regions. In some embodiments, the heavy chain constant comprises an amino acid sequence set forth in Table X, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, a nucleic acid encoding the heavy chain constant region comprises a nucleotide sequence set forth in Table X, or a nucleotide sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0183] In some embodiments, the anti-tau antibody comprises a light chain constant region, *e.g.*, a kappa light chain constant region, *e.g.*, a human kappa or lambda light chain constant region or a murine kappa or lambda light chain constant region. In some embodiments, the light chain constant comprises an amino acid sequence set forth in Table X, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, nucleic acid encoding the light chain constant region comprises a nucleotide sequence set forth in Table X, or a nucleotide sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0184] In some embodiments, the anti-tau antibody comprises a heavy chain constant region and a light chain constant region. In some embodiments, the heavy chain constant region and the light chain constant region comprise an amino acid sequence set forth in Table X, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the anti-tau

antibody comprises the nucleotide sequence of a heavy chain constant region and the nucleotide sequence of a kappa or lambda light chain constant region. In some embodiments, the nucleotide sequence encoding the heavy chain constant region and light chain constant region comprise a nucleotide sequence set forth in Table X, or a nucleotide sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0185] In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a constant region, a light chain variable region and a constant region, or both, comprising an amino acid sequence of Table 3, 6, or 4 for variable region, and an amino acid sequence of Table X for constant region; or is encoded by a nucleic acid sequence of Table 3, 6, or 4, and X; or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences.

[0186] In some embodiments, the anti-tau antibody comprises at least one, two, three, or four framework regions from a heavy chain variable region of an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 7 or 4, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, one or more of the framework regions (or collectively all of the framework regions) have one, two, three, four, five, or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence shown in Table 7 or 4. In some embodiments, the anti-tau antibody includes a substitution in a heavy chain framework region, *e.g.*, one or more substitutions in a FRH1, FRH2, FRH3, and/or FRH4 of the heavy chain.

[0187] In some embodiments, the anti-tau antibody comprises at least one, two, three, or four framework regions from a light chain variable region of an antibody described herein, *e.g.*, chosen from V0001-V0065, V1001-V1005, or V2001-V2005, *e.g.*, as described in Table 7 or 4, or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, one or more of the framework regions (or collectively all of the framework regions) have one, two, three, four, five, or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence shown in Table 7 or 4. In some embodiments, the anti-tau antibody includes a substitution in a light chain framework region, *e.g.*, one or more substitutions in a FRL1, FRL2, FRL3, and/or FRL4 of the light chain.

[0188] In some embodiments, the anti-tau antibody comprises at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region comprising an amino acid sequence in Table 2A-2C, 3, 6, 4, or 5, or is encoded by a nucleic acid sequence in Table 4; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments,

one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence shown in Table 2A-2C, 6, 4, or 5, or encoded by a nucleotide sequence shown in Table 4. In some embodiments, the encoded anti-tau antibody includes a substitution in a heavy chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the heavy chain.

[0189] In some embodiments, the anti-tau antibody comprises at least one, two, or three complementarity determining regions (CDRs) from a light chain variable region comprising an amino acid sequence in Table 2A-2C, 6, 4, or 5, or is encoded by a nucleic acid sequence in Table 4; or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence shown in Table 2A-2C, 6, 4, or 5, or encoded by a nucleotide sequence shown in Table 4. In some embodiments, the anti-tau antibody includes a substitution in a light chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain.

[0190] In some embodiments, the anti-tau antibody comprises at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 2A-2C, 6, 4, or 5, or is encoded by a nucleotide sequence shown in Table 4. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the CDRs shown in Table 2A-2C, 6, 4, or 5, or encoded by a nucleotide sequence shown in Table 4.

[0191] In some embodiments, the anti-tau antibody comprises all three CDRs from a heavy chain variable region, all three CDRs from light chain variable region, or both (*e.g.*, all six CDRs from a heavy chain variable region and a light chain variable region) comprising an amino acid sequence shown in Table 2A-2C, 6, 4, or 5, or is encoded by a nucleotide sequence shown in Table 4.

[0192] In some embodiments, an anti-tau antibody of the present disclosure may include CDRs identified through CDR analysis of variable domain sequences presented herein via co-crystallography with bound antigen; by computational assessments based on comparisons with other antibodies (*e.g.*, see Strohl, W.R. *Therapeutic Antibody Engineering*. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54); or Kabat, Chothia, Al-Lazikani, Lefranc, or Honegger numbering schemes, as described previously.

Table 2A: CDR sequences of selected antibodies based on Kabat numbering system

Ab ID	HC CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3
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V0004	NYWMH (SEQ ID NO: 1140)	RIDPNSGGT RYNEKFKN (SEQ ID NO: 1141)	DFDV (SEQ ID NO: 395)	RASGNIH NYLA (SEQ ID NO: 460)	NAKTLPD (SEQ ID NO: 518)	QHFWSPTLT (SEQ ID NO: 557)
V0009	DYYMS (SEQ ID NO: 1142)	LIRNKAKGF TTEYSASVK G (SEQ ID NO: 1143)	DINY (SEQ ID NO: 400)	KSSQSL YSTNQEN YLA (SEQ ID NO: 464)	WASSRES (SEQ ID NO: 523)	QQYYSYPT (SEQ ID NO: 562)
V0022	RYWMH (SEQ ID NO: 1144)	NINPNNGGT DFNEKFKN (SEQ ID NO: 1145)	GTGTGAM DY (SEQ ID NO: 410)	RSSQSLV HNNGITY LY (SEQ ID NO: 1146)	RVSNRFS (SEQ ID NO: 529)	FQGTHTPT (SEQ ID NO: 571)
V0023	IFWMH (SEQ ID NO: 1147)	KINPNNGGG DYNEKFKS (SEQ ID NO: 1148)	GTGTGAM DY (SEQ ID NO: 410)	RSSQSLV HSNGITH LY (SEQ ID NO: 474)	RVSNRFS (SEQ ID NO: 529)	FQGTHTPT (SEQ ID NO: 571)
V0024	RFWMH (SEQ ID NO: 1149)	NINPNNGGT DNNEKFKS (SEQ ID NO: 1150)	GTGTGAM DY (SEQ ID NO: 410)	RSSQSLV HSNGNTH LY (SEQ ID NO: 475)	RVSSRFS (SEQ ID NO: 530)	FQGTHTPT (SEQ ID NO: 571)
V0052	TSAMGVS (SEQ ID NO: 1152)	HIYWDDDKR YNPSLKS (SEQ ID NO: 1153)	RRRGYGM DY	KASQSVS NDVA	YASNRCT (SEQ ID NO: 540)	QQDYRSPT (SEQ ID NO: 587)

			(SEQ ID NO: 435)	(SEQ ID NO: 495)		
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Table 2B: CDR sequences of selected antibodies based on Chothia numbering system

Ab ID	HC CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3
V0004	DYTFTNY (SEQ ID NO: 299)	DPNSGG (SEQ ID NO: 343)	DFDV (SEQ ID NO: 395)	RASGNIH NYLA (SEQ ID NO: 460)	NAKTLPD (SEQ ID NO: 518)	QHFWSTPLT (SEQ ID NO: 557)
V0009	GFTFTDY (SEQ ID NO: 304)	RNKAKGFT (SEQ ID NO: 347)	DINY (SEQ ID NO: 400)	KSSQSL YSTNQEN YLA (SEQ ID NO: 464)	WASSRES (SEQ ID NO: 523)	QQYYSYPRT (SEQ ID NO: 562)
V0022	GFTFTRY (SEQ ID NO: 314)	NPNNGG (SEQ ID NO: 341)	GTGTGAM DY (SEQ ID NO: 410)	RSSQSLV HNNGITY LY (SEQ ID NO: 1154)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0023	GYTFTIF (SEQ ID NO: 315)	NPNNGG (SEQ ID NO: 341)	GTGTGAM DY (SEQ ID NO: 410)	RSSQSLV HSNGITH LY (SEQ ID NO: 474)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0024	GYTFTRF (SEQ ID NO: 316)	NPNNGG (SEQ ID NO: 341)	GTGTGAM DY	RSSQSLV HSNGNTH LY	RVSSRFS (SEQ ID NO: 530)	FQGTHVPRT (SEQ ID NO: 571)

			(SEQ ID NO: 410)	(SEQ ID NO: 475)		
V0052	GFSLSTSA M (SEQ ID NO: 325)	YWDDD (SEQ ID NO: 362)	RRRGYGM DY (SEQ ID NO: 435)	KASQSVS NDVA (SEQ ID NO: 495)	YASNRCT (SEQ ID NO: 540)	QQDYRSPLT (SEQ ID NO: 587)

Table 2C: CDR sequences of selected antibodies based on IMGT numbering system

Ab ID	HC CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3
V0004	DYTFITNYW (SEQ ID NO: 1155)	IDPNSGGT (SEQ ID NO: 1156)	AGDFDV (SEQ ID NO: 1157)	GNIHNY (SEQ ID NO: 1158)	NAK ()	QHFWSTPLT (SEQ ID NO: 557)
V0009	GFTFTDYY (SEQ ID NO: 1160)	IRNKAKGFT T (SEQ ID NO: 1161)	VRDINY (SEQ ID NO: 1162)	QSLLYST NQENY (SEQ ID NO: 1163)	WAS	QQYYSPRT (SEQ ID NO: 562)
V0022	GFTFTRYW (SEQ ID NO: 1165)	INPNNGGT (SEQ ID NO: 1166)	ARGTGTGA MDY (SEQ ID NO: 1167)	QSLVHNN GITY (SEQ ID NO: 473)	RVS	FQGTHVPRT (SEQ ID NO: 571)
V0023	GYTFTIFW (SEQ ID NO: 1168)	INPNNGGG (SEQ ID NO: 1169)	ARGTGTGA MDY (SEQ ID NO: 1167)	QSLVHSN GITH (SEQ ID NO: 1170)	RVS	FQGTHVPRT (SEQ ID NO: 571)
V0024	GYTFTRFW	INPNNGGT	ARGTGTGA MDY	QSLVHSN GNTH	RVS	FQGTHVPRT

	(SEQ ID NO: 1171)	(SEQ ID NO: 1166)	(SEQ ID NO: 1167)	(SEQ ID NO: 1172)		(SEQ ID NO: 571)
V0052	GFSLSTSA MG (SEQ ID NO: 1173)	IYWDDDK (SEQ ID NO: 1174)	ARRRRGYG MDY (SEQ ID NO: 1175)	QSVSND (SEQ ID NO: 1176)	YAS	QQDYRSPLT (SEQ ID NO: 587)

Table 3. Amino acid and nucleotide sequences of the heavy and light chain variable regions of exemplary anti-Tau antibodies

ID#	VH SEQ ID NO amino acid	VH SEQ ID NO nucleotide	VL SEQ ID NO amino acid	VL SEQ ID NO nucleotide
V0001	1	147	75	221
V0002	2	148	76	222
V0003	3	149	77	223
V0004	4	150	78	224
V0005	5	151	79	225
V0006	6	152	80	226
V0007	7	153	81	227
V0008	8	154	82	228
V0009	9	155	83	229
V00010	10	156	84	230
V00011	11	157	85	231
V00012	12	158	86	232
V00014	13	159	87	233
V00015	14	160	87	234
V00016	15	161	88	235
V00017	16	162	88	236
V00018	17	163	89	237
V00019	18	164	90	238
V0020	19	165	91	239
V0021	20	166	92	240

V0022	21	167	93	241
V0023	22	168	94	242
V0024	23	169	95	243
V0025	24	170	96	244
V0026	25	171	97	245
V0027	26	172	98	246
V0028	27	173	99	247
V0029	28	174	100	248
V0030	29	175	101	249
V0031	30	176	102	250
V0032	31	177	103	251
V0033	32	178	104	252
V0034	33	179	105	253
V0035	34	180	106	254
V0036	35	181	107	255
V0037	36	182	108	256
V0038	37	183	109	257
V0039	38	184	110	258
V0040	39	185	111	259
V0041	40	186	112	260
V0042	41	187	113	261
V0043	42	188	114	262
V0044	43	189	115	263
V0045	44	190	116	264
V0046	45	191	117	265
V0047	46	192	118	266
V0048	47	193	119	267
V0049	48	194	120	268
V0050	49	195	121	269
V0051	50	196	121	269
V0052	51	197	122	270
V0053	52	198	123	271
V0054	53	199	124	272
V0055	54	200	125	273
V0056	55	201	126	274

V0057	56	202	125	275
V0058	57	203	127	276
V0059	58	204	128	277
V0060	59	205	129	278
V0061	60	206	130	279
V0062	61	207	131	280
V0063	62	208	132	281
V0064	63	209	133	282
V0065	64	210	134	283
V1001	65	211	135	284
V1002	66	212	136	285
V1003	67	213	137	286
V1004	68	214	138	287
V1005	69	215	139	288
V1006	69	215	140	289
V1007	69	215	141	290
V2001	70	216	142	291
V2002	71	217	143	292
V2003	72	218	144	293
V2004	73	219	145	294
V2005	74	220	146	295

Table 4. Exemplary anti-tau antibodies

Ab ID	SEQ ID NO	Description	Sequence
V0004	299	HC CDR1 (Chothia)	DYTFTNY
	343	HC CDR2 (Chothia)	DPNSGG
	395	HC CDR3 (Chothia)	DFDV
	1140	HC CDR1 (Kabat)	NYWMH
	1141	HC CDR2	RIDPNSGGTRYNEKFKN

		(Kabat)	
395	HC CDR3 (Kabat)	DFDV	
1155	HC CDR1 (IMGT)	DYTFNTYW	
1156	HC CDR2 (IMGT)	IDPNSGGT	
1157	HC CDR3 (IMGT)	AGDFDV	
604	FR H1 (corresponding to the Chothia CDR definition)	QVQLQQPGAELVKPGASVKLSCKAS	
647	FR H2 (corresponding to the Chothia CDR definition)	WMHWVKQRPGRGLEWIGRI	
700	FR H3 (corresponding to the Chothia CDR definition)	TRYNEKFKNKATLTVDKPSSTAYMHLSSLTSEDSAVYYC AG	
770	FR H4 (corresponding to the Chothia CDR definition)	WGTGTTVTVSS	
4	VH	QVQLQQPGAELVKPGASVKLSCKASDYTFNTYWMHWVKQ RPGRGLEWIGRIDPNSGGTRYNEKFKNKATLTVDKPSST AYMHLSSLTSEDSAVYYCAGDFDVWGTGTTVTVSS	
150	DNA VH	CAGGTCCAACCTGCAGCAGCCTGGGGCTGAGCTTGTGAAG CCTGGGGCTTCAGTGAAGCTGTCCTGCAAGGCTTCTGAC TACACCTTCACCAACTACTGGATGCACTGGGTGAAGCAG AGGCCTGGACGAGGCCTTGAGTGGATAGGAAGGATTGAT CCTAATAGTGGTGGTACTAGGTACAATGAGAAGTTCAAG AACAAGGCCACACTGACTGTTGACAAACCCTCCAGCACA GCCTACATGCATCTCAGCAGCCTGACATCTGAGGACTCT	

			GCGGTCTATTATTGTGCAGGGGACTTCGATGTCTGGGGC ACAGGGACCACGGTCACCGTCTCCTCA
460	LC CDR1 (Chothia)		RASGNIHNYLA
518	LC CDR2 (Chothia)		NAKTLPD
557	LC CDR3 (Chothia)		QHFWSTPLT
460	LC CDR1 (Kabat)		RASGNIHNYLA
518	LC CDR2 (Kabat)		NAKTLPD
557	LC CDR3 (Kabat)		QHFWSTPLT
1158	LC CDR1 (IMGT)		GNIHNY
	LC CDR2 (IMGT)		NAK
557	LC CDR3 (IMGT)		QHFWSTPLT
779	FR L1 (corresponding to the Chothia CDR definition)		DIQMTQSPASLSASVGETVTITC
825	FR L2 (corresponding to the Chothia CDR definition)		WYQQRQGKSPQLLVY
861	FR L3 (corresponding to the Chothia CDR definition)		GVPSRFSGSGSGTQYSLKINSLQPEDFGSYCC
908	FR L4 (corresponding to the Chothia CDR definition)		FGAGTKLELK

	78	VL	DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQR QGKSPQLLVYNAKTLPDGVPSRFSGSGSGTQYSLKINSL QPEDFGSYCCQHFWSSTPLTFGAGTKLELK
	224	DNA VL	GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCA TCTGTGGGAGAACTGTCACCATCACATGTCGAGCAAGT GGGAATATTACAATTATTTAGCATGGTATCAGCAGAGA CAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAA ACCTTACCAGATGGTGTGCCATCAAGGTTAGTGGCAGT GGATCAGGAACACAATATTCTCTCAAGATCAACAGCCTG CAGCCTGAAGATTTTGGGAGTTATTGCTGTCAACATTTT TGGAGTACTCCGCTCACGTTCCGGTGCTGGGACCAAGTTG GAGCTGAAA
V000 9	304	HC CDR1 (Chothia)	GFTFTDY
	347	HC CDR2 (Chothia)	RNKAKGFT
	400	HC CDR3 (Chothia)	DINY
	1142	HC CDR1 (Kabat)	DYYMS
	1143	HC CDR2 (Kabat)	LIRNKAKGFTTEYSASVKG
	400	HC CDR3 (Kabat)	DINY
	1160	HC CDR1 (IMGT)	GFTFTDYY
	1161	HC CDR2 (IMGT)	IRNKAKGFTT
	1162	HC CDR3 (IMGT)	VRDINY
	608	FR H1 (corresponding to the Chothia CDR definition)	EVQLVESGGALVQPGGSLSLSCAAS
	652	FR H2	YMSWVRQPPGKALEWLALI

		(corresponding to the Chothia CDR definition)	
705	FR H3 (corresponding to the Chothia CDR definition)	TEYSASVKGRFTISRDNSSQSILLFQMNDLRADDSATYYC VR	
767	FR H4 (corresponding to the Chothia CDR definition)	WGQGTTLTVSS	
9	VH	EVQLVESGGALVQPGGSLSLSCAASGFTFTDYMSWVRQ PPGKALEWLALIRNKAKGFTTEYSASVKGRFTISRDNSSQ SILLFQMNDLRADDSATYYCVRDINYWGQGTTLTVSS	
155	DNA VH	GAGGTGCAGCTGGTGGAGTCTGGAGGAGCCTTGGTACAG CCTGGGGGTTCTCTGAGTCTCTCCTGTGCAGCTTCTGGA TTCACCTTCACTGATTACTACATGAGCTGGGTCCGCCAG CCTCCAGGGAAGGCACTTGAGTGGCTGGCTTTGATTAGA AACAAAGCTAAAGGTTTCACAACAGAATACAGTGCATCT GTGAAGGGTCGGTTCACCATCTCCAGAGATAATTCCCAA AGCATCCTCCTTTTTTCAAATGAATGACCTGAGAGCTGAC GACAGTGCCACTTATTACTGTGTAAGAGATATAAACTAC TGGGGCCAAGGCACCACTCTCACAGTCTCCTCA	
464	LC CDR1 (Chothia)	KSSQSLLYSTNQENYLA	
523	LC CDR2 (Chothia)	WASSRES	
562	LC CDR3 (Chothia)	QQYYSYPRT	
464	LC CDR1 (Kabat)	KSSQSLLYSTNQENYLA	
523	LC CDR2 (Kabat)	WASSRES	
562	LC CDR3 (Kabat)	QQYYSYPRT	

	1163	LC CDR1 (IMGT)	QSLLYSTNQENY
		LC CDR2 (IMGT)	WAS
	562	LC CDR3 (IMGT)	QQYYSYPRT
	783	FR L1 (corresponding to the Chothia CDR definition)	DIVMSQSPSSLAVSVGEKVTMSC
	830	FR L2 (corresponding to the Chothia CDR definition)	WYQQKPGQSPKLLIY
	866	FR L3 (corresponding to the Chothia CDR definition)	GVPDRFTGSGSGTDFTLTISSVKAEDLAVYYC
	906	FR L4 (corresponding to the Chothia CDR definition)	FGGGTKLEIK
	83	VL	DIVMSQSPSSLAVSVGEKVTMSCCKSSQSLLYSTNQENYL AWYQQKPGQSPKLLIYWASSRESGVPDRFTGSGSGTDFT LTISSVKAEDLAVYYCQQYYSYPRTFGGGTKLEIK
	229	DNA VL	GACATTGTGATGTCACAGTCTCCATCCTCCCTAGCTGTG TCAGTTGGAGAGAAGGTTACTATGAGCTGCAAGTCCAGT CAGAGCCTTTTATATAGTACCAATCAAGAGAACTACTTG GCCTGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTG CTGATTTACTGGGCATCCTCTAGGGAATCTGGGGTCCCT GATCGCTTTACAGGCAGTGGATCTGGGACAGATTTCACT CTCACCATCAGCAGTGTGAAGGCTGAAGACCTGGCAGTT TATTACTGTCAGCAATATTATAGCTATCCTCGGACGTTC GGTGGAGGCACCAAGCTGGAAATCAAA
V002 2	314	HC CDR1 (Chothia)	GFTFTRY

	341	HC CDR2 (Chothia)	NPNNGG
	410	HC CDR3 (Chothia)	GTGTGAMDY
	1144	HC CDR1 (Kabat)	RYWMH
	1145	HC CDR2 (Kabat)	NINPNNGGTDFNEKFKN
	410	HC CDR3 (Kabat)	GTGTGAMDY
	1165	HC CDR1 (IMGT)	GFTFTRYW
	1166	HC CDR2 (IMGT)	INPNNGGT
	1167	HC CDR3 (IMGT)	ARGTGTGAMDY
	619	FR H1 (corresponding to the Chothia CDR definition)	QVQLQQPGTELVKPGSSVNLSCAS
	663	FR H2 (corresponding to the Chothia CDR definition)	WMHWVKERPGHGLEWIGNI
	717	FR H3 (corresponding to the Chothia CDR definition)	TDFNEKFKNKATLTVHKSSTTVFIQLSSLTSEDSAVYYC AR
	771	FR H4 (corresponding to the Chothia CDR definition)	WGQGTSVTVSS
	21	VH	QVQLQQPGTELVKPGSSVNLSCASGFTFTRYWMHWVKE RPGHGLEWIGNINPNNGGTDFNEKFKNKATLTVHKSSTT VFIQLSSLTSEDSAVYYCARGTGTGAMDYWGQGTSVTVS S

167	DNA VH	CAGGTCCAACCTGCAGCAGCCTGGGACTGAACTGGTGAAG CCTGGGTCTTCAGTGAACCTGTCCTGCAAGGCTTCTGGC TTCACCTTCACCAGGTACTGGATGCACTGGGTGAAGGAG AGGCCTGGACATGGCCTTGAGTGGATTGGAAATATTAAT CCTAACAAATGGTGGTACTGACTTCAATGAGAAGTTCAAG AACAAGGCCACACTGACTGTACACAAGTCCTCCACCACA GTCTTCATCCAACCTCAGCAGCCTGACATCTGAGGACTCT GCGGTCTATTATTGTGCAAGAGGAAGTGGGACGGGAGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC TCA
1154	LC CDR1 (Chothia)	RSSQSLVHNNGITYLY
529	LC CDR2 (Chothia)	RVSNRFS
571	LC CDR3 (Chothia)	FQGTHVPRT
1146	LC CDR1 (Kabat)	RSSQSLVHNNGITYLY
529	LC CDR2 (Kabat)	RVSNRFS
571	LC CDR3 (Kabat)	FQGTHVPRT
473	LC CDR1 (IMGT)	QSLVHNNGITY
	LC CDR2 (IMGT)	RVS
571	LC CDR3 (IMGT)	FQGTHVPRT
1178	FR L1 (corresponding to the Chothia CDR definition)	DVVMQTPLSLPVSLGDQASISC
831	FR L2	WYLQKPGQSPKLLIY

		(corresponding to the Chothia CDR definition)	
	1179	FR L3 (corresponding to the Chothia CDR definition)	GVPDRFGGSGSGTDFTLKISRVEAEDLGVYFC
	906	FR L4 (corresponding to the Chothia CDR definition)	FGGGTKLEIK
	93	VL	DVVMQTPLSLPVSLGDQASISCRSSQSLVHNNGITYLY WYLQKPGQSPKLLIYRVSNRFSGVPDRFGGSGSGTDFTL KISRVEAEDLGVYFCFQGTHVPRTFGGGTKLEIK
	241	DNA VL	GATGTTGTGATGACCCAACTCCACTCTCCCTGCCTGTC AGTCTTGGAGATCAAGCTTCCATCTCTTGCAGATCTAGT CAGAGCCTTGTACACAACAATGGAATCACCTATTTATAT TGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTCCTG ATCTACAGGGTTTCCAACCGATTTTCTGGGGTCCCAGAC AGGTTTCGGTGGCAGTGGATCAGGGACAGATTTACACTC AAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTAT TTCTGCTTTCAAGGTACACATGTTCTCGGACGTTCCGGT GGAGGCACCAAGCTGGAAATCAAA
V002 3	315	HC CDR1 (Chothia)	GYTFTIF
	341	HC CDR2 (Chothia)	NPNNGG
	410	HC CDR3 (Chothia)	GTGTGAMDY
	1147	HC CDR1 (Kabat)	IFWMH
	1148	HC CDR2 (Kabat)	KINPNNGGGDYNEKFKS
	410	HC CDR3 (Kabat)	GTGTGAMDY

	1168	HC CDR1 (IMGT)	GYTFTIEW
	1169	HC CDR2 (IMGT)	INPNNGGG
	1167	HC CDR3 (IMGT)	ARGTGTGAMDY
	603	FR H1 (corresponding to the Chothia CDR definition)	QVQLQQPGTELVKPGASVKLSCKAS
	664	FR H2 (corresponding to the Chothia CDR definition)	WMHWVKQRPGHGLEWIGKI
	718	FR H3 (corresponding to the Chothia CDR definition)	GDYNEKFKSKATLTVDKSSTTAYLQLSSLTSEDSAVYYC AR
	771	FR H4 (corresponding to the Chothia CDR definition)	WGQGTSVTVSS
	22	VH	QVQLQQPGTELVKPGASVKLSCKASGYTFTIFWMHWVKQ RPGHGLEWIGKINPNNGGGDYNEKFKSKATLTVDKSSTT AYLQLSSLTSEDSAVYYCARGTGTGAMDYWGQGTSVTVS S
	168	DNA VH	CAGGTCCAAGTGCAGCAGCCTGGGACTGAACTGGTGAAG CCTGGGGCTTCAGTGAAGCTGTCCTGCAAGGCTTCTGGC TACACCTTCACCATCTTCTGGATGCACTGGGTGAAGCAG AGGCCTGGACATGGCCTTGAGTGGATTGGAAAGATTAAT CCTAACAATGGAGGTGGTGAAGTACAATGAGAAATTCAAG AGTAAGGCCACATTGACTGTAGACAAATCCTCCACCACA GCCTACTTGCACTCAGCAGCCTGACATCTGAGGACTCT GCGGTCTATTATTGTGCAAGAGGAAGTGGGACGGGAGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC TCA

	474	LC CDR 1 (Chothia)	RSSQSLVHSNGITHLY
	529	LC CDR2 (Chothia)	RVSNRFS
	571	LC CDR3 (Chothia)	FQGTHVPRT
	474	LC CDR1 (Kabat)	RSSQSLVHSNGITHLY
	529	LC CDR2 (Kabat)	RVSNRFS
	571	LC CDR3 (Kabat)	FQGTHVPRT
	1170	LC CDR1 (IMGT)	QSLVHSNGITH
		LC CDR2 (IMGT)	RVS
	571	LC CDR3 (IMGT)	FQGTHVPRT
	793	FR L1 (corresponding to the Chothia CDR definition)	DVVMTQTPLSLPVSLGDHASISC
	836	FR L2 (corresponding to the Chothia CDR definition)	WYLQRPGQTPKLLIY
	874	FR L3 (corresponding to the Chothia CDR definition)	GVPDRFSGSGGTDFTLKISSVEAEDLG VYFC
	910	FR L4 (corresponding to the Chothia CDR definition)	FGGGTKLEIE

	94	VL	DVVMTQTPLSLPVSLGDHASISCRSSQSLVHSNGITHLY WYLQRPQGTPKLLIYRVSNRFSGVPDFRSGSGSGTDFTL KISSVEAEDLGVFYFCFQGTHVPRTFGGGTKLEIE
	242	DNA VL	GATGTTGTGATGACCCAACTCCACTCTCCCTGCCTGTC AGTCTTGGAGATCACGCTTCCATCTCTTGACAGATCTAGT CAGAGCCTTGTACACAGCAATGGAATCACCCATTTATAT TGGTACCTGCAGAGGCCAGGCCAGACTCCAAAGCTCCTG ATCTACAGGGTTTCCAACCGATTTTCTGGGGTCCCAGAC AGGTTTCAAGTGGCAGTGGATCAGGGACAGATTTACACTC AAGATCAGCAGCGTGGAGGCTGAGGATCTGGGAGTTTAT TTCTGCTTTCAAGGTACACATGTTCTCTCGGACGTTCCGGT GGAGGCACCAAGCTGGAAATCGAA
V002 4	316	HC CDR1 (Chothia)	GYTFTRF
	341	HC CDR2 (Chothia)	NPNNGG
	410	HC CDR3 (Chothia)	GTGTGAMDY
	1149	HC CDR1 (Kabat)	RFWMH
	1150	HC CDR2 (Kabat)	NINPNNGGTDNNERFKS
	410	HC CDR3 (Kabat)	GTGTGAMDY
	1171	HC CDR1 (IMGT)	GYTFTRFW
	1166	HC CDR2 (IMGT)	INPNNGGT
	1167	HC CDR3 (IMGT)	ARGTGTGAMDY
	603	FR H1 (corresponding to the Chothia CDR definition)	QVQLQQPGTELVKPGASVKLSCKAS
	665	FR H2	WMHWVKQRPQGGLWIGNI

		(corresponding to the Chothia CDR definition)	
719	FR H3 (corresponding to the Chothia CDR definition)	TDNNERFKSKATLTVDRSSSTAYMQLSSLTSEDSAVYYCAR	
771	FR H4 (corresponding to the Chothia CDR definition)	WGQGTSTVTVSS	
23	VH	QVQLQQPGTELVKPGASVKLSCKASGYTFTRFWMHWVKQRPGQGLEWIGNINPNNGGTDNNERFKSKATLTVDRSSSTAYMQLSSLTSEDSAVYYCARGTGTGAMDYWGQGTSTVTVSS	
169	DNA VH	CAGGTCCAACCTGCAGCAGCCTGGGACTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACCAGGTTCTGGATGCACTGGGTGAAGCAGAGGCCTGGACAAGGCCTTGAGTGGATTGGAATATTAATCCTAACAATGGTGGTACTGACAATAATGAGAGGTTCAAGAGCAAGGCCACACTGACTGTAGACAGATCCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTATTGTGCAAGAGGAACTGGGACGGGAGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	
475	LC CDR 1 (Chothia)	RSSQSLVHSNGNTHLY	
530	LC CDR2 (Chothia)	RVSSRFS	
571	LC CDR3 (Chothia)	FQGTHVPRT	
475	LC CDR1 (Kabat)	RSSQSLVHSNGNTHLY	
530	LC CDR2 (Kabat)	RVSSRFS	
571	LC CDR3	FQGTHVPRT	

		(Kabat)	
1172	LC CDR1 (IMGT)	QSLVHSNGNTH	
	LC CDR2 (IMGT)	RVS	
571	LC CDR3 (IMGT)	FQGTHVPRT	
787	FR L1 (corresponding to the Chothia CDR definition)	DVVMQTPLSLPVSLGDQASISC	
831	FR L2 (corresponding to the Chothia CDR definition)	WYLQKPGQSPKLLIY	
870	FR L3 (corresponding to the Chothia CDR definition)	GVPDRFSGSGSGTDFTLKISRVEAEDLGVYFC	
906	FR L4 (corresponding to the Chothia CDR definition)	FGGGTKLEIK	
95	VL	DVVMQTPLSLPVSLGDQASISCRSSQSLVHSNGNTHLY WYLQKPGQSPKLLIYRVSSRFSGVPDRFSGSGSGTDFTL KISRVEAEDLGVYFCFQGTHVPRTFGGGTKLEIK	
243	DNA VL	GATGTGGTGATGACCCAACTCCACTCTCCCTGCCTGTC AGTCTTGAGATCAGGCTTCCATCTCTTGCAGATCTAGT CAGAGCCTTGTACACAGCAATGGAAACACCCATTTATAT TGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTCCTG ATCTACAGGGTTTCCAGCCGATTTTCTGGGGTCCCAGAC AGGTTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTC AAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTAT TTCTGCTTTCAGGGTACACATGTTCCCTCGGACGTTCCGT GGAGGCACCAAGCTGGAAATCAAA	
325	HC CDR1	GFSLSTSAM	

V005 2		(Chothia)	
	362	HC CDR2 (Chothia)	YWDDD
	435	HC CDR3 (Chothia)	RRRGYGMDY
	1152	HC CDR1 (Kabat)	TSAMGVS
	1153	HC CDR2 (Kabat)	HIYWDDDKRYNPSLKS
	435	HC CDR3 (Kabat)	RRRGYGMDY
	1173	HC CDR1 (IMGT)	GFSLSTSAMG
	1174	HC CDR2 (IMGT)	IYWDDDK
	1175	HC CDR3 (IMGT)	ARRRRGYGMDY
	633	FR H1 (corresponding to the Chothia CDR definition)	QITLKESGPGILQSSQTLSTCSFS
	682	FR H2 (corresponding to the Chothia CDR definition)	GVSWIRQPSGEGLEWLAHI
	745	FR H3 (corresponding to the Chothia CDR definition)	KRYNPSLKSRLTISKDTSRNQVFLKITSVDTADTATYYC AR
	771	FR H4 (corresponding to the Chothia CDR definition)	WGQGTSTVTVSS
	51	VH	QITLKESGPGILQSSQTLSTCSFSGFSLSTSAMGVSWI RQPSGEGLEWLAHIYWDDDKRYNPSLKSRLTISKDTSRN

			QVFLKITSVDTADTATYYCARRRRGYGMDYWQGTSVTV SS
197	DNA VH		CAGATTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAG TCCTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGG TTTTCACTGAGCACTTCTGCTATGGGTGTGAGTTGGATT CGTCAGCCTTCAGGAGAGGGTCTGGAGTGGCTGGCACAC ATTTACTGGGATGATGACAAGCGCTATAACCCATCCCTG AAGAGCCGGCTCACAATCTCCAAGGATACCTCCAGAAAC CAGGTATTCTCAAGATCACCAGTGTGGACACTGCAGAT ACTGCCACATACTACTGTGCTCGAAGAAGGAGGGGGTAT GGTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTC TCCTCA
495	LC CDR 1 (Chothia)		KASQSVSNDVA
540	LC CDR2 (Chothia)		YASNRCT
587	LC CDR3 (Chothia)		QQDYRSPLT
495	LC CDR1 (Kabat)		KASQSVSNDVA
540	LC CDR2 (Kabat)		YASNRCT
587	LC CDR3 (Kabat)		QQDYRSPLT
1176	LC CDR1 (IMGT)		QSVSND
	LC CDR2 (IMGT)		YAS
587	LC CDR3 (IMGT)		QQDYRSPLT
807	FR L1 (corresponding to the Chothia CDR definition)		SIVMTQTPKFLVLSAGDRVITIC
830	FR L2		WYQQKPGQSPKLLIY

		(corresponding to the Chothia CDR definition)	
	888	FR L3 (corresponding to the Chothia CDR definition)	GVPDRFTGSGYGTDFTFTISTVQAEDLAVYFC
	908	FR L4 (corresponding to the Chothia CDR definition)	FGAGTKLELK
	122	VL	SIVMTQTPKFLLVSAGDRVITITCKASQSVSNDVAWYQQK PGQSPKLLIYYASNRCTGVPDRFTGSGYGTDFTFTISTV QAEDLAVYFCQQDYRSPLTFGAGTKLELK
	270	DNA VL	AGTATTGTGATGACCCAGACTCCCAAATTCCTGCTTGTA TCAGCAGGAGACAGGGTTACCATAACCTGCAAGGCCAGT CAGAGTGTGAGTAATGATGTAGCTTGGTACCAACAGAAG CCAGGGCAGTCTCCTAAACTGCTAATATACTATGCATCC AATCGCTGCACTGGAGTCCCTGATCGCTTCACTGGCAGT GGATATGGGACGGATTTCACTTTACCACATCAGCACTGTA CAGGCTGAAGACCTGGCAGTTTATTTCTGTCAGCAGGAT TATAGGTCTCCGCTCACGTTCGGTGCTGGGACCAAGCTG GAGCTGAAA

Table 6. Exemplary heavy and light chain CDR amino acid sequences of anti-tau antibodies

ID#	CDRH1 SEQ ID NO	CDRH2 SEQ ID NO	CDRH3 SEQ ID NO	CDRL1 SEQ ID NO	CDRL2 SEQ ID NO	CDRL3 SEQ ID NO
V0001	296	340	392	457	515	554
V0002	297	341	393	458	516	555
V0003	298	342	394	459	517	556
V0004	299	343	395	460	518	557
V0005	300	344	396	461	519	558
V0006	301	345	397	462	520	559
V0007	302	346	398	463	521	560
V0008	303	345	399	457	522	561

V0009	304	347	400	464	523	562
V00010	305	348	401	465	524	563
V00011	306	349	402	466	525	564
V00012	307	350	403	467	526	565
V00014	308	351	404	468	525	566
V00015	309	341	405	468	525	566
V00016	310	352	406	469	524	567
V00017	310	353	406	469	524	567
V00018	311	354	407	470	527	568
V00019	312	355	408	471	527	569
V0020	308	356	409	472	525	570
V0021	313	357	409	472	525	570
V0022	314	341	410	1154	529	571
V0023	315	341	410	474	529	571
V0024	316	341	410	475	530	571
V0025	317	358	410	476	531	571
V0026	318	359	411	477	525	572
V0027	319	360	412	478	525	573
V0028	320	361	413	479	525	573
V0029	321	362	414	480	529	574
V0030	308	363	415	480	525	572
V0031	308	363	416	479	525	572
V0032	297	364	417	481	525	572
V0033	308	365	418	482	532	575
V0034	308	366	419	483	532	576
V0035	308	367	420	482	532	576
V0036	321	362	421	484	532	576
V0037	308	368	422	484	532	577
V0038	308	369	423	485	526	578
V0039	308	370	423	486	526	578
V0040	301	371	424	487	533	579
V0041	301	371	424	487	534	579
V0042	322	372	425	488	535	580
V0043	323	373	426	488	535	581
V0044	322	374	427	489	536	581

V0045	322	375	428	490	535	582
V0046	306	376	429	491	525	583
V0047	306	377	430	468	525	583
V0048	321	378	431	492	537	584
V0049	321	362	432	493	538	585
V0050	297	341	433	494	539	586
V0051	324	362	434	494	539	586
V0052	325	362	435	495	540	587
V0053	321	362	436	496	541	588
V0054	326	362	437	496	542	588
V0055	321	362	438	496	543	588
V0056	321	362	439	496	543	588
V0057	321	362	438	496	543	588
V0058	327	362	440	497	543	588
V0059	328	348	441	498	544	589
V0060	329	348	441	499	544	589
V0061	330	379	442	500	545	590
V0062	331	380	443	501	546	583
V0063	332	381	444	502	547	572
V0064	330	382	445	503	546	591
V0065	333	383	446	504	548	592
V1001	334	384	447	505	549	593
V1002	335	385	448	506	550	594
V1003	334	386	449	507	549	593
V1004	334	387	450	507	549	595
V1005	336	388	451	508	551	596
V1006	336	388	451	509	551	596
V1007	336	388	451	509	551	596
V2001	337	389	452	510	525	597
V2002	338	390	453	511	552	597
V2003	306	391	454	512	532	598
V2004	339	361	455	513	553	599
V2005	308	361	456	514	553	600

Table 7. Exemplary FR amino acid sequences of anti-tau antibodies

ID#	FRH1 SEQ ID NO	FRH2 SEQ ID NO	FRH3 SEQ ID NO	FRH4 SEQ ID NO	FRL1 SEQ ID NO	FRL2 SEQ ID NO	FRL3 SEQ ID NO	FRL4 SEQ ID NO
V0001	601	644	697	767	776	823	858	905
V0002	602	645	698	768	777	823	859	906
V0003	603	646	699	769	778	824	860	907
V0004	604	647	700	770	779	825	861	908
V0005	605	648	701	768	780	826	862	908
V0006	606	649	702	768	781	827	863	906
V0007	607	650	703	771	782	828	864	908
V0008	606	651	704	771	777	829	865	909
V0009	608	652	705	767	783	830	866	906
V00010	609	653	706	767	784	830	867	906
V00011	610	654	707	770	785	831	868	906
V00012	611	655	708	767	786	832	869	906
V00014	612	656	709	771	787	831	870	906
V00015	613	657	710	768	787	831	870	906
V00016	614	658	711	771	788	830	871	906
V00017	614	659	712	771	788	830	871	906
V00018	615	660	713	768	789	833	872	906
V00019	616	661	714	768	789	833	872	906
V0020	617	662	715	768	790	834	870	905
V0021	618	662	716	768	791	834	870	905
V0022	619	663	717	771	1178	831	1179	906
V0023	603	664	718	771	793	836	874	910
V0024	603	665	719	771	787	831	870	906
V0025	603	665	720	771	787	831	875	906
V0026	620	666	721	771	794	831	868	906
V0027	620	667	722	771	794	831	868	905
V0028	620	668	723	771	794	831	868	905
V0029	621	669	724	768	794	831	876	911
V0030	603	665	725	771	794	831	868	906
V0031	603	665	726	771	795	837	868	906
V0032	622	670	727	771	794	831	868	906
V0033	623	671	728	767	796	838	877	908

V0034	623	672	729	768	797	839	878	906
V0035	624	671	729	768	798	840	878	906
V0036	625	673	730	767	797	839	878	906
V0037	626	674	731	767	797	839	878	906
V0038	627	675	732	772	799	841	869	906
V0039	627	675	733	772	800	841	879	912
V0040	628	676	734	773	779	842	880	909
V0041	628	676	735	771	779	843	880	906
V0042	629	677	736	767	801	830	881	913
V0043	630	678	737	768	802	830	882	908
V0044	629	677	738	768	803	844	883	908
V0045	629	677	739	767	801	830	883	914
V0046	610	679	740	771	787	831	884	906
V0047	610	679	740	771	787	831	870	906
V0048	631	680	741	767	804	845	885	915
V0049	631	673	742	767	805	845	886	906
V0050	632	681	743	771	806	846	887	916
V0051	631	673	744	771	806	846	887	916
V0052	633	682	745	771	807	830	888	908
V0053	631	673	746	771	808	833	871	906
V0054	631	683	747	771	808	833	871	906
V0055	631	673	745	771	808	833	871	906
V0056	631	673	748	771	809	833	871	906
V0057	631	673	749	771	808	833	871	906
V0058	631	673	730	771	808	833	871	906
V0059	609	653	750	767	789	847	889	906
V0060	609	653	751	767	810	847	889	906
V0061	634	684	752	767	811	848	890	906
V0062	610	685	753	770	792	849	891	906
V0063	635	686	754	767	812	850	892	906
V0064	604	687	755	771	792	851	893	908
V0065	626	688	756	768	813	852	894	906
V1001	636	689	757	768	814	853	895	917
V1002	637	690	758	771	815	854	896	906
V1003	638	691	759	774	816	853	897	908

V1004	636	689	760	768	817	853	898	908
V1005	639	692	761	771	818	855	899	908
V1006	639	692	761	771	819	855	899	908
V1007	639	692	761	771	819	856	900	908
V2001	640	679	762	771	794	831	868	906
V2002	640	693	763	771	820	831	901	906
V2003	641	694	764	768	821	839	902	906
V2004	642	695	765	767	797	857	903	918
V2005	643	696	766	775	822	839	904	919

Table X. Constant Regions of Heavy Chains and Light Chains

SEQ ID NO	Description	Sequence
1189	Constant Region of Heavy Chain, secreted form & membrane-bound form (mIgG1)	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTF PAVLQSDLYTLSSSVTVPSSPRPSETVTCNVAHPASSTKVDKKIVPRDCGCKP CICTVPEVSSVFIFPPKPKDVLITITLTPKVTCTVVDISKDDPEVQFSWFVDDV EVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKT ISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPA ENYKNTQPIMNNTNGSYFVYSKLVQKSNWEAGNTFTCSVLHEGLHNHHTTEKSL SHSPGK
1190	Constant Region of murine Heavy Chain, (mIgG2A)	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTF PAVLQSDLYTLSSSVTVPSSPRPSETVTCNVAHPASSTKVDKKIVPRDCGCKP CICTVPEVSSVFIFPPKPKDVLITITLTPKVTCTVVDISKDDPEVQFSWFVDDV EVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKT ISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPA ENYKNTQPIMNNTNGSYFVYSKLVQKSNWEAGNTFTCSVLHEGLHNHHTTEKSL SHSPGLQLDETCAEAQDGLDGLWTTITIFISLFLLSVCYSAAVTLFKVKWIF SSVVELKQTLVPEYKNMIGQAP
1191	Constant Region of murine Heavy Chain, (mIgG2A)	AKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTF PAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKP CPPCKCPAPNLLGGPSVFIFPPKIKDVLMLSLSPIVTCVVVDVSEDDPDVQIS WVNNVEVHTAQTPQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLF APIERTISKPKGSVRAPQVYVLPPEEEMTKKQVTLTCMVTDFMPEDIYVEWT

		NNGKTELNYKNTEPVLDSGYSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNH HTTKSFSRTPGK
1192	DNA Constant Region of Heavy Chain (mIgG2A)	GCTAAACAACAGCCCCATCGGTCTATCCACTGGCCCCCTGTGTGTGGAGATAC AACTGGCTCCTCGGTGACTCTAGGATGCCTGGTCAAGGGTTATTTCCCTGAGC CAGTGACCTTGACCTGGAACCTCTGGATCCCTGTCCAGTGGTGTGCACACCTTC CCAGCTGTCCTGCAGTCTGACCTCTACACCCTCAGCAGCTCAGTGACTGTAAC CTCGAGCACCTGGCCCAGCCAGTCCATCACCTGCAATGTGGCCCACCCGGCAA GCAGCACCAAGGTGGACAAGAAAATTGAGCCCAGAGGGCCCACAATCAAGCCC TGTCTCCATGCAAATGCCAGCACCTAACCTCTTGGGTGGACCATCCGTCTT CATCTTCCCTCCAAAGATCAAGGATGTACTCATGATCTCCCTGAGCCCCATAG TCACATGTGTGGTGGTGGATGTGAGCGAGGATGACCCAGATGTCCAGATCAGC TGGTTTGTGAACAACGTGGAAGTACACACAGCTCAGACACAAACCCATAGAGA GGATTACAACAGTACTCTCCGGGTGGTCAGTGCCCTCCCCATCCAGCACCAGG ACTGGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACAACAAAGACCTCCCA GCGCCCATCGAGAGAACCATCTCAAAACCCAAAGGGTCAGTAAGAGCTCCACA GGTATATGTCTTGCCTCCACCAGAAGAAGAGATGACTAAGAAACAGGTCACTC TGACCTGCATGGTCACAGACTTCATGCCTGAAGACATTTACGTGGAGTGGACC AACAACGGGAAAACAGAGCTAAACTACAAGAACACTGAACCAGTCCTGGACTC TGATGGTTCTTACTTCATGTACAGCAAGCTGAGAGTGGAAAAGAAGAACTGGG TGGAAGAAATAGCTACTCCTGTTTCAAGTGGTCCACGAGGGTCTGCACAATCAC CACACGACTAAGAGCTTCTCCCGGACTCCGGGTAAA
1193	Constant Region of Heavy Chain, secreted form (mIgG2A)	AKTTAPSVYPLVPVCGGTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTF PALLQSGLYTLSSSVTVTSNTWPSQTITCNVAHPASSTKVDKKIEPRVPITQN PCPPHQRVPPCAAPDLLGGPSVFIFPPKIKDVLMLISLSPMVTVCVVVDVSEDDP DVQISWVFNNEVHTAQQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVN NRALPSPIEKTISKPRGPVRAPQVYVLPPEAEEMTKKEFSLTCMITGFLPAEI AVDWTSNGRTEQNYKNTATVLDSDGYSYFMYSKLRVQKSTWERGSLFACSVVHE VLHNHLTTKTISRSLGK
1194	Constant Region of murine Heavy Chain, secreted form (mIgG2B)	KTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTWNSGSLSSSVHTFP ALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPASSTVDDKKLEPSGPISTIN PCPPCKECHKCPAPNLEGGPSVFIFPPNIKDVLMLISLTPKVTVCVVVDVSEDDP DVQISWVFNNEVHTAQQTQTHREDYNSTIRVVSTLPIQHQDWMSGKEFKCKVN NKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVVGFNPGDI SVEWTSNGHTEENYKDTAPVLDSDGYSYFIYSKLNMKTSKWEKTDSFSCNVRHE GLKNYYLKKTISRSPGLDLDDICAEAKDGELDGLWTTITIFISLFLLSVCYSA SVTLFKVKWIFSSVVELKQKISPDRNMIGQGA

1195	Constant Region of murine Heavy Chain, (mIgG2B)	KTTAPSVYPLAPVCGGTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP ALLQSGLYTLSSSVTVTSNTWPSQTITCNVAHPASSTKVDDKIEPRVPITQNP CPPLKECPPCAAPDLLGGPSVFIFPPKIKDVLMLISLSPMVTCTVVDVSEDDPD VQISWFVNNVEVHTAQQTQTHREDYNSTLRVVSALPIQHQDWMMSGKEFKCKVNN RALPSPIEKTISKPRGPVRAPQVYVLPPPAEEMTKKEFSLTCMITGFLPAEIA VDWTISNGRTEQNYKNTATVLDSDGSYFMYSKLRVQKSTWERSLFCVSVHEG LHNHLTTKTISRSLGLDLDDVCTEAQDGEGLDGLWTTITIFISLFLLSVCYSAS VTFLFKVKWIFSSVVELKQKISPDYRNMIGQGA
1196	Constant Region of murine Heavy Chain, secreted form (mIgG3)	TTTAPSVYPLVPGCSDTSGSSVTLGCLVKGYFPEPVTVKWNYGALSSGVRTVS SVLQSGFYSLSSLVTVPSSTWPSQTVICNVAHPASKTELKRIEPRIPKPSTP PGSSCPPGNILGGPSVFIFPPKPKDALMISLTPKVTCVVDVSEDDPDVHVS FVDNKEVHTAWTQPREAQYNSTFRVVSALPIQHQDWMRGKEFKCKVNNKALPA PIERTISKPKGRAQTPQVYTIPPPREQMSKKKVSILTCLVTNFFSEAISVEWER NGELEQDYKNTPPILDSGTYFLYSKLTVDTD SWLQGEIFTCSVVHEALHNHH TQKNLSRSPELELN ~~ET~~ CAEAQDGEGLDGLWTTITIFISLFLLSVCYSASVTFLFK VKWIFSSVVQVKQTAIPDYRNMIGQGA
1197	Constant Region of Murine Kappa Light Chain	ADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSRQNGVLN SWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC
1198	DNA Constant Region of Murine Kappa Light Chain	GCAGATGCTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAAC ATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAAAGACA TCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAAC AGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCCT CACGTTGACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCA CTCACAAGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAATGAGTGT
1199	Constant Region of murine	QPKSSPSVTLFPPSSEELTNKATLVCTITDFYPGVVTVDWKVDGTPVTQGME TTQPSKQSNKYMSSYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS
1200	Lambda Light Chain	QPKSTPTLTVFPPSSEELKENKATLVCLISNFSPSGVTVAWKANGTPITQGVD TSNPTKEGNKFMASSFLHLTSDQWRSHNSFTCQVTHEGDTVEKSLSPAECLE
1201		

	(subclasses 1, 2, and 3)	QPKSTPTLTMFPPSPEELQENKATLVCLISNFSPSGVTVAWKANGTPITQGVD TSNPTKEDNKYMASSFLHLTSDQWRSHNSFTCQVTHEGDTVEKSLSPAEC
1202	Constant Region of human Heavy Chain (hIgG1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNH YTQKSLSLSPG
1203	DNA Constant Region of human Heavy Chain (hIgG1)	GCCAGCACAAAAGGGCCCAGTGTGTTCGCTCGCACCAAGCAGCAAATCAAC GTCAGGCGGCACAGCCGCGTTGGGTTGCCTTGTAAGACTACTTCCCAGAAC CAGTTACGGTGTTCATGGAACAGTGGTGCCTCAGAGCGGCGTTCATACCTTC CCCGCCGTACTTCAGAGTTCAGGTCTTTACTCACTTTCCAGCGTGGTCACAGT ACCGTCAAGCTCTCTTGAACACAGACATATATCTGTAACGTAAATCATAAGC CTAGCAATACCAAAGTCGATAAACGAGTGAACCCAAGAGTTGTGATAAAACC CACACCTGTCCCCCTTGCCCGGCACCGGAAGTGTGGGTGGTCCATCAGTATT CTTGTTTCCGCCTAAGCCAAAGGACACACTGATGATATCCAGAACTCCAGAGG TTACGTGCGTAGTCGTGGACGTCAGTCATGAAGACCCCGAAGTTAAGTTCAAC TGGTACGTGGATGGTGTGGAAGTACATAATGCGAAGACGAAACCCAGGGAAGA ACAATATAACTCAACTTATAGGGTAGTCAGCGTCTTGACTGTACTTCACCAAG ATTGGTTGAATGGCAAAGAGTACAAATGCAAGGTAAGCAACAAAGCATTGCCT GCGCCAATCGAAAAGACTATCTCAAAGCAAAGGGCCAGCCACGCGAACCACA AGTGTATACATTGCCGCCCAGTCGGGAAGAAATGACGAAAAATCAAGTCAGTC TCACATGCCTCGTGAAAGGATTTTATCCCTCTGACATAGCTGTGGAGTGGGAA AGTAATGGCCAACCCGAAAATAATTACAAAACGACGCCTCCCGTTTTGGACTC AGATGGGAGTTTTTTCTTTACAGTAAGCTGACGGTTGACAAAAGCAGGTGGC AACAAGGGAACGTCTTTTCTTGTAGTGTGATGCATGAGGCGCTCCACAATCAT TAACTCAAAAATCCTTGAGCCTGTCTCCAGGC
1204	Constant Region of Heavy Chain (hIgG2)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVEC PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQ PENNYKTTTPMLDSGDSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQK SLSLSPGK

1205	Constant Region of Heavy Chain (hIgG3)	ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGD THTCPRCPEPKSCDTPPCPRCPEPKSCDTPPCPRCPEPKSCDTPPCPRC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFKWYVDGV EVHNAKTKPREEQYNSTFRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPE NNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMEALHNRFQKSL SLSPGK
1206	Constant Region of human Heavy Chain (hIgG4)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVESKYGPCC PSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK
1207	Constant Region of human	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGV ETTKPSKQSNNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
1208	Light Chain (hIgG	GQPKAAPSVTTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
1209	Lambda, subclasses 1, 2, 3, 6,	GQPKAAPSVTTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
1210	and 7)	GQPKAAPSVTTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGV ETTTPSKQSNNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECs
1211		GQPKAAPSVTTLFPPSSEELQANKATLVCLVSDFNPGAVTVAWKADGSPVKGV ETTKPSKQSNNKYAASSYLSTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECs
1212	Constant Region of human Light Chain (hIgG Kappa)	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

1213	DNA Constant Region of human Light Chain (hIgG kappa)	ACTGTCGCAGCACCTTCTGTCTTCATCTTTCCGCCAAGCGATGAACAGTTGAA ATCTGGAACAGCGTCCGTGGTGTGCCTGCTCAACAACCTTCTATCCTCGGGAAG CGAAGGTGCAATGGAAGGTAGATAATGCTCTTCAGAGTGGCAATTCCCAAGAG TCAGTTACGGAGCAAGATAGCAAGGACAGCACGTATTCCTGTCTAGTACGTT GACTCTTTCCAAGGCTGACTATGAAAAGCACAAGGTGTATGCCTGTGAAGTAA CCCACCAAGGTCTCTCAAGTCCTGTAACCTAAGAGCTTTAATCGAGGAGAATGC
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[0193] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 299, 343, and 395, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 460, 518, and 557, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 299, 343, 395, 460, 518, and 557, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 299, 343, 395, 460, 518, or 557.

[0194] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1140, 1141, and 395, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 460, 518, and 557, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1140, 1141, 395, 460, 518, and 557, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1140, 1141, 395, 460, 518, and 557.

[0195] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1155, 1156, and 1157, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1158, NAK, and SEQ ID NO: 557, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1155, SEQ ID NO: 1156, SEQ ID NO: 1157, SEQ ID NO: 1158, NAK, and SEQ ID NO: 557, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1155, SEQ ID NO: 1156, SEQ ID NO: 1157, SEQ ID NO: 1158, NAK, and SEQ ID NO: 557.

[0196] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 304, 347, and 400, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 464, 523, and 562, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 304, 347, 400, 464, 523, and 562, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 304, 347, 400, 464, 523, and 562.

[0197] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1142, 1143, and 400, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 464, 523, and 562, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1142, 1143,

400, 464, 523, and 562, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1142, 1143, 400, 464, 523, and 562.

[0198] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1160, 1161, and 1162, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1163, WAS, and SEQ ID NO: 562, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1160, SEQ ID NO: 1161, SEQ ID NO: 1162, SEQ ID NO: 1163, WAS, and SEQ ID NO: 562, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1160, SEQ ID NO: 1161, SEQ ID NO: 1162, SEQ ID NO: 1163, WAS, and SEQ ID NO: 562.

[0199] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 314, 341, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1154, 529, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 314, 341, 410, 1154, 529, and 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 314, 341, 410, 1154, 529, and 571.

[0200] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1144, 1145, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC

CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1146, 529, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1144, 1145, 410, 1146, 529, and 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1144, 1145, 410, 1146, 529, and 571.

[0201] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1165, 1166, and 1167, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 473, RVS, and SEQ ID NO: 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1165, 1166, SEQ ID NO: 1167, SEQ ID NO: 473, RVS, and SEQ ID NO: 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1165, SEQ ID NO: 1166, SEQ ID NO: 1167, SEQ ID NO: 473, RVS, and SEQ ID NO: 571.

[0202] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 315, 341, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 474, 529, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 315, 341, 410, 474, 529, and 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 315, 341, 410, 474, 529, and 571.

[0203] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1147, 1148, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 474, 529, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1147, 1148, 410, 474, 529, and 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1147, 1148, 410, 474, 529, and 571.

[0204] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1168, 1169, and 1167, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1170, RVS, and SEQ ID NO: 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1168, SEQ ID NO: 1169, SEQ ID NO: 1167, SEQ ID NO: 1170, RVS, and SEQ ID NO: 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1168, SEQ ID NO: 1169, SEQ ID NO: 1167, SEQ ID NO: 1170, RVS, and SEQ ID NO: 571.

[0205] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 316, 341, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 475, 530, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 316, 341, 410, 475, 530, and

571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 316, 341, 410, 475, 530, and 571.

[0206] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1149, 1150, and 410, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 475, 530, and 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1149, 1150, 410, 475, 530, and 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1149, 1150, 410, 475, 530, and 571.

[0207] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1171, 1166, and 1167, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1172, RVS, and SEQ ID NO: 571, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1171, SEQ ID NO: 1166, SEQ ID NO: 1167, SEQ ID NO: 1172, RVS, and SEQ ID NO: 571, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1171, SEQ ID NO: 1166, SEQ ID NO: 1167, SEQ ID NO: 1172, RVS, and SEQ ID NO: 571.

[0208] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 325, 362, and 435, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2,

and LC CDR3 sequences comprise the sequences of SEQ ID NO: 495, 540, and 587, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 325, 362, 435, 495, 540, and 587, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 325, 362, 435, 495, 540, and 587.

[0209] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1152, 1153, and 435, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 495, 540, and 587, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1152, 1153, 435, 495, 540, and 587, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1152, 1153, 435, 495, 540, and 587.

[0210] In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a heavy chain complementary determining region 1 (HC CDR1), a HC CDR2, and/or a HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 sequences comprise the sequences of SEQ ID NO: 1173, 1174, and 1175, respectively. In some embodiments, the anti-tau antibody comprises at least one, two, three, or all of a LC CDR1, a LC CDR2 and/or an LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1176, YAS, and SEQ ID NO: 587, respectively. In some embodiments, the anti-tau antibody comprises a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2 and an LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 sequences comprise the sequences of SEQ ID NO: 1173, SEQ ID NO: 1174, SEQ ID NO: 1175, SEQ ID NO: 1176, YAS, and SEQ ID NO: 587, respectively. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NO: 1173, SEQ ID NO: 1174, SEQ ID NO: 1175, SEQ ID NO: 1176, YAS, and SEQ ID NO: 587.

[0211] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4; or encoded by the nucleotide sequence of SEQ ID NO: 150; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78; or encoded by the nucleotide sequence of SEQ ID NO: 224; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 4 and 78, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 150 and 224, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 150, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 224, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0212] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 9; or encoded by the nucleotide sequence of SEQ ID NO: 155; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 83; or encoded by the nucleotide sequence of SEQ ID NO: 229; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 9 and 83, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 155 and 229, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 155, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 229, or a sequence substantially

identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0213] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 21; or encoded by the nucleotide sequence of SEQ ID NO: 167; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 93; or encoded by the nucleotide sequence of SEQ ID NO: 241; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 21 and 93, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 167 and 241, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 167, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 241, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0214] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22; or encoded by the nucleotide sequence of SEQ ID NO: 168; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94; or encoded by the nucleotide sequence of SEQ ID NO: 242; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 22 and 94, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 168 and 242, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 168, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%,

97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 242, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0215] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 23; or encoded by the nucleotide sequence of SEQ ID NO: 169; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 95; or encoded by the nucleotide sequence of SEQ ID NO: 243; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 23 and 95, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 169 and 243, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 169, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 243, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0216] In some embodiments, the anti-tau antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 51; or encoded by the nucleotide sequence of SEQ ID NO: 197; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 122; or encoded by the nucleotide sequence of SEQ ID NO: 270; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the anti-tau antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 51 and 122, respectively; or encoded by the nucleotide sequences of SEQ ID NO: 197 and 270, respectively; or a sequence substantially identical (*e.g.*, having at least about 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) to any of the aforesaid sequences. In some embodiments, the nucleotide sequence

encoding the heavy chain variable region of the anti-tau antibody comprises the nucleotide sequence of SEQ ID NO: 197, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity); and/or the nucleotide sequence encoding the light chain variable region comprises the nucleotide sequence of SEQ ID NO: 270, or a sequence substantially identical (*e.g.*, having at least about 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity).

[0217] In some embodiments, the anti-tau antibody comprises a VH and/or VL encoded by a codon-optimized nucleic acid sequence. Codon-optimization may be achieved by any method known to one with skill in the art such as, but not limited to, by a method according to Genescript, EMBOSS, Bioinformatics, NUS, NUS2, Geneinfinity, IDT, NUS3, GregThatcher, Insilico, Molbio, N2P, Snapgene, and/or VectorNTI.

[0218] Anti-tau antibodies according to the present disclosure may be prepared using any of the antibody sequences (*e.g.*, variable domain amino acid sequences, variable domain amino acid sequence pairs, CDR amino acid sequences, variable domain CDR amino acid sequence sets, variable domain CDR amino acid sequence set pairs, and/or framework region amino acid sequences) presented herein, any may be prepared, for example, as monoclonal antibodies, multispecific antibodies, chimeric antibodies, antibody mimetics, scFvs, or antibody fragments.

[0219] In some embodiments, anti-tau antibodies using any of the antibody sequences presented herein may be prepared as IgA, IgD, IgE, IgG, or IgM antibodies. When prepared as mouse IgG antibodies, anti-tau antibodies may be prepared as IgG1, IgG2a, IgG2b, IgG2c, or IgG3 isotypes. When prepared as human IgG antibodies, anti-tau antibodies may be prepared as IgG1, IgG2, IgG3, or IgG4 isotypes. Anti-tau antibodies prepared as human or humanized antibodies may include one or more human constant domains.

[0220] This present disclosure provides in some embodiments, a nucleic acid (*e.g.*, an isolated nucleic acid) encoding any of the above described antibodies, and viral genomes, vectors, AAV particles, and cells comprising the same.

Tau protein antigens

[0221] In some embodiments, anti-tau antibodies bind to tau protein antigens, *e.g.*, an epitope on a tau protein. Tau protein antigens may include human microtubule-associated protein tau, isoform 2 (SEQ ID NO: 920) or fragments thereof. Tau protein antigens may include ePHF or fragments thereof. Tau protein antigens may include one or more phosphorylated residues. Such phosphorylated residues may correspond to those found with pathological tau. In some embodiments tau protein antigens include any of those listed in Table 8. In the Table, phosphorylated residues associated with each antigen are double-underlined. In some embodiments, tau proteins may include variants (*e.g.*, phosphorylated or unphosphorylated variants) or fragments of the sequences listed.

Table 8. Tau protein antigen sequences

Antigen	Sequence	SEQ ID NO
human microtubule-associated protein tau, isoform 2	MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ TPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIP EGTTAEEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADG KTKIATPRGAAPPQGQKQANATRIPAKTPPAPKTPPSSGEPPKSGDRSG YSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQT APVPMPLKKNVSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSK DNIKHVPGGGSVQIVYKPVDLKVTSCGSLGNIHHKPGGGQVEVKSEK LDFKDRVQSKIGSLDNITHVPGGNKKIETHKLTFRENAKAKTDHGAEI VYKSPVVS GDTSPRHL SNVSSTGSIDMVDS PQLATLADEV SASLAKQGL	920
PT3 epitope peptide (pT212/pT217)	TPGSRSRTPSLPTPPTREP <u>K</u>	921
Peptide 5 (pT212/pS214/pT217)	GTPGSRSRTPSLPTPPTRE	922
Peptide 12 (pS396/pS404/pS409)	RENAKAKTDHGAEIVYKSPVVS GDTSPRHL SNVSSTG	923
Peptide 1 (AT120 epitope)	PTREP <u>K</u> KV	924
6C5 epitope peptide	ARMVSKS	925
UCB D & PT76 epitope peptide	SPSSAKSRLQTAPVPMPLKKNVKS	926

[0222] In some embodiments, anti-tau antibodies of the present disclosure bind to tau protein epitopes on tau protein antigens described herein. Such tau protein epitopes may include or be included within a tau protein antigen amino acid sequence listed in Table 8. In some embodiments, anti-tau antibodies of the present disclosure bind to tau protein epitopes that include a region formed by a complex of at least two tau proteins.

[0223] In some embodiments, disclosed herein is an encoded an antibody that competes for binding to tau with the aforesaid antibodies. In some embodiments, disclosed herein is an antibody that binds to the same epitope as, substantially the same epitope as, an epitope that overlaps with, or an epitope that substantially overlaps with, the epitope of the aforesaid anti-tau antibody.

[0224] In some embodiment, compete or cross-compete refers to the ability of an antibody to interfere with binding of an anti-tau antibody, *e.g.*, an anti-tau antibody provided herein, to a target,

e.g., tau protein. The interference with binding can be direct or indirect (*e.g.*, through an allosteric modulation of the antibody or the target). The extent to which an antibody is able to interfere with the binding of another antibody to the target, and therefore whether it can be said to compete, can be determined using a competition binding assay, for example, a FACS assay, an ELISA or BIACORE assay. In some embodiments, a competition binding assay is a quantitative competition assay. In some embodiments, a first anti-tau antibody is said to compete for binding to the target with a second anti-tau antibody when the binding of the first antibody to the target is reduced by 10% or more, *e.g.*, 20% or more, 30% or more, 40% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, 99% or more in a competition binding assay (*e.g.*, a competition assay described herein).

[0225] In some embodiments, an epitope comprises the moieties of an antigen (*e.g.*, a tau protein antigen) that specifically interact with an antibody. Such moieties, referred to herein as epitopic determinants, typically comprise, or are part of, elements such as amino acid side chains or sugar side chains. An epitopic determinant can be defined by methods known in the art or disclosed herein, *e.g.*, by crystallography or by hydrogen-deuterium exchange. At least one or some of the moieties on the antibody, that specifically interact with an epitopic determinant, are typically located in a CDR(s). Typically, an epitope has a specific three dimensional structural characteristics. Typically, an epitope has specific charge characteristics. Some epitopes are linear epitopes while others are conformational epitopes.

[0226] In an embodiment, an epitopic determinant is a moiety on the antigen, *e.g.*, such as amino acid side chain or sugar side chain, or part thereof, which, when the antigen and antibody are co-crystallized, is within a predetermined distance, *e.g.*, within 5 Angstroms, of a moiety on the antibody, referred to herein as a crystallographic epitopic determinant. In some embodiments, the crystallographic epitopic determinants of an epitope are collectively referred to as a crystallographic epitope.

[0227] A first antibody binds the same epitope as a second antibody (*e.g.*, a reference antibody, *e.g.*, an antibody disclosed herein) if the first antibody specifically interacts with the same epitopic determinants on the antigen as does the second or reference antibody, *e.g.*, when interaction is measured in the same way for both the antibody and the second or reference antibody. Epitopes that overlap share at least one epitopic determinant. A first antibody binds an overlapping epitope with a second antibody (*e.g.*, a reference antibody, *e.g.*, an antibody disclosed herein) when both antibodies specifically interact with a common epitopic determinant. A first and a second antibody (*e.g.*, a reference antibody, *e.g.*, an antibody disclosed herein) bind substantially overlapping epitopes if at least half of the epitopic determinants of the second or reference antibody are found as epitopic determinants in the epitope of the first antibody. A first and a second antibody (*e.g.*, a reference antibody, *e.g.*, an antibody disclosed herein) bind substantially the same epitope if the first antibody

binds at least half of the core epitopic determinants of the epitope of the second or reference antibody, wherein the core epitopic determinants are defined by crystallography.

Epitope specificity

[0228] Antibodies of the present disclosure may bind to tau protein epitopes, which may include or be included within the residues of SEQ ID NOs: 920-926. Antibodies may compete for binding to tau protein epitopes with other anti-tau antibodies, including, but not limited to, AT100, AT120, PT3, C10.2, PT76, IPN002, 6C5, and UCB D. Tau protein epitopes may include C-terminal residues 409-436 of human tau (SEQ ID NO: 920). Such epitopes may include residues 413-430 of human tau (SEQ ID NO: 920). Antibody binding to such residues may exhibit a K_D of from about 0.1 nM to about 0.5 nM. In some embodiments, tau protein epitopes may include residues 55-76, 159-194, 219-247, and/or 381-426 of human tau (SEQ ID NO: 920). Such epitopes may include residues 57-72, 175-191, 223-238, and/or 383-400 of human tau (SEQ ID NO: 920). Antibodies binding to such residues may exhibit a K_D of from about 0.5 nM to about 5 nM.

[0229] In some embodiments, the present disclosure provides antibodies that compete for binding with second antibodies to tau protein epitopes. Such epitopes may include one or more of residues 32-49, 55-76, 57-72, 159-194, 175-191, 185-200, 219-247, 223-238, 381-426, 383-400, 409-436, and 413-430 of human tau (SEQ ID NO: 920).

[0230] Tau protein epitopes may include one or more of residues 409-436 and 413-430 of human tau (SEQ ID NO: 920). Second antibodies competing for binding to such epitopes may include variable domain pairs selected from the group consisting of: a VH with the amino acid sequence of SEQ ID NO: 21 and a VL with the amino acid sequence of SEQ ID NO: 93; a VH with the amino acid sequence of SEQ ID NO: 22 and a VL with the amino acid sequence of SEQ ID NO: 94; and a VH with the amino acid sequence of SEQ ID NO: 23 and a VL with the amino acid sequence of SEQ ID NO: 95.

[0231] Antibodies competing for tau epitope binding with such second antibodies may include a CDRH1 that includes the amino acid sequence of G [F/Y] TFT [R/I] [Y/F] (SEQ ID NO: 931), or more generally G-X1-TFT-X2-X3 (SEQ ID NO: 932), where X1, X2, and X3 may be any amino acid, *e.g.*, X1 and/or X3 may be an amino acid with a hydrophobic and/or aromatic side chain, such as F or Y, and/or X2 may be a positively charged residue (such as R, K, H) or a residue with aliphatic side chain (such as A, V, I, or L); a CDRH2 that includes the amino acid sequence NPNNGG (SEQ ID NO: 341); a CDRH3 that includes the amino acid sequence GTGTGAMDY (SEQ ID NO: 410); a CDRL1 that includes the amino acid sequence RSSQSLVH [N/S] NG [I/N] T [H/Y] LY (SEQ ID NO: 933), or more generally RSSQSLVH-X1-NG-X2-T-X3-LY (SEQ ID NO: 934), where X1, X2, and X3 may be any amino acid, *e.g.*, X1 is Q/N/S/T and/or X2 is A/V/I/L/Q/N and/or X3 is H/R/K/Y/F; a CDRL2 that includes the amino acid sequence RVS [N/S] RFS (SEQ ID NO: 935), or more generally RVSXRF (SEQ ID NO: 936), where X may be any amino acid, *e.g.*, X1 is

Q/N/S/T; and/or a CDRL3 that includes the amino acid sequence FQGTHVPRT (SEQ ID NO: 571).

[0232] In some embodiments, the CDRH1 may include the amino acid sequence G[F/Y]TFT[R/I][Y/F] (SEQ ID NO: 931). The CDRH2 may include the amino acid sequence NPNNGG (SEQ ID NO: 341). The CDRH3 may include the amino acid sequence GTGTGAMDY (SEQ ID NO: 410). The CDRL1 may include the amino acid sequence RSSQSLVH [N/S] NG [I/N] T [H/Y] LY (SEQ ID NO: 933). The CDRL2 may include the amino acid sequence RVS [N/S] RFS (SEQ ID NO: 935). The CDRL3 may include the amino acid sequence FQGTHVPRT (SEQ ID NO: 571).

[0233] In some embodiments, tau protein epitopes may include one or more of residues 57-72, 175-191, 223-238, and 383-400 of human tau (SEQ ID NO: 920). Second antibodies competing for binding to such epitopes may include variable domain pairs selected from the group consisting of: a VH with the amino acid sequence of SEQ ID NO: 51 and a VL with the amino acid sequence of SEQ ID NO: 122; a VH with the amino acid sequence of SEQ ID NO: 53 and a VL with the amino acid sequence of SEQ ID NO: 124; a VH with the amino acid sequence of SEQ ID NO: 54 and a VL with the amino acid sequence of SEQ ID NO: 125; a VH with the amino acid sequence of SEQ ID NO: 56 and a VL with the amino acid sequence of SEQ ID NO: 125; a VH with the amino acid sequence of SEQ ID NO: 57 and a VL with the amino acid sequence of SEQ ID NO: 126; a VH with the amino acid sequence of SEQ ID NO: 35 and a VL with the amino acid sequence of SEQ ID NO: 107; and a VH with the amino acid sequence of SEQ ID NO: 48 and a VL with the amino acid sequence of SEQ ID NO: 120.

[0234] Antibodies competing for tau epitope binding with such second antibodies may include a CDRH1 that includes the amino acid sequence of GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964), or more generally GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), where X1-X3 may be any amino acid, *e.g.*, X1 is S/T/N/Q and/or X2 is S/T/F/Y and/or X3 is G/A/I/L/V; a CDRH2 that includes the amino acid sequence YWDDD (SEQ ID NO: 362); a CDRH3 that includes the amino acid sequence R [R/V/K/S/G] [Y/R] [Y/absent] [S/absent] [absent/N] [G/S/Y/R] [Y/N/G] [G/A/Y/N] [M/F/Y] DY, or more generally R-X1-X2-X3-X4-X5-X6-X7-X8-X9-DY, where each of X1-X9 may be any amino acid and/or where one or more of X3-X5 may be absent, *e.g.*, X1 is R/K/H/A/V/I/L/G/S/T and/or X2 is Y/F/R/K/H and/or X3 is Y/F/absent and/or X4 is S/T/absent and/or X5 is N/Q/absent and/or X6 is G/A/V/I/L/S/T/Y/F/R/K/H and/or X7 is Y/F/N/Q/G/A/V/I/L and/or X8 is G/A/V/I/L/Y/F/N/Q and/or X9 is M/F/Y; a CDRL1 that includes the amino acid sequence [K/S] [S/A] S [Q/S] S [L/I/V] [L/S] [N/S/D] [D/S/T] [V/G/D/Y] [N/G/absent] [Q/absent] [K/absent] [N/T/absent] [Y/absent] [L/absent] [A/H/N], or more generally X1-X2-S-X3-S-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15, where each

of X1-X15 may be any amino acid and/or where one or more of X9-X14 may be absent, *e.g.*, X1 is K/R/H/S/T and/or X2 is S/T/A/V/I/L and/or X3 is Q/N/S/T and/or X4 is L/I/V/A and/or X5 is A/V/I/L/S/T and/or X6 is N/Q/S/T/D/E and/or X7 is D/E/S/T and/or X8 is G/A/V/I/L/D/E/Y/F and/or X9 is N/Q/G/A/absent and/or X10 is Q/N/absent and/or X11 is K/R/H/absent and/or X12 is N/Q/T/S/absent and/or X13 is Y/F/absent and/or X14 is A/V/I/L/absent and/or X15 is A/V/I/L/H/K/R/N/Q; a CDRL2 that includes the amino acid sequence [Y/G/L/R] [A/T/V] S [N/T/K] [R/L] [C/E/D/A] [T/S], or more generally X1-X2-S-X3-X4-X5-X6, where X1-X6 may be any amino acid, *e.g.*, X1 is Y/F/G/A/V/I/L/R/K/H and/or X2 is A/V/I/L/T/S and/or X3 is N/Q/T/S/K/R/H and/or X4 is R/K/H/A/V/I/L and/or X5 is C/S/E/D/A/V/I/L and/or X6 is T/S; and/or a CDRL3 that includes the amino acid sequence [W/Q] [Q/N] [G/D] [T/S/Y/H] [H/S/R] [F/I/S/H] P [Q/R/L/Y] [absent/Y] T, or more generally X1-X2-X3-X4-X5-X6-P-X7-X8-T, where each of X1-X8 may be any amino acid and/or where X8 may be absent, *e.g.*, X1 is Q/N/W/F/Y and/or X2 is Q/N and/or X3 is G/A/V/I/L/D/E and/or X4 is T/S/Y/F/H/K/R and/or X5 is H/K/R/S/T and/or X6 is F/Y/A/V/I/L/S/T/H/K/R and/or X7 is Q/N/R/K/H/A/V/I/L/Y/F and/or X8 is Y/F/absent.

[0235] The CDRH1 may include the amino acid sequence GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964). The CDRH2 may include the amino acid sequence YWDDD (SEQ ID NO: 362). The CDRH3 may include the amino acid sequence R [R/V/K/S/G] [Y/R] [Y/absent] [S/absent] [absent/N] [G/S/Y/R] [Y/N/G] [G/A/Y/N] [M/F/Y] DY. The CDRL1 may include the amino acid sequence [K/S] [S/A] S [Q/S] S [L/I/V] [L/S] [N/S/D] [D/S/T] [V/G/D/Y] [N/G/absent] [Q/absent] [K/absent] [N/T/absent] [Y/absent] [L/absent] [A/H/N]. The CDRL2 may include the amino acid sequence [Y/G/L/R] [A/T/V] S [N/T/K] [R/L] [C/E/D/A] [T/S]. The CDRL3 may include the amino acid sequence [W/Q] [Q/N] [G/D] [T/S/Y/H] [H/S/R] [F/I/S/H] P [Q/R/L/Y] [absent/Y] T.

II. VECTORIZATION

[0236] According to the present disclosure, compositions for delivering anti-tau antibodies or functional variants thereof by adeno-associated virus particles (AAVs) are provided. In some embodiments, an AAV particle, *e.g.*, an AAV particle as described herein, or plurality of particles, may be provided, *e.g.*, delivered, via any of several routes of administration, to a cell, tissue, organ, or organism, *in vivo*, *ex vivo*, or *in vitro*.

[0237] As used herein, an “AAV particle” is a virus which comprises a capsid and a viral genome with at least one payload region and at least one inverted terminal repeat (ITR) region.

[0238] As used herein, “viral genome” or “vector genome” refers to the nucleic acid sequence(s) encapsulated in an AAV particle. Viral genomes comprise at least one payload region encoding polypeptides, *e.g.*, antibodies, antibody-based compositions or fragments thereof.

[0239] As used herein, a “payload” or “payload region” is any nucleic acid molecule which encodes one or more polypeptides. At a minimum, a payload region comprises nucleic acid sequences that encode an antibody, an antibody-based composition, or a fragment thereof, but may also optionally comprise one or more functional or regulatory elements to facilitate transcriptional expression and/or polypeptide translation.

[0240] In some embodiments, AAV particles, viral genomes and/or payloads, and the methods of their use may be as described in WO2017189963 or WO2020223276, the contents of each of which are herein incorporated by reference in their entirety.

[0241] The nucleic acid sequences, viral genomes, and polypeptides disclosed herein may be engineered to contain modular elements and/or sequence motifs assembled to enable expression of an antibody or functional variant thereof, *e.g.*, an antibody described herein. In some embodiments, the nucleic acid sequence encodes an antibody comprising one or more of the CDRs (*e.g.*, heavy chain and/or light chain CDRs) of an antibody, a variable heavy (VH) chain region and/or variable light (VL) chain region, a heavy and/or light chain constant region, or a combination thereof. In some embodiments, the nucleic acid sequence encoding the antibody may also encode a linker, *e.g.*, such that the VH/heavy chain and the VL/light chain of the antibody are connected via a linker. In some embodiments, the viral genome may further comprise a promoter region, an intron, a Kozak sequence, an enhancer, or a polyadenylation sequence. The order of expression, structural position, or concatemer count (*e.g.*, the VH, VL, heavy chain, light chain, and/or linker) may be different within or among different payload regions. The identity, position and number of linkers expressed by payload regions may also vary. In some embodiments, the payload is a region comprising one or more humanized antibody sequences, such as but not limited to, a humanized antibody VL, light chain domain and/or a humanized antibody VH, heavy chain domain, or fragments thereof.

[0242] In some embodiments, the present disclosure provides methods for delivering an antibody (*e.g.*, an anti-tau antibody described herein) and/or a nucleic acid sequence encoding an antibody (*e.g.*, an anti-tau antibody described herein) comprised within the viral genome comprised within a recombinant, AAV particle (*e.g.*, an AAV particle described herein) to a cell, tissue, organ, or subject.

Adeno-associated viruses (AAVs) and AAV particles

[0243] In some embodiments, adeno-associated viruses (AAV) are small non-enveloped icosahedral capsid viruses of the Parvoviridae family characterized by a single stranded DNA viral genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. The Parvoviridae family comprises the Dependovirus genus which includes AAV. In some embodiments, the AAV is capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0244] The parvoviruses and other members of the Parvoviridae family are generally described in Kenneth I. Berns, “Parvoviridae: The Viruses and Their Replication,” Chapter 69 in *FIELDS VIROLOGY* (3d Ed. 1996), the contents of which are incorporated by reference in their entirety.

[0245] AAV have proven to be useful as a biological tool due to their relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload.

[0246] The wild-type AAV vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. Inverted terminal repeats (ITRs) traditionally cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. While not wishing to be bound by theory, an AAV viral genome typically comprises two ITR sequences. These ITRs have a characteristic T-shaped hairpin structure defined by a self-complementary region (145nt in wild-type AAV) at the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[0247] The wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are important for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a

non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In other words, VP1 is the full-length capsid sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region, are also changes to VP1 and VP2, however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid protein. While not wishing to be bound by theory, the AAV capsid protein typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3. As used herein, an “AAV serotype” is defined primarily by the AAV capsid. In some instances, the ITRs are also specifically described by the AAV serotype (*e.g.*, AAV2/9).

[0248] For use as a biological tool, the wild-type AAV viral genome can be modified to replace the rep/cap sequences with a nucleic acid sequence comprising a payload region with at least one ITR region. Typically, in recombinant AAV viral genomes there are two ITR regions. The rep/cap sequences can be provided *in trans* during production to generate AAV particles.

[0249] In addition to the encoded heterologous payload, AAV vectors may comprise the viral genome, in whole or in part, of any naturally occurring and/or recombinant AAV serotype nucleotide sequence or variant. AAV variants may have sequences of significant homology at the nucleic acid (genome or capsid) and amino acid levels (capsids), to produce constructs which are generally physical and functional equivalents, replicate by similar mechanisms, and assemble by similar mechanisms. Chiorini *et al.*, J. Vir. 71: 6823-33(1997); Srivastava *et al.*, J. Vir. 45:555-64 (1983); Chiorini *et al.*, J. Vir. 73:1309-1319 (1999); Rutledge *et al.*, J. Vir. 72:309-319 (1998); and Wu *et al.*, J. Vir. 74: 8635-47 (2000), the contents of each of which are incorporated herein by reference in their entirety.

[0250] In some embodiments, AAV particles of the present disclosure are recombinant AAV viral vectors which are replication defective and lacking sequences encoding functional Rep and Cap proteins within their viral genome. These defective AAV vectors may lack most or all parental coding sequences and essentially carry only one or two AAV ITR sequences and the nucleic acid of interest for delivery to a cell, a tissue, an organ, or an organism.

[0251] In some embodiments, the viral genome of the AAV particles of the present disclosure comprise at least one control element which provides for the replication, transcription, and translation of a coding sequence encoded therein. Not all of the control elements need always be present as long as the coding sequence is capable of being replicated, transcribed, and/or translated in an appropriate host cell. Non-limiting examples of expression control elements

include sequences for transcription initiation and/or termination, promoter and/or enhancer sequences, efficient RNA processing signals such as splicing and polyadenylation signals, sequences that stabilize cytoplasmic mRNA, sequences that enhance translation efficacy (*e.g.*, Kozak consensus sequence), sequences that enhance protein stability, and/or sequences that enhance protein processing and/or secretion.

[0252] According to the present disclosure, AAV particles for use in therapeutics and/or diagnostics comprise a virus that has been distilled or reduced to the minimum components necessary for transduction of a nucleic acid payload or cargo of interest. In this manner, AAV particles are engineered as vehicles for specific delivery while lacking the deleterious replication and/or integration features found in wild-type viruses.

[0253] AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. As used herein, a “vector” is any molecule or moiety which transports, transduces, or otherwise acts as a carrier of a heterologous molecule such as the nucleic acids described herein.

[0254] In addition to single stranded AAV viral genomes (*e.g.*, ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) viral genomes. scAAV vector genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the transduced cell.

[0255] In some embodiments, the AAV particle of the present disclosure is an scAAV.

[0256] In some embodiments, the AAV particle of the present disclosure is an ssAAV.

[0257] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV vectors (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0258] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles can be packaged efficiently and be used to successfully infect the target cells at high frequency and with minimal toxicity. In some embodiments, the capsids of the AAV particles are engineered according to the methods described in US Publication Number US20130195801, the contents of which are incorporated herein by reference in their entirety.

[0259] In some embodiments, the AAV particles comprising a payload region encoding the polypeptides may be introduced into mammalian cells.

AAV serotypes

[0260] In some embodiments, the AAV particle, *e.g.*, an AAV particle for the vectorized delivery of an antibody described herein (*e.g.*, an anti-tau antibody), may comprise or be derived

from any natural or recombinant AAV serotype. AAV particles of the present disclosure may comprise or be derived from any natural or recombinant AAV serotype. According to the present disclosure, the AAV particles may utilize or be based on a serotype or include a peptide selected from any of the following 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), PHP.S, AAV1, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV5, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9, AAV9 K449R, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84, AAV9.9, AAV10, AAV11, AAV12, AAV16.3, AAV24.1, AAV27.3, AAV42.12, AAV42-1b, AAV42-2, AAV42-3a, AAV42-3b, AAV42-4, AAV42-5a, AAV42-5b, AAV42-6b, AAV42-8, AAV42-10, AAV42-11, AAV42-12, AAV42-13, AAV42-15, AAV42-aa, AAV43-1, AAV43-12, AAV43-20, AAV43-21, AAV43-23, AAV43-25, AAV43-5, AAV44.1, AAV44.2, AAV44.5, AAV223.1, AAV223.2, AAV223.4, AAV223.5, AAV223.6, AAV223.7, AAV1-7/rh.48, AAV1-8/rh.49, AAV2-15/rh.62, AAV2-3/rh.61, AAV2-4/rh.50, AAV2-5/rh.51, AAV3.1/hu.6, AAV3.1/hu.9, AAV3-9/rh.52, AAV3-11/rh.53, AAV4-8/rh.64, AAV4-9/rh.54, AAV4-19/rh.55, AAV5-3/rh.57, AAV5-22/rh.58, AAV7.3/hu.7, AAV16.8/hu.10, AAV16.12/hu.11, AAV29.3/bb.1, AAV29.5/bb.2, AAV106.1/hu.37, AAV114.3/hu.40, AAV127.2/hu.41, AAV127.5/hu.42, AAV128.3/hu.44, AAV130.4/hu.48, AAV145.1/hu.53, AAV145.5/hu.54, AAV145.6/hu.55, AAV161.10/hu.60, AAV161.6/hu.61, AAV33.12/hu.17, AAV33.4/hu.15, AAV33.8/hu.16, AAV52/hu.19, AAV52.1/hu.20, AAV58.2/hu.25, AAVA3.3, AAVA3.4, AAVA3.5, AAVA3.7, AAVC1, AAVC2, AAVC5, AAV-DJ, AAV-DJ8, AAVF3, AAVF5, AAVH2, AAVrh.72, AAVhu.8, AAVrh.68, AAVrh.70, AAVpi.1, AAVpi.3, AAVpi.2, AAVrh.60, AAVrh.44, AAVrh.65, AAVrh.55, AAVrh.47, AAVrh.69, AAVrh.45, AAVrh.59, AAVhu.12, AAVH6, AAVLK03, AAVH-1/hu.1, AAVH-5/hu.3, AAVLG-10/rh.40, AAVLG-4/rh.38, AAVLG-9/hu.39, AAVN721-8/rh.43, AAVCh.5, AAVCh.5R1, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVCy.5R1, AAVCy.5R2, AAVCy.5R3, AAVCy.5R4, AAVcy.6, AAVhu.1, AAVhu.2, AAVhu.3, AAVhu.4, AAVhu.5, AAVhu.6, AAVhu.7, AAVhu.9, AAVhu.10, AAVhu.11, AAVhu.13, AAVhu.15, AAVhu.16, AAVhu.17, AAVhu.18, AAVhu.20, AAVhu.21, AAVhu.22,

AAVhu.23.2, AAVhu.24, AAVhu.25, AAVhu.27, AAVhu.28, AAVhu.29, AAVhu.29R, AAVhu.31, AAVhu.32, AAVhu.34, AAVhu.35, AAVhu.37, AAVhu.39, AAVhu.40, AAVhu.41, AAVhu.42, AAVhu.43, AAVhu.44, AAVhu.44R1, AAVhu.44R2, AAVhu.44R3, AAVhu.45, AAVhu.46, AAVhu.47, AAVhu.48, AAVhu.48R1, AAVhu.48R2, AAVhu.48R3, AAVhu.49, AAVhu.51, AAVhu.52, AAVhu.54, AAVhu.55, AAVhu.56, AAVhu.57, AAVhu.58, AAVhu.60, AAVhu.61, AAVhu.63, AAVhu.64, AAVhu.66, AAVhu.67, AAVhu.14/9, AAVhu.t 19, AAVrh.2, AAVrh.2R, AAVrh.8, AAVrh.8R, AAVrh.10, AAVrh.12, AAVrh.13, AAVrh.13R, AAVrh.14, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.20, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.37R2, AAVrh.38, AAVrh.39, AAVrh.40, AAVrh.46, AAVrh.48, AAVrh.48.1, AAVrh.48.1.2, AAVrh.48.2, AAVrh.49, AAVrh.51, AAVrh.52, AAVrh.53, AAVrh.54, AAVrh.56, AAVrh.57, AAVrh.58, AAVrh.61, AAVrh.64, AAVrh.64R1, AAVrh.64R2, AAVrh.67, AAVrh.73, AAVrh.74, AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAV, BAAV, caprine AAV, bovine AAV, AAVhE1.1, AAVhEr1.5, AAVhEr1.14, AAVhEr1.8, AAVhEr1.16, AAVhEr1.18, AAVhEr1.35, AAVhEr1.7, AAVhEr1.36, AAVhEr2.29, AAVhEr2.4, AAVhEr2.16, AAVhEr2.30, AAVhEr2.31, AAVhEr2.36, AAVhEr1.23, AAVhEr3.1, AAV2.5T , AAV-PAEC, AAV-LK01, AAV-LK02, AAV-LK03, AAV-LK04, AAV-LK05, AAV-LK06, AAV-LK07, AAV-LK08, AAV-LK09, AAV-LK10, AAV-LK11, AAV-LK12, AAV-LK13, AAV-LK14, AAV-LK15, AAV-LK16, AAV-LK17, AAV-LK18, AAV-LK19, AAV-PAEC2, AAV-PAEC4, AAV-PAEC6, AAV-PAEC7, AAV-PAEC8, AAV-PAEC11, AAV-PAEC12, AAV-2-pre-miRNA-101 , AAV-8h, AAV-8b, AAV-h, AAV-b, AAV SM 10-2 , AAV Shuffle 100-1 , AAV Shuffle 100-3, AAV Shuffle 100-7, AAV Shuffle 10-2, AAV Shuffle 10-6, AAV Shuffle 10-8, AAV Shuffle 100-2, AAV SM 10-1, AAV SM 10-8 , AAV SM 100-3, AAV SM 100-10, BNP61 AAV, BNP62 AAV, BNP63 AAV, AAVrh.50, AAVrh.43, AAVrh.62, AAVrh.48, AAVhu.19, AAVhu.11, AAVhu.53, AAV4-8/rh.64, AAVLG-9/hu.39, AAV54.5/hu.23, AAV54.2/hu.22, AAV54.7/hu.24, AAV54.1/hu.21, AAV54.4R/hu.27, AAV46.2/hu.28, AAV46.6/hu.29, AAV128.1/hu.43, true type AAV (ttAAV), UPENN AAV 10, Japanese AAV 10 serotypes, AAV CBr-7.1, AAV CBr-7.10, AAV CBr-7.2, AAV CBr-7.3, AAV CBr-7.4, AAV CBr-7.5, AAV CBr-7.7, AAV CBr-7.8, AAV CBr-B7.3, AAV CBr-B7.4, AAV CBr-E1, AAV CBr-E2, AAV CBr-E3, AAV CBr-E4, AAV CBr-E5, AAV CBr-e5, AAV CBr-E6, AAV CBr-E7, AAV CBr-E8, AAV CHt-1, AAV CHt-2, AAV CHt-3, AAV CHt-6.1, AAV CHt-6.10, AAV CHt-6.5, AAV CHt-6.6, AAV CHt-6.7, AAV CHt-6.8, AAV CHt-P1, AAV CHt-P2, AAV CHt-P5, AAV CHt-P6, AAV CHt-P8, AAV CHt-P9, AAV CKd-1, AAV CKd-10, AAV CKd-2, AAV CKd-3, AAV CKd-4, AAV CKd-6, AAV CKd-7, AAV CKd-8, AAV CKd-B1, AAV CKd-B2, AAV CKd-B3, AAV CKd-

B4, AAV CKd-B5, AAV CKd-B6, AAV CKd-B7, AAV CKd-B8, AAV CKd-H1, AAV CKd-H2, AAV CKd-H3, AAV CKd-H4, AAV CKd-H5, AAV CKd-H6, AAV CKd-N3, AAV CKd-N4, AAV CKd-N9, AAV CLg-F1, AAV CLg-F2, AAV CLg-F3, AAV CLg-F4, AAV CLg-F5, AAV CLg-F6, AAV CLg-F7, AAV CLg-F8, AAV CLv-1, AAV CLv1-1, AAV Clv1-10, AAV CLv1-2, AAV CLv-12, AAV CLv1-3, AAV CLv-13, AAV CLv1-4, AAV Clv1-7, AAV Clv1-8, AAV Clv1-9, AAV CLv-2, AAV CLv-3, AAV CLv-4, AAV CLv-6, AAV CLv-8, AAV CLv-D1, AAV CLv-D2, AAV CLv-D3, AAV CLv-D4, AAV CLv-D5, AAV CLv-D6, AAV CLv-D7, AAV CLv-D8, AAV CLv-E1, AAV CLv-K1, AAV CLv-K3, AAV CLv-K6, AAV CLv-L4, AAV CLv-L5, AAV CLv-L6, AAV CLv-M1, AAV CLv-M11, AAV CLv-M2, AAV CLv-M5, AAV CLv-M6, AAV CLv-M7, AAV CLv-M8, AAV CLv-M9, AAV CLv-R1, AAV CLv-R2, AAV CLv-R3, AAV CLv-R4, AAV CLv-R5, AAV CLv-R6, AAV CLv-R7, AAV CLv-R8, AAV CLv-R9, AAV CSp-1, AAV CSp-10, AAV CSp-11, AAV CSp-2, AAV CSp-3, AAV CSp-4, AAV CSp-6, AAV CSp-7, AAV CSp-8, AAV CSp-8.10, AAV CSp-8.2, AAV CSp-8.4, AAV CSp-8.5, AAV CSp-8.6, AAV CSp-8.7, AAV CSp-8.8, AAV CSp-8.9, AAV CSp-9, AAV.hu.48R3, AAV.VR-355, AAV3B, AAV4, AAV5, AAVF1/HSC1, AAVF11/HSC11, AAVF12/HSC12, AAVF13/HSC13, AAVF14/HSC14, AAVF15/HSC15, AAVF16/HSC16, AAVF17/HSC17, AAVF2/HSC2, AAVF3/HSC3, AAVF4/HSC4, AAVF5/HSC5, AAVF6/HSC6, AAVF7/HSC7, AAVF8/HSC8, and/or AAVF9/HSC9 and variants thereof.

[0261] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Publication No. US20030138772, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO: 5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10 (amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772), AAV16.3 (US20030138772 SEQ ID NO: 10), AAV29.3/bb.1 (US20030138772 SEQ ID NO: 11), AAV29.4 (US20030138772 SEQ ID NO: 12), AAV29.5/bb.2 (US20030138772 SEQ ID NO: 13), AAV1.3 (US20030138772 SEQ ID NO: 14), AAV13.3 (US20030138772 SEQ ID NO: 15), AAV24.1 (US20030138772 SEQ ID NO: 16), AAV27.3 (US20030138772 SEQ ID NO: 17), AAV7.2 (US20030138772 SEQ ID NO: 18), AAVC1 (US20030138772 SEQ ID NO: 19), AAVC3 (US20030138772 SEQ ID NO: 20), AAVC5 (US20030138772 SEQ ID NO: 21), AAVF1 (US20030138772 SEQ ID NO: 22), AAVF3 (US20030138772 SEQ ID NO: 23), AAVF5 (US20030138772 SEQ ID NO: 24),

AAVH6 (US20030138772 SEQ ID NO: 25), AAVH2 (US20030138772 SEQ ID NO: 26), AAV42-8 (US20030138772 SEQ ID NO: 27), AAV42-15 (US20030138772 SEQ ID NO: 28), AAV42-5b (US20030138772 SEQ ID NO: 29), AAV42-1b (US20030138772 SEQ ID NO: 30), AAV42-13 (US20030138772 SEQ ID NO: 31), AAV42-3a (US20030138772 SEQ ID NO: 32), AAV42-4 (US20030138772 SEQ ID NO: 33), AAV42-5a (US20030138772 SEQ ID NO: 34), AAV42-10 (US20030138772 SEQ ID NO: 35), AAV42-3b (US20030138772 SEQ ID NO: 36), AAV42-11 (US20030138772 SEQ ID NO: 37), AAV42-6b (US20030138772 SEQ ID NO: 38), AAV43-1 (US20030138772 SEQ ID NO: 39), AAV43-5 (US20030138772 SEQ ID NO: 40), AAV43-12 (US20030138772 SEQ ID NO: 41), AAV43-20 (US20030138772 SEQ ID NO: 42), AAV43-21 (US20030138772 SEQ ID NO: 43), AAV43-23 (US20030138772 SEQ ID NO: 44), AAV43-25 (US20030138772 SEQ ID NO: 45), AAV44.1 (US20030138772 SEQ ID NO: 46), AAV44.5 (US20030138772 SEQ ID NO: 47), AAV223.1 (US20030138772 SEQ ID NO: 48), AAV223.2 (US20030138772 SEQ ID NO: 49), AAV223.4 (US20030138772 SEQ ID NO: 50), AAV223.5 (US20030138772 SEQ ID NO: 51), AAV223.6 (US20030138772 SEQ ID NO: 52), AAV223.7 (US20030138772 SEQ ID NO: 53), AAVA3.4 (US20030138772 SEQ ID NO: 54), AAVA3.5 (US20030138772 SEQ ID NO: 55), AAVA3.7 (US20030138772 SEQ ID NO: 56), AAVA3.3 (US20030138772 SEQ ID NO: 57), AAV42.12 (US20030138772 SEQ ID NO: 58), AAV44.2 (US20030138772 SEQ ID NO: 59), AAV42-2 (US20030138772 SEQ ID NO: 9), or variants thereof.

[0262] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Publication No. US20150159173, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV2 (SEQ ID NO: 7 and 23 of US20150159173), rh20 (SEQ ID NO: 1 of US20150159173), rh32/33 (SEQ ID NO: 2 of US20150159173), rh39 (SEQ ID NO: 3, 20 and 36 of US20150159173), rh46 (SEQ ID NO: 4 and 22 of US20150159173), rh73 (SEQ ID NO: 5 of US20150159173), rh74 (SEQ ID NO: 6 of US20150159173), AAV6.1 (SEQ ID NO: 29 of US20150159173), rh.8 (SEQ ID NO: 41 of US20150159173), rh.48.1 (SEQ ID NO: 44 of US20150159173), hu.44 (SEQ ID NO: 45 of US20150159173), hu.29 (SEQ ID NO: 42 of US20150159173), hu.48 (SEQ ID NO: 38 of US20150159173), rh54 (SEQ ID NO: 49 of US20150159173), AAV2 (SEQ ID NO: 7 of US20150159173), cy.5 (SEQ ID NO: 8 and 24 of US20150159173), rh.10 (SEQ ID NO: 9 and 25 of US20150159173), rh.13 (SEQ ID NO: 10 and 26 of US20150159173), AAV1 (SEQ ID NO: 11 and 27 of US20150159173), AAV3 (SEQ ID NO: 12 and 28 of US20150159173), AAV6 (SEQ ID NO: 13 and 29 of US20150159173), AAV7 (SEQ ID NO: 14 and 30 of US20150159173), AAV8 (SEQ ID NO: 15 and 31 of US20150159173), hu.13 (SEQ ID NO: 16 and 32 of US20150159173), hu.26 (SEQ ID NO: 17 and 33 of US20150159173), hu.37 (SEQ ID

NO: 18 and 34 of US20150159173), hu.53 (SEQ ID NO: 19 and 35 of US20150159173), rh.43 (SEQ ID NO: 21 and 37 of US20150159173), rh2 (SEQ ID NO: 39 of US20150159173), rh.37 (SEQ ID NO: 40 of US20150159173), rh.64 (SEQ ID NO: 43 of US20150159173), rh.48 (SEQ ID NO: 44 of US20150159173), ch.5 (SEQ ID NO 46 of US20150159173), rh.67 (SEQ ID NO: 47 of US20150159173), rh.58 (SEQ ID NO: 48 of US20150159173), or variants thereof including, but not limited to Cy5R1, Cy5R2, Cy5R3, Cy5R4, rh.13R, rh.37R2, rh.2R, rh.8R, rh.48.1, rh.48.2, rh.48.1.2, hu.44R1, hu.44R2, hu.44R3, hu.29R, ch.5R1, rh64R1, rh64R2, AAV6.2, AAV6.1, AAV6.12, hu.48R1, hu.48R2, and hu.48R3.

[0263] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent No. US 7198951, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 1-3 of US 7198951), AAV2 (SEQ ID NO: 4 of US 7198951), AAV1 (SEQ ID NO: 5 of US 7198951), AAV3 (SEQ ID NO: 6 of US 7198951), and AAV8 (SEQ ID NO: 7 of US7198951).

[0264] In some embodiments, the AAV serotype may be, or have a mutation in the AAV9 sequence as described by N Pulicherla *et al.* (Molecular Therapy 19(6):1070-1078 (2011), herein incorporated by reference in its entirety), such as but not limited to, AAV9.9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84.

[0265] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent No. US 6156303, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV3B (SEQ ID NO: 1 and 10 of US 6156303), AAV6 (SEQ ID NO: 2, 7 and 11 of US 6156303), AAV2 (SEQ ID NO: 3 and 8 of US 6156303), AAV3A (SEQ ID NO: 4 and 9, of US 6156303), or derivatives thereof.

[0266] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Publication No. US20140359799, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV8 (SEQ ID NO: 1 of US20140359799), AAVDJ (SEQ ID NO: 2 and 3 of US20140359799), or variants thereof.

[0267] In some embodiments, the serotype may be AAVDJ or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm *et al.* (Journal of Virology 82(12): 5887-5911 (2008), herein incorporated by reference in its entirety). The amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). As a non-limiting example, the AAV-DJ sequence described as SEQ ID NO: 1 in US Patent No. 7,588,772, the contents of which are herein incorporated by reference in their entirety, may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). As another non-limiting example, may comprise three mutations: (1) K406R

where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[0268] In some embodiments, the AAV serotype may be, or have a sequence of AAV4 as described in International Publication No. WO1998011244, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV4 (SEQ ID NO: 1-20 of WO1998011244).

[0269] In some embodiments, the AAV serotype may be, or have a mutation in the AAV2 sequence to generate AAV2G9 as described in International Publication No. WO2014144229 and herein incorporated by reference in its entirety.

[0270] In some embodiments, the AAV serotype may be, or have a sequence as described in International Publication No. WO2005033321, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV3-3 (SEQ ID NO: 217 of WO2005033321), AAV1 (SEQ ID NO: 219 and 202 of WO2005033321), AAV106.1/hu.37 (SEQ ID No: 10 of WO2005033321), AAV114.3/hu.40 (SEQ ID No: 11 of WO2005033321), AAV127.2/hu.41 (SEQ ID NO:6 and 8 of WO2005033321), AAV128.3/hu.44 (SEQ ID No: 81 of WO2005033321), AAV130.4/hu.48 (SEQ ID NO: 78 of WO2005033321), AAV145.1/hu.53 (SEQ ID No: 176 and 177 of WO2005033321), AAV145.6/hu.56 (SEQ ID NO: 168 and 192 of WO2005033321), AAV16.12/hu.11 (SEQ ID NO: 153 and 57 of WO2005033321), AAV16.8/hu.10 (SEQ ID NO: 156 and 56 of WO2005033321), AAV161.10/hu.60 (SEQ ID No: 170 of WO2005033321), AAV161.6/hu.61 (SEQ ID No: 174 of WO2005033321), AAV1-7/rh.48 (SEQ ID NO: 32 of WO2005033321), AAV1-8/rh.49 (SEQ ID NOs: 103 and 25 of WO2005033321), AAV2 (SEQ ID NO: 211 and 221 of WO2005033321), AAV2-15/rh.62 (SEQ ID No: 33 and 114 of WO2005033321), AAV2-3/rh.61 (SEQ ID NO: 21 of WO2005033321), AAV2-4/rh.50 (SEQ ID No: 23 and 108 of WO2005033321), AAV2-5/rh.51 (SEQ ID NO: 104 and 22 of WO2005033321), AAV3.1/hu.6 (SEQ ID NO: 5 and 84 of WO2005033321), AAV3.1/hu.9 (SEQ ID NO: 155 and 58 of WO2005033321), AAV3-11/rh.53 (SEQ ID NO: 186 and 176 of WO2005033321), AAV3-3 (SEQ ID NO: 200 of WO2005033321), AAV33.12/hu.17 (SEQ ID NO:4 of WO2005033321), AAV33.4/hu.15 (SEQ ID No: 50 of WO2005033321), AAV33.8/hu.16 (SEQ ID No: 51 of WO2005033321), AAV3-9/rh.52 (SEQ ID NO: 96 and 18 of WO2005033321), AAV4-19/rh.55 (SEQ ID NO: 117 of WO2005033321), AAV4-4 (SEQ ID NO: 201 and 218 of WO2005033321), AAV4-9/rh.54 (SEQ ID NO: 116 of WO2005033321), AAV5 (SEQ ID NO: 199 and 216 of WO2005033321), AAV52.1/hu.20 (SEQ ID NO: 63 of WO2005033321), AAV52/hu.19 (SEQ ID NO: 133 of WO2005033321), AAV5-22/rh.58 (SEQ ID No: 27 of WO2005033321), AAV5-3/rh.57 (SEQ ID NO: 105 of WO2005033321), AAV5-

3/rh.57 (SEQ ID No: 26 of WO2005033321), AAV58.2/hu.25 (SEQ ID No: 49 of WO2005033321), AAV6 (SEQ ID NO: 203 and 220 of WO2005033321), AAV7 (SEQ ID NO: 222 and 213 of WO2005033321), AAV7.3/hu.7 (SEQ ID No: 55 of WO2005033321), AAV8 (SEQ ID NO: 223 and 214 of WO2005033321), AAVH-1/hu.1 (SEQ ID No: 46 of WO2005033321), AAVH-5/hu.3 (SEQ ID No: 44 of WO2005033321), AAVhu.1 (SEQ ID NO: 144 of WO2005033321), AAVhu.10 (SEQ ID NO: 156 of WO2005033321), AAVhu.11 (SEQ ID NO: 153 of WO2005033321), AAVhu.12 (WO2005033321 SEQ ID NO: 59), AAVhu.13 (SEQ ID NO: 129 of WO2005033321), AAVhu.14/AAV9 (SEQ ID NO: 123 and 3 of WO2005033321), AAVhu.15 (SEQ ID NO: 147 of WO2005033321), AAVhu.16 (SEQ ID NO: 148 of WO2005033321), AAVhu.17 (SEQ ID NO: 83 of WO2005033321), AAVhu.18 (SEQ ID NO: 149 of WO2005033321), AAVhu.19 (SEQ ID NO: 133 of WO2005033321), AAVhu.2 (SEQ ID NO: 143 of WO2005033321), AAVhu.20 (SEQ ID NO: 134 of WO2005033321), AAVhu.21 (SEQ ID NO: 135 of WO2005033321), AAVhu.22 (SEQ ID NO: 138 of WO2005033321), AAVhu.23.2 (SEQ ID NO: 137 of WO2005033321), AAVhu.24 (SEQ ID NO: 136 of WO2005033321), AAVhu.25 (SEQ ID NO: 146 of WO2005033321), AAVhu.27 (SEQ ID NO: 140 of WO2005033321), AAVhu.29 (SEQ ID NO: 132 of WO2005033321), AAVhu.3 (SEQ ID NO: 145 of WO2005033321), AAVhu.31 (SEQ ID NO: 121 of WO2005033321), AAVhu.32 (SEQ ID NO: 122 of WO2005033321), AAVhu.34 (SEQ ID NO: 125 of WO2005033321), AAVhu.35 (SEQ ID NO: 164 of WO2005033321), AAVhu.37 (SEQ ID NO: 88 of WO2005033321), AAVhu.39 (SEQ ID NO: 102 of WO2005033321), AAVhu.4 (SEQ ID NO: 141 of WO2005033321), AAVhu.40 (SEQ ID NO: 87 of WO2005033321), AAVhu.41 (SEQ ID NO: 91 of WO2005033321), AAVhu.42 (SEQ ID NO: 85 of WO2005033321), AAVhu.43 (SEQ ID NO: 160 of WO2005033321), AAVhu.44 (SEQ ID NO: 144 of WO2005033321), AAVhu.45 (SEQ ID NO: 127 of WO2005033321), AAVhu.46 (SEQ ID NO: 159 of WO2005033321), AAVhu.47 (SEQ ID NO: 128 of WO2005033321), AAVhu.48 (SEQ ID NO: 157 of WO2005033321), AAVhu.49 (SEQ ID NO: 189 of WO2005033321), AAVhu.51 (SEQ ID NO: 190 of WO2005033321), AAVhu.52 (SEQ ID NO: 191 of WO2005033321), AAVhu.53 (SEQ ID NO: 186 of WO2005033321), AAVhu.54 (SEQ ID NO: 188 of WO2005033321), AAVhu.55 (SEQ ID NO: 187 of WO2005033321), AAVhu.56 (SEQ ID NO: 192 of WO2005033321), AAVhu.57 (SEQ ID NO: 193 of WO2005033321), AAVhu.58 (SEQ ID NO: 194 of WO2005033321), AAVhu.6 (SEQ ID NO: 84 of WO2005033321), AAVhu.60 (SEQ ID NO: 184 of WO2005033321), AAVhu.61 (SEQ ID NO: 185 of WO2005033321), AAVhu.63 (SEQ ID NO: 195 of WO2005033321), AAVhu.64 (SEQ ID NO: 196 of WO2005033321), AAVhu.66 (SEQ ID NO: 197 of WO2005033321), AAVhu.67 (SEQ ID NO: 198 of WO2005033321), AAVhu.7 (SEQ ID NO: 150 of WO2005033321), AAVhu.8

(WO2005033321 SEQ ID NO: 12), AAVhu.9 (SEQ ID NO: 155 of WO2005033321), AAVLG-10/rh.40 (SEQ ID No: 14 of WO2005033321), AAVLG-4/rh.38 (SEQ ID NO: 86 of WO2005033321), AAVLG-4/rh.38 (SEQ ID No: 7 of WO2005033321), AAVN721-8/rh.43 (SEQ ID NO: 163 of WO2005033321), AAVN721-8/rh.43 (SEQ ID No: 43 of WO2005033321), AAVpi.1 (WO2005033321 SEQ ID NO: 28), AAVpi.2 (WO2005033321 SEQ ID NO: 30), AAVpi.3 (WO2005033321 SEQ ID NO: 29), AAVrh.38 (SEQ ID NO: 86 of WO2005033321), AAVrh.40 (SEQ ID NO: 92 of WO2005033321), AAVrh.43 (SEQ ID NO: 163 of WO2005033321), AAVrh.44 (WO2005033321 SEQ ID NO: 34), AAVrh.45 (WO2005033321 SEQ ID NO: 41), AAVrh.47 (WO2005033321 SEQ ID NO: 38), AAVrh.48 (SEQ ID NO: 115 of WO2005033321), AAVrh.49 (SEQ ID NO: 103 of WO2005033321), AAVrh.50 (SEQ ID NO: 108 of WO2005033321), AAVrh.51 (SEQ ID NO: 104 of WO2005033321), AAVrh.52 (SEQ ID NO: 96 of WO2005033321), AAVrh.53 (SEQ ID NO: 97 of WO2005033321), AAVrh.55 (WO2005033321 SEQ ID NO: 37), AAVrh.56 (SEQ ID NO: 152 of WO2005033321), AAVrh.57 (SEQ ID NO: 105 of WO2005033321), AAVrh.58 (SEQ ID NO: 106 of WO2005033321), AAVrh.59 (WO2005033321 SEQ ID NO: 42), AAVrh.60 (WO2005033321 SEQ ID NO: 31), AAVrh.61 (SEQ ID NO: 107 of WO2005033321), AAVrh.62 (SEQ ID NO: 114 of WO2005033321), AAVrh.64 (SEQ ID NO: 99 of WO2005033321), AAVrh.65 (WO2005033321 SEQ ID NO: 35), AAVrh.68 (WO2005033321 SEQ ID NO: 16), AAVrh.69 (WO2005033321 SEQ ID NO: 39), AAVrh.70 (WO2005033321 SEQ ID NO: 20), AAVrh.72 (WO2005033321 SEQ ID NO: 9), or variants thereof including, but not limited to, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVcy.6, AAVrh.12, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.25/42 15, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.14. Non limiting examples of variants include SEQ ID NO: 13, 15, 17, 19, 24, 36, 40, 45, 47, 48, 51-54, 60-62, 64-77, 79, 80, 82, 89, 90, 93-95, 98, 100, 101, 109-113, 118-120, 124, 126, 131, 139, 142, 151, 154, 158, 161, 162, 165-183, 202, 204-212, 215, 219, 224-236, of WO2005033321, the contents of which are herein incorporated by reference in their entirety.

[0271] In some embodiments, the AAV serotype may be, or have a sequence as described in International Publication No. WO2015168666, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh8R (SEQ ID NO: 9 of WO2015168666), AAVrh8R A586R mutant (SEQ ID NO: 10 of WO2015168666), AAVrh8R R533A mutant (SEQ ID NO: 11 of WO2015168666), or variants thereof.

[0272] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent No. US9233131, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVhE1.1 (SEQ ID NO: 44 of US9233131),

AAVhEr1.5 (SEQ ID NO:45 of US9233131), AAVhEr1.14 (SEQ ID NO:46 of US9233131), AAVhEr1.8 (SEQ ID NO:47 of US9233131), AAVhEr1.16 (SEQ ID NO:48 of US9233131), AAVhEr1.18 (SEQ ID NO:49 of US9233131), AAVhEr1.35 (SEQ ID NO:50 of US9233131), AAVhEr1.7 (SEQ ID NO:51 of US9233131), AAVhEr1.36 (SEQ ID NO:52 of US9233131), AAVhEr2.29 (SEQ ID NO:53 of US9233131), AAVhEr2.4 (SEQ ID NO:54 of US9233131), AAVhEr2.16 (SEQ ID NO:55 of US9233131), AAVhEr2.30 (SEQ ID NO:56 of US9233131), AAVhEr2.31 (SEQ ID NO:58 of US9233131), AAVhEr2.36 (SEQ ID NO:57 of US9233131), AAVhEr1.23 (SEQ ID NO:53 of US9233131), AAVhEr3.1 (SEQ ID NO:59 of US9233131), AAV2.5T (SEQ ID NO:42 of US9233131), or variants thereof.

[0273] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent Publication No. US20150376607, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-PAEC (SEQ ID NO:1 of US20150376607), AAV-LK01 (SEQ ID NO:2 of US20150376607), AAV-LK02 (SEQ ID NO:3 of US20150376607), AAV-LK03 (SEQ ID NO:4 of US20150376607), AAV-LK04 (SEQ ID NO:5 of US20150376607), AAV-LK05 (SEQ ID NO:6 of US20150376607), AAV-LK06 (SEQ ID NO:7 of US20150376607), AAV-LK07 (SEQ ID NO:8 of US20150376607), AAV-LK08 (SEQ ID NO:9 of US20150376607), AAV-LK09 (SEQ ID NO:10 of US20150376607), AAV-LK10 (SEQ ID NO:11 of US20150376607), AAV-LK11 (SEQ ID NO:12 of US20150376607), AAV-LK12 (SEQ ID NO:13 of US20150376607), AAV-LK13 (SEQ ID NO:14 of US20150376607), AAV-LK14 (SEQ ID NO:15 of US20150376607), AAV-LK15 (SEQ ID NO:16 of US20150376607), AAV-LK16 (SEQ ID NO:17 of US20150376607), AAV-LK17 (SEQ ID NO:18 of US20150376607), AAV-LK18 (SEQ ID NO:19 of US20150376607), AAV-LK19 (SEQ ID NO:20 of US20150376607), AAV-PAEC2 (SEQ ID NO:21 of US20150376607), AAV-PAEC4 (SEQ ID NO:22 of US20150376607), AAV-PAEC6 (SEQ ID NO:23 of US20150376607), AAV-PAEC7 (SEQ ID NO:24 of US20150376607), AAV-PAEC8 (SEQ ID NO:25 of US20150376607), AAV-PAEC11 (SEQ ID NO:26 of US20150376607), AAV-PAEC12 (SEQ ID NO:27, of US20150376607), or variants thereof.

[0274] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent No. US9163261, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-2-pre-miRNA-101 (SEQ ID NO: 1 US9163261), or variants thereof.

[0275] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent Publication No. US20150376240, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-8h (SEQ ID NO: 6 of

US20150376240), AAV-8b (SEQ ID NO: 5 of US20150376240), AAV-h (SEQ ID NO: 2 of US20150376240), AAV-b (SEQ ID NO: 1 of US20150376240), or variants thereof.

[0276] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent Publication No. US20160017295, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV SM 10-2 (SEQ ID NO: 22 of US20160017295), AAV Shuffle 100-1 (SEQ ID NO: 23 of US20160017295), AAV Shuffle 100-3 (SEQ ID NO: 24 of US20160017295), AAV Shuffle 100-7 (SEQ ID NO: 25 of US20160017295), AAV Shuffle 10-2 (SEQ ID NO: 34 of US20160017295), AAV Shuffle 10-6 (SEQ ID NO: 35 of US20160017295), AAV Shuffle 10-8 (SEQ ID NO: 36 of US20160017295), AAV Shuffle 100-2 (SEQ ID NO: 37 of US20160017295), AAV SM 10-1 (SEQ ID NO: 38 of US20160017295), AAV SM 10-8 (SEQ ID NO: 39 of US20160017295), AAV SM 100-3 (SEQ ID NO: 40 of US20160017295), AAV SM 100-10 (SEQ ID NO: 41 of US20160017295), or variants thereof.

[0277] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent Publication No. US20150238550, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BNP61 AAV (SEQ ID NO: 1 of US20150238550), BNP62 AAV (SEQ ID NO: 3 of US20150238550), BNP63 AAV (SEQ ID NO: 4 of US20150238550), or variants thereof.

[0278] In some embodiments, the AAV serotype may be or may have a sequence as described in United States Patent Publication No. US20150315612, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh.50 (SEQ ID NO: 108 of US20150315612), AAVrh.43 (SEQ ID NO: 163 of US20150315612), AAVrh.62 (SEQ ID NO: 114 of US20150315612), AAVrh.48 (SEQ ID NO: 115 of US20150315612), AAVhu.19 (SEQ ID NO: 133 of US20150315612), AAVhu.11 (SEQ ID NO: 153 of US20150315612), AAVhu.53 (SEQ ID NO: 186 of US20150315612), AAV4-8/rh.64 (SEQ ID No: 15 of US20150315612), AAVLG-9/hu.39 (SEQ ID No: 24 of US20150315612), AAV54.5/hu.23 (SEQ ID No: 60 of US20150315612), AAV54.2/hu.22 (SEQ ID No: 67 of US20150315612), AAV54.7/hu.24 (SEQ ID No: 66 of US20150315612), AAV54.1/hu.21 (SEQ ID No: 65 of US20150315612), AAV54.4R/hu.27 (SEQ ID No: 64 of US20150315612), AAV46.2/hu.28 (SEQ ID No: 68 of US20150315612), AAV46.6/hu.29 (SEQ ID No: 69 of US20150315612), AAV128.1/hu.43 (SEQ ID No: 80 of US20150315612), or variants thereof.

[0279] In some embodiments, the AAV serotype may be, or have a sequence as described in International Publication No. WO2015121501, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, true type AAV (ttAAV) (SEQ ID NO: 2 of

WO2015121501), “UPenn AAV10” (SEQ ID NO: 8 of WO2015121501), “Japanese AAV10” (SEQ ID NO: 9 of WO2015121501), or variants thereof.

[0280] According to the present disclosure, AAV capsid serotype selection or use may be from a variety of species. In some embodiments, the AAV may be an avian AAV (AAAV). The AAAV serotype may be, or have a sequence as described in United States Patent No. US 9238800, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAAV (SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 of US 9,238,800), or variants thereof.

[0281] In some embodiments, the AAV may be a bovine AAV (BAAV). The BAAV serotype may be, or have a sequence as described in United States Patent No. US 9,193,769, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 1 and 6 of US 9,193,769), or variants thereof. The BAAV serotype may be or have a sequence as described in United States Patent No. US 7,427,396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 5 and 6 of US 7,427,396), or variants thereof.

[0282] In some embodiments, the AAV may be a caprine AAV. The caprine AAV serotype may be, or have a sequence as described in United States Patent No. US 7,427,396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, caprine AAV (SEQ ID NO: 3 of US 7,427,396), or variants thereof.

[0283] In other embodiments the AAV may be engineered as a hybrid AAV from two or more parental serotypes. In some embodiments, the AAV may be AAV2G9 which comprises sequences from AAV2 and AAV9. The AAV2G9 AAV serotype may be, or have a sequence as described in United States Patent Publication No. US 20160017005, the contents of which are herein incorporated by reference in its entirety.

[0284] In some embodiments, the AAV may be a serotype generated by the AAV9 capsid library with mutations in amino acids 390-627 (VP1 numbering) as described by Pulicherla *et al.* (Molecular Therapy 19(6):1070-1078 (2011), the contents of which are herein incorporated by reference in their entirety. The serotype and corresponding nucleotide and amino acid substitutions may be, but are not limited to, AAV9.1 (G1594C; D532H), AAV6.2 (T1418A and T1436X; V473D and I479K), AAV9.3 (T1238A; F413Y), AAV9.4 (T1250C and A1617T; F417S), AAV9.5 (A1235G, A1314T, A1642G, C1760T; Q412R, T548A, A587V), AAV9.6 (T1231A; F411I), AAV9.9 (G1203A, G1785T; W595C), AAV9.10 (A1500G, T1676C; M559T), AAV9.11 (A1425T, A1702C, A1769T; T568P, Q590L), AAV9.13 (A1369C, A1720T; N457H, T574S), AAV9.14 (T1340A, T1362C, T1560C, G1713A; L447H), AAV9.16 (A1775T; Q592L), AAV9.24 (T1507C, T1521G; W503R), AAV9.26 (A1337G, A1769C; Y446C, Q590P),

AAV9.33 (A1667C; D556A), AAV9.34 (A1534G, C1794T; N512D), AAV9.35 (A1289T, T1450A, C1494T, A1515T, C1794A, G1816A; Q430L, Y484N, N98K, V606I), AAV9.40 (A1694T, E565V), AAV9.41 (A1348T, T1362C; T450S), AAV9.44 (A1684C, A1701T, A1737G; N562H, K567N), AAV9.45 (A1492T, C1804T; N498Y, L602F), AAV9.46 (G1441C, T1525C, T1549G; G481R, W509R, L517V), 9.47 (G1241A, G1358A, A1669G, C1745T; S414N, G453D, K557E, T582I), AAV9.48 (C1445T, A1736T; P482L, Q579L), AAV9.50 (A1638T, C1683T, T1805A; Q546H, L602H), AAV9.53 (G1301A, A1405C, C1664T, G1811T; R134Q, S469R, A555V, G604V), AAV9.54 (C1531A, T1609A; L511I, L537M), AAV9.55 (T1605A; F535L), AAV9.58 (C1475T, C1579A; T492I, H527N), AAV.59 (T1336C; Y446H), AAV9.61 (A1493T; N498I), AAV9.64 (C1531A, A1617T; L511I), AAV9.65 (C1335T, T1530C, C1568A; A523D), AAV9.68 (C1510A; P504T), AAV9.80 (G1441A,;G481R), AAV9.83 (C1402A, A1500T; P468T, E500D), AAV9.87 (T1464C, T1468C; S490P), AAV9.90 (A1196T; Y399F), AAV9.91 (T1316G, A1583T, C1782G, T1806C; L439R, K528I), AAV9.93 (A1273G, A1421G, A1638C, C1712T, G1732A, A1744T, A1832T; S425G, Q474R, Q546H, P571L, G578R, T582S, D611V), AAV9.94 (A1675T; M559L) and AAV9.95 (T1605A; F535L).

[0285] In some embodiments, the AAV serotype may be, or have a sequence as described in International Publication No. WO2016049230, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAVF1/HSC1 (SEQ ID NO: 2 and 20 of WO2016049230), AAVF2/HSC2 (SEQ ID NO: 3 and 21 of WO2016049230), AAVF3/HSC3 (SEQ ID NO: 5 and 22 of WO2016049230), AAVF4/HSC4 (SEQ ID NO: 6 and 23 of WO2016049230), AAVF5/HSC5 (SEQ ID NO: 11 and 25 of WO2016049230), AAVF6/HSC6 (SEQ ID NO: 7 and 24 of WO2016049230), AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230), AAVF8/HSC8 (SEQ ID NO: 9 and 28 of WO2016049230), AAVF9/HSC9 (SEQ ID NO: 10 and 29 of WO2016049230), AAVF11/HSC11 (SEQ ID NO: 4 and 26 of WO2016049230), AAVF12/HSC12 (SEQ ID NO: 12 and 30 of WO2016049230), AAVF13/HSC13 (SEQ ID NO: 14 and 31 of WO2016049230), AAVF14/HSC14 (SEQ ID NO: 15 and 32 of WO2016049230), AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230), AAVF16/HSC16 (SEQ ID NO: 17 and 34 of WO2016049230), AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230), or variants or derivatives thereof.

[0286] In some embodiments, the AAV serotype may be, or have a sequence as described in United States Patent No. US 8734809, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV CBr-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CBr-E2 (SEQ ID NO: 14 and 88 of US8734809), AAV CBr-E3 (SEQ ID NO: 15 and 89 of US8734809), AAV CBr-E4 (SEQ ID NO: 16 and 90 of US8734809), AAV CBr-E5 (SEQ ID NO: 17 and 91 of US8734809), AAV CBr-e5 (SEQ ID NO: 18 and 92 of

US8734809), AAV CBr-E6 (SEQ ID NO: 19 and 93 of US8734809), AAV CBr-E7 (SEQ ID NO: 20 and 94 of US8734809), AAV CBr-E8 (SEQ ID NO: 21 and 95 of US8734809), AAV CLv-D1 (SEQ ID NO: 22 and 96 of US8734809), AAV CLv-D2 (SEQ ID NO: 23 and 97 of US8734809), AAV CLv-D3 (SEQ ID NO: 24 and 98 of US8734809), AAV CLv-D4 (SEQ ID NO: 25 and 99 of US8734809), AAV CLv-D5 (SEQ ID NO: 26 and 100 of US8734809), AAV CLv-D6 (SEQ ID NO: 27 and 101 of US8734809), AAV CLv-D7 (SEQ ID NO: 28 and 102 of US8734809), AAV CLv-D8 (SEQ ID NO: 29 and 103 of US8734809), AAV CLv-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CLv-R1 (SEQ ID NO: 30 and 104 of US8734809), AAV CLv-R2 (SEQ ID NO: 31 and 105 of US8734809), AAV CLv-R3 (SEQ ID NO: 32 and 106 of US8734809), AAV CLv-R4 (SEQ ID NO: 33 and 107 of US8734809), AAV CLv-R5 (SEQ ID NO: 34 and 108 of US8734809), AAV CLv-R6 (SEQ ID NO: 35 and 109 of US8734809), AAV CLv-R7 (SEQ ID NO: 36 and 110 of US8734809), AAV CLv-R8 (SEQ ID NO: X and X of US8734809), AAV CLv-R9 (SEQ ID NO: X and X of US8734809), AAV CLg-F1 (SEQ ID NO: 39 and 113 of US8734809), AAV CLg-F2 (SEQ ID NO: 40 and 114 of US8734809), AAV CLg-F3 (SEQ ID NO: 41 and 115 of US8734809), AAV CLg-F4 (SEQ ID NO: 42 and 116 of US8734809), AAV CLg-F5 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F6 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F7 (SEQ ID NO: 44 and 118 of US8734809), AAV CLg-F8 (SEQ ID NO: 43 and 117 of US8734809), AAV CSp-1 (SEQ ID NO: 45 and 119 of US8734809), AAV CSp-10 (SEQ ID NO: 46 and 120 of US8734809), AAV CSp-11 (SEQ ID NO: 47 and 121 of US8734809), AAV CSp-2 (SEQ ID NO: 48 and 122 of US8734809), AAV CSp-3 (SEQ ID NO: 49 and 123 of US8734809), AAV CSp-4 (SEQ ID NO: 50 and 124 of US8734809), AAV CSp-6 (SEQ ID NO: 51 and 125 of US8734809), AAV CSp-7 (SEQ ID NO: 52 and 126 of US8734809), AAV CSp-8 (SEQ ID NO: 53 and 127 of US8734809), AAV CSp-9 (SEQ ID NO: 54 and 128 of US8734809), AAV CHt-2 (SEQ ID NO: 55 and 129 of US8734809), AAV CHt-3 (SEQ ID NO: 56 and 130 of US8734809), AAV CKd-1 (SEQ ID NO: 57 and 131 of US8734809), AAV CKd-10 (SEQ ID NO: 58 and 132 of US8734809), AAV CKd-2 (SEQ ID NO: 59 and 133 of US8734809), AAV CKd-3 (SEQ ID NO: 60 and 134 of US8734809), AAV CKd-4 (SEQ ID NO: 61 and 135 of US8734809), AAV CKd-6 (SEQ ID NO: 62 and 136 of US8734809), AAV CKd-7 (SEQ ID NO: 63 and 137 of US8734809), AAV CKd-8 (SEQ ID NO: 64 and 138 of US8734809), AAV CLv-1 (SEQ ID NO: 35 and 139 of US8734809), AAV CLv-12 (SEQ ID NO: 66 and 140 of US8734809), AAV CLv-13 (SEQ ID NO: 67 and 141 of US8734809), AAV CLv-2 (SEQ ID NO: 68 and 142 of US8734809), AAV CLv-3 (SEQ ID NO: 69 and 143 of US8734809), AAV CLv-4 (SEQ ID NO: 70 and 144 of US8734809), AAV CLv-6 (SEQ ID NO: 71 and 145 of US8734809), AAV CLv-8 (SEQ ID NO: 72 and 146 of US8734809), AAV CKd-B1 (SEQ ID NO: 73 and 147 of US8734809), AAV CKd-B2 (SEQ ID

NO: 74 and 148 of US8734809), AAV CKd-B3 (SEQ ID NO: 75 and 149 of US8734809), AAV CKd-B4 (SEQ ID NO: 76 and 150 of US8734809), AAV CKd-B5 (SEQ ID NO: 77 and 151 of US8734809), AAV CKd-B6 (SEQ ID NO: 78 and 152 of US8734809), AAV CKd-B7 (SEQ ID NO: 79 and 153 of US8734809), AAV CKd-B8 (SEQ ID NO: 80 and 154 of US8734809), AAV CKd-H1 (SEQ ID NO: 81 and 155 of US8734809), AAV CKd-H2 (SEQ ID NO: 82 and 156 of US8734809), AAV CKd-H3 (SEQ ID NO: 83 and 157 of US8734809), AAV CKd-H4 (SEQ ID NO: 84 and 158 of US8734809), AAV CKd-H5 (SEQ ID NO: 85 and 159 of US8734809), AAV CKd-H6 (SEQ ID NO: 77 and 151 of US8734809), AAV CHt-1 (SEQ ID NO: 86 and 160 of US8734809), AAV CLv1-1 (SEQ ID NO: 171 of US8734809), AAV CLv1-2 (SEQ ID NO: 172 of US8734809), AAV CLv1-3 (SEQ ID NO: 173 of US8734809), AAV CLv1-4 (SEQ ID NO: 174 of US8734809), AAV CLv1-7 (SEQ ID NO: 175 of US8734809), AAV CLv1-8 (SEQ ID NO: 176 of US8734809), AAV CLv1-9 (SEQ ID NO: 177 of US8734809), AAV CLv1-10 (SEQ ID NO: 178 of US8734809), AAV.VR-355 (SEQ ID NO: 181 of US8734809), AAV.hu.48R3 (SEQ ID NO: 183 of US8734809), or variants or derivatives thereof.

[0287] In some embodiments, the AAV serotype may be, or have a sequence as described in International Publication No. WO2016065001, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV CHt-P2 (SEQ ID NO: 1 and 51 of WO2016065001), AAV CHt-P5 (SEQ ID NO: 2 and 52 of WO2016065001), AAV CHt-P9 (SEQ ID NO: 3 and 53 of WO2016065001), AAV CBr-7.1 (SEQ ID NO: 4 and 54 of WO2016065001), AAV CBr-7.2 (SEQ ID NO: 5 and 55 of WO2016065001), AAV CBr-7.3 (SEQ ID NO: 6 and 56 of WO2016065001), AAV CBr-7.4 (SEQ ID NO: 7 and 57 of WO2016065001), AAV CBr-7.5 (SEQ ID NO: 8 and 58 of WO2016065001), AAV CBr-7.7 (SEQ ID NO: 9 and 59 of WO2016065001), AAV CBr-7.8 (SEQ ID NO: 10 and 60 of WO2016065001), AAV CBr-7.10 (SEQ ID NO: 11 and 61 of WO2016065001), AAV CKd-N3 (SEQ ID NO: 12 and 62 of WO2016065001), AAV CKd-N4 (SEQ ID NO: 13 and 63 of WO2016065001), AAV CKd-N9 (SEQ ID NO: 14 and 64 of WO2016065001), AAV CLv-L4 (SEQ ID NO: 15 and 65 of WO2016065001), AAV CLv-L5 (SEQ ID NO: 16 and 66 of WO2016065001), AAV CLv-L6 (SEQ ID NO: 17 and 67 of WO2016065001), AAV CLv-K1 (SEQ ID NO: 18 and 68 of WO2016065001), AAV CLv-K3 (SEQ ID NO: 19 and 69 of WO2016065001), AAV CLv-K6 (SEQ ID NO: 20 and 70 of WO2016065001), AAV CLv-M1 (SEQ ID NO: 21 and 71 of WO2016065001), AAV CLv-M11 (SEQ ID NO: 22 and 72 of WO2016065001), AAV CLv-M2 (SEQ ID NO: 23 and 73 of WO2016065001), AAV CLv-M5 (SEQ ID NO: 24 and 74 of WO2016065001), AAV CLv-M6 (SEQ ID NO: 25 and 75 of WO2016065001), AAV CLv-M7 (SEQ ID NO: 26 and 76 of WO2016065001), AAV CLv-M8 (SEQ ID NO: 27 and 77 of WO2016065001), AAV CLv-M9 (SEQ ID NO: 28 and 78 of

WO2016065001), AAV CHt-P1 (SEQ ID NO: 29 and 79 of WO2016065001), AAV CHt-P6 (SEQ ID NO: 30 and 80 of WO2016065001), AAV CHt-P8 (SEQ ID NO: 31 and 81 of WO2016065001), AAV CHt-6.1 (SEQ ID NO: 32 and 82 of WO2016065001), AAV CHt-6.10 (SEQ ID NO: 33 and 83 of WO2016065001), AAV CHt-6.5 (SEQ ID NO: 34 and 84 of WO2016065001), AAV CHt-6.6 (SEQ ID NO: 35 and 85 of WO2016065001), AAV CHt-6.7 (SEQ ID NO: 36 and 86 of WO2016065001), AAV CHt-6.8 (SEQ ID NO: 37 and 87 of WO2016065001), AAV CSp-8.10 (SEQ ID NO: 38 and 88 of WO2016065001), AAV CSp-8.2 (SEQ ID NO: 39 and 89 of WO2016065001), AAV CSp-8.4 (SEQ ID NO: 40 and 90 of WO2016065001), AAV CSp-8.5 (SEQ ID NO: 41 and 91 of WO2016065001), AAV CSp-8.6 (SEQ ID NO: 42 and 92 of WO2016065001), AAV CSp-8.7 (SEQ ID NO: 43 and 93 of WO2016065001), AAV CSp-8.8 (SEQ ID NO: 44 and 94 of WO2016065001), AAV CSp-8.9 (SEQ ID NO: 45 and 95 of WO2016065001), AAV CBr-B7.3 (SEQ ID NO: 46 and 96 of WO2016065001), AAV CBr-B7.4 (SEQ ID NO: 47 and 97 of WO2016065001), AAV3B (SEQ ID NO: 48 and 98 of WO2016065001), AAV4 (SEQ ID NO: 49 and 99 of WO2016065001), AAV5 (SEQ ID NO: 50 and 100 of WO2016065001), or variants or derivatives thereof.

[0288] In some embodiments, the AAV particle may have, or may be a serotype selected from any of those found in Table 9.

[0289] In some embodiments, the AAV capsid may comprise a sequence, fragment or variant thereof, of any of the sequences in Table 9.

[0290] In some embodiments, the AAV capsid may be encoded by a sequence, fragment or variant as described in Table 9.

[0291] In any of the DNA and RNA sequences referenced and/or described herein, the single letter symbol has the following description: A for adenine; C for cytosine; G for guanine; T for thymine; U for Uracil; W for weak bases such as adenine or thymine; S for strong nucleotides such as cytosine and guanine; M for amino nucleotides such as adenine and cytosine; K for keto nucleotides such as guanine and thymine; R for purines adenine and guanine; Y for pyrimidine cytosine and thymine; B for any base that is not A (*e.g.*, cytosine, guanine, and thymine); D for any base that is not C (*e.g.*, adenine, guanine, and thymine); H for any base that is not G (*e.g.*, adenine, cytosine, and thymine); V for any base that is not T (*e.g.*, adenine, cytosine, and guanine); N for any nucleotide (which is not a gap); and Z is for zero.

[0292] In any of the amino acid sequences referenced and/or described herein, the single letter symbol has the following description: G (Gly) for Glycine; A (Ala) for Alanine; L (Leu) for Leucine; M (Met) for Methionine; F (Phe) for Phenylalanine; W (Trp) for Tryptophan; K (Lys) for Lysine; Q (Gln) for Glutamine; E (Glu) for Glutamic Acid; S (Ser) for Serine; P (Pro) for Proline; V (Val) for Valine; I (Ile) for Isoleucine; C (Cys) for Cysteine; Y (Tyr) for Tyrosine; H

(His) for Histidine; R (Arg) for Arginine; N (Asn) for Asparagine; D (Asp) for Aspartic Acid; T (Thr) for Threonine; B (Asx) for Aspartic acid or Asparagine; J (Xle) for Leucine or Isoleucine; O (Pyl) for Pyrrolysine; U (Sec) for Selenocysteine; X (Xaa) for any amino acid; and Z (Glx) for Glutamine or Glutamic acid.

Table 9. AAV Serotypes

Serotype	SEQ ID NO	Reference Information
AAV1 (nt)	982	US20030138772 SEQ ID NO: 6
AAV1 (aa)	983	US20160017295 SEQ ID NO: 1, US20030138772 SEQ ID NO: 64, US20150159173 SEQ ID NO: 27, US20150315612 SEQ ID NO: 219, US7198951 SEQ ID NO: 5
AAV2 (nt)	984	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2 (aa)	985	US20030138772 SEQ ID NO: 70, US20150159173 SEQ ID NO: 23, US20150315612 SEQ ID NO: 221, US20160017295 SEQ ID NO: 2, US6156303 SEQ ID NO: 4, US7198951 SEQ ID NO: 4, WO2015121501 SEQ ID NO: 1
AAV3 (nt)	986	US20030138772 SEQ ID NO: 8
AAV3 (aa)	987	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV4 (nt)	988	US20140348794 SEQ ID NO: 1
AAV4 (nt)	989	WO2016065001 SEQ ID NO: 49
AAV4 (aa)	990	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV5 (nt)	991	US7427396 SEQ ID NO: 1
AAV5 (aa)	992	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV6 (nt)	993	US6156303 SEQ ID NO: 2
AAV6 (nt)	994	US20150315612 SEQ ID NO: 203
AAV6 (aa)	995	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV7 (nt)	996	US20150159173 SEQ ID NO: 14

AAV7 (nt)	997	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7 (aa)	998	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV8 (nt)	999	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8 (nt)	1000	US20150159173 SEQ ID NO: 15
AAV8 (aa)	1001	US20030138772 SEQ ID NO: 95, US20140359799 SEQ ID NO: 1, US20150159173 SEQ ID NO: 31, US20160017295 SEQ ID NO: 8, US7198951 SEQ ID NO: 7, US20150315612 SEQ ID NO: 223
AAV9/hu.14 (nt)	1002	SEQ ID NO: 3; US7906111
AAV9/hu.14 (aa)	1003	SEQ ID NO: 123; US7906111
AAV PHP.B (nt)	1004	SEQ ID NO: 9; WO2015038958
AAV PHP.B (aa) (K449R)	1005	SEQ ID NO: 8; WO2015038958
AAVG2B-13	1006	SEQ ID NO: 12; WO2015038958
AAVTH1.1-32	1007	SEQ ID NO: 14; WO2015038958
AAVTH1.1-35	1008	SEQ ID NO: 15; WO2015038958
PHP.N/PHP.B-DGT	1009	SEQ ID NO: 46; WO2017100671
PHP.S/G2A12	1010	SEQ ID NO: 47; WO2017100671
AAV9/hu.14 K449R	1011	SEQ ID NO: 45; WO2017100671
AAVrh10 (nt) (referred to as clone 44.2)	1012	US20030138772 SEQ ID NO: 59
AAVrh10 (aa) (referred to as clone 44.2)	1013	US20030138772 SEQ ID NO: 81
AAV-DJ (nt)	1014	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAV-DJ (aa)	1015	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1
AAV-DJ8 (2 mutations)	1016	US7588772; Grimm et al 2008

AAV-DJ8 (3 mutations)	1017	US7588772; Grimm et al 2008
rh74 (nt)	1018	US9434928B2 SEQ ID NO: 1; US2015023924A1 SEQ ID NO: 2
rh74 (aa)	1019	US9434928B2 SEQ ID NO: 2; US2015023924A1 SEQ ID NO: 1
AAV10 (aa)	1020	WO2015121501 SEQ ID NO: 9
AAV10 (aa)	1021	WO2015121501 SEQ ID NO: 8
VOY101 (nt)	1022	-
VOY101 (aa)	1023	-
VOY201 (nt)	1024	-
VOY201 (aa)	1025	-
AAV2 variant (aa)	1026	WO2018071831 SEQ ID NO: 358
AAV2/3 variant (aa)	1027	WO2018071831 SEQ ID NO: 513
AAV2/3 variant (aa)	1028	WO2018071831 SEQ ID NO: 575

[0293] In some embodiments the AAV serotype is VOY101, or a variant thereof. In some embodiments, the VOY101 capsid comprises the amino acid sequence SEQ ID NO: 1023. In some embodiments, the VOY101 amino acid sequence is encoded by a nucleotide sequence comprising SEQ ID NO: 1022. In some embodiments, the VOY101 capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1023, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. In some embodiments, the VOY101 capsid comprises a nucleotide sequence at least 70% identical to SEQ ID NO: 1022, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0294] In some embodiments, the AAV serotype is VOY201, or a variant thereof. In some embodiments, the VOY201 capsid comprises the amino acid sequence SEQ ID NO: 1025. In some embodiments, the VOY201 amino acid sequence is encoded by a nucleotide sequence comprising SEQ ID NO: 1024. In some embodiments, the VOY201 capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1025, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. In some embodiments, the VOY201 capsid comprises a nucleotide sequence at least 70% identical to SEQ ID NO: 1024, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0295] In some embodiments, the AAV serotype is PHP.B, or a variant thereof. In some embodiments, the PHP.B capsid comprises the amino acid sequence SEQ ID NO: 1005. In some embodiments, the PHP.B amino acid sequence is encoded by a nucleotide sequence comprising SEQ ID NO: 1004. In some embodiments, the PHP.B capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1005, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. In some embodiments, the PHP.B capsid comprises a nucleotide sequence at least 70% identical to SEQ ID NO: 1004, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0296] In some embodiments, the AAV serotype is PHP.N, or a variant thereof. In some embodiments, the PHP.N capsid comprises the amino acid sequence SEQ ID NO: 1009. In some embodiments, the PHP.N capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1009, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0297] In some embodiments the AAV serotype is AAV9, or a variant thereof. In some embodiments, the AAV9 capsid comprises the amino acid sequence SEQ ID NO: 1003. In some embodiments, the AAV9 amino acid sequence is encoded by a nucleotide sequence comprising SEQ ID NO: 1002. In some embodiments, the AAV9 capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1003, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. In some embodiments, the AAV9 capsid comprises a nucleotide sequence at least 70% identical to SEQ ID NO: 1002, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0298] In some embodiments, the capsid protein comprises an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151). In some embodiments, the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003. In some embodiments, the capsid protein comprises the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.

[0299] In some embodiments, the capsid protein comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 1003; and an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003.

[0300] In some embodiments, the capsid protein comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 1003; an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), wherein the insert is present immediately subsequent to

position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.

[0301] In some embodiments, the capsid protein comprises an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.

[0302] In some embodiments, the AAV serotype is AAV9 K449R, or a variant thereof. In some embodiments, the AAV9 K449R capsid comprises the amino acid sequence SEQ ID NO: 1011. In some embodiments, the AAV9 K449R capsid comprises an amino acid sequence at least 70% identical to SEQ ID NO: 1011, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0303] In some embodiments, the AAV capsid allows for blood brain barrier penetration following intravenous administration. Non-limiting examples of such AAV capsids include AAV9, AAV9 K449R, VOY101, VOY201, or AAV capsids comprising a peptide insert such as, but not limited to, AAVPHP.N (PHP.N), AAVPHP.B (PHP.B), PHP.S, G2A3, G2B4, G2B5, G2A12, G2A15, PHP.B2, PHP.B3, or AAVPHP.A (PHP.A).

[0304] In some embodiments, the AAV capsid is suitable for intramuscular administration and/or transduction of muscle fibers. Non-limiting examples of such AAV capsids include AAV2, AAV3, AAV8 and variants thereof such as, but not limited to, AAV2 variants, AAV2/3 variants, AAV8 variants, and/or AAV2/3/8 variants.

[0305] In some embodiments, the AAV serotype is an AAV2 variant. As a non-limiting example, the AAV serotype is an AAV2 variant comprising SEQ ID NO: 1026 or a fragment or variant thereof. As a non-limiting example, the AAV serotype is at least 70% identical to SEQ ID NO: 1026, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0306] In some embodiments, the AAV serotype is an AAV2/3 variant. As a non-limiting example, the AAV serotype is an AAV2/3 variant comprising SEQ ID NO: 1027 or a fragment or variant thereof. As a non-limiting example, the AAV serotype is an AAV2/3 variant which is at least 70% identical to SEQ ID NO: 1027, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%. As a non-limiting example, the AAV serotype is an AAV2/3 variant comprising SEQ ID NO: 1028 or a fragment or variant thereof. As a non-limiting example, the AAV serotype is an AAV2/3 variant which is at least 70% identical to SEQ ID NO: 1028, such as, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater than 99%.

[0307] In some embodiments, the AAV serotype may comprise a capsid amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein.

[0308] In some embodiments, the AAV serotype may be encoded by a capsid nucleic acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described herein.

[0309] In some embodiments, the AAV serotype is selected for use due to its tropism for cells of the central nervous system. In some embodiments, the cells of the central nervous system are neurons. In another embodiment, the cells of the central nervous system are astrocytes.

[0310] In some embodiments, the AAV serotype is selected for use due to its tropism for cells of the muscle(s).

[0311] In some embodiments, the initiation codon for translation of the AAV VP1 capsid protein may be CTG, TTG, or GTG as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in their entirety.

[0312] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell (*i.e.* capsid) of a viral vector such as AAV. VP capsid proteins synthesized from Cap polynucleotides generally include a methionine as the first amino acid in the peptide sequence (Met1), which is associated with the start codon (AUG or ATG) in the corresponding Cap nucleotide sequence. However, it is common for a first-methionine (Met1) residue or generally any first amino acid (AA1) to be cleaved off after or during polypeptide synthesis by protein processing enzymes such as Met-aminopeptidases. This “Met/AA-clipping” process often correlates with a corresponding acetylation of the second amino acid in the polypeptide sequence (*e.g.*, alanine, valine, serine, threonine, *etc.*). Met-clipping commonly occurs with VP1 and VP3 capsid proteins but can also occur with VP2 capsid proteins.

[0313] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, *et al.* Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid

Proteins. *Hum Gene Ther Methods*. 2017 Oct. 28(5):255-267; Hwang, *et al*. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science*. 2010 February 19. 327(5968): 973–977; the contents of which are each incorporated herein by reference in its entirety.

[0314] According to the present disclosure, references to capsid proteins is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid proteins of the present disclosure. A direct reference to a “capsid protein” or “capsid polypeptide” (such as VP1, VP2 or VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0315] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes, respectively, one or more capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0316] As a non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes a “Met1” amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the “Met1” amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes an “AA1” amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the “AA1” amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0317] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0318] As a non-limiting example, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3

(Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

AAV Particles Comprising anti-tau antibody payloads

[0319] AAV particles as described herein may be used for the delivery of an antibody payload (e.g., anti-tau antibody) to a target tissue (e.g., CNS). In some embodiments, a viral genome encoding an anti-tau antibody polypeptide may be packaged into a viral particle, e.g., an AAV particle. A target cell transduced with a viral particle comprising one or more anti-tau antibody polynucleotides may express the encoded antibody or antibodies in a single cell.

[0320] In some embodiments, the AAV particles comprising anti-tau antibody polynucleotide sequences which comprise a nucleic acid sequence encoding at least one antibody heavy and/or light chain may be introduced into mammalian cells.

[0321] The AAV viral genomes encoding anti-tau antibody polypeptides described herein may be useful in the fields of human disease, viruses, infections veterinary applications and a variety of *in vivo* and *in vitro* settings. In some embodiments, the AAV viral genomes encoding anti-tau antibody polypeptides are used for the prevention and/or treatment of a tauopathy.

[0322] A viral genome of an AAV particle as described herein, comprises a nucleic acid sequence encoding a payload, and at least one ITR. In some embodiments, a viral genome comprises two ITR sequences, one at each of the 5' and 3' ends. Further, a viral genome of the AAV particles described herein may comprise nucleic acid sequences for additional components, such as, but not limited to, a regulatory element (e.g., promoter), untranslated regions (UTR), a polyadenylation sequence (polyA), a filler sequence, an intron, and/or a linker sequence for enhanced expression. These viral genome components can be selected and/or engineered to further tailor the specificity and efficiency of expression of a given payload in a target tissue.

[0323] The viral genome of the AAV particles of the present disclosure may comprise any combination of the sequence regions described in Tables 10-18 encapsulated in any of the capsids listed in Table 9 or described herein.

[0324] In some embodiments, the viral genome may comprise at least one sequence region as described in Tables 10-18. The regions may be located before or after any of the other sequence regions described herein. Viral genomes may further comprise more than one copy of one or more sequence regions as described in Tables 10-18.

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0325] In some embodiments, the viral genome may comprise at least one inverted terminal repeat (ITR) region. In some embodiments, the viral genome comprises at least one ITR region and a nucleic acid encoding a payload, e.g., an antibody molecule (e.g., an anti-tau antibody

molecule). In some embodiments, viral genome comprises two ITRs. In some embodiments, the two ITRs flank the nucleic acid encoding the transgene at the 5' and 3' ends. In some embodiments, the ITR functions as an origin of replication comprising recognition sites for replication. In some embodiments, the ITRs comprise sequence regions which can be complementary and symmetrically arranged. In some embodiments, the ITR incorporated into viral genome may be comprised of naturally occurring nucleic acid sequences or recombinantly derived nucleic acid sequences.

[0326] In some embodiments, the ITR may be of the same AAV serotype as the capsid, *e.g.*, a capsid protein selected from any of the AAV serotypes listed in Table 9, or a functional variant thereof. In some embodiments, the ITR may be of a different AAV serotype than the capsid protein. In some embodiments, the AAV particle comprises a viral genome comprising two ITRs wherein the two ITRs of viral genome are of the same AAV serotype. In other embodiments, the two ITRs of a viral genome are of different AAV serotypes. In some embodiments both ITRs of the viral genome of the AAV particle are AAV2 ITRs or a functional variant thereof.

[0327] The ITR region(s) may, independently, have a length such as, but not limited to, about 100 to about 150 nucleotides in length. An ITR may be about 100-180 nucleotides in length, *e.g.*, about 100-115, about 100-120, about 100-130, about 100-140, about 100-150, about 100-160, about 100-170, about 100-180, about 110-120, about 110-130, about 110-140, about 110-150, about 110-160, about 110-170, about 110-180, about 120-130, about 120-140, about 120-150, about 120-160, about 120-170, about 120-180, about 130-140, about 130-150, about 130-160, about 130-170, about 130-180, about 140-150, about 140-160, about 140-170, about 140-180, about 150-160, about 150-170, about 150-180, about 160-170, about 160-180, or about 170-180 nucleotides in length. In some embodiments, the ITR comprises about 120-140 nucleotides in length, *e.g.*, about 130 nucleotides in length. In some embodiments, the ITR comprises about 140-150 nucleotides in length, about 141 nucleotides in length. In some embodiments, the viral genome comprises an ITR region comprising the nucleotide sequence of any of the sequences provided in Table 10 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the viral genome comprises two ITR regions comprising the nucleotide sequence of any of the sequences provided in Table 10 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto, wherein the first and second ITR comprise the same sequence or wherein the first and second ITR comprise different sequences.

[0328] As a non-limiting example, the viral genome comprises a 5' ITR that is about 141 nucleotides in length. As a non-limiting example, the viral genome comprises a 5' ITR that is about 130 nucleotides in length. As a non-limiting example, the viral genome comprises a 3' ITR

that is about 141 nucleotides in length. As a non-limiting example, the viral genome comprises a 3' ITR that is about 130 nucleotides in length. In some embodiments, the AAV particles comprise two ITRs and one ITR is 141 nucleotides in length and the other ITR is 130 nucleotides in length.

[0329] In some embodiments, the AAV particle viral genome comprises a 5' inverted terminal repeat (5' ITR) sequence region. In some embodiments, the viral genome comprises a 3' inverted terminal repeat (3' ITR) sequence region. Non-limiting examples of 5' ITR and 3' ITR sequence regions are described in Table 10.

Table 10. Inverted Terminal Repeat (ITR) Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
ITR1	130	1035
ITR2	141	1036
ITR3	130	1037
ITR4	141	1038

[0330] In some embodiment, the viral genome comprises an ITR provided in Table 10. In some embodiments, the viral genome comprises an ITR chosen from any one of ITR1-ITR4 or a functional variant thereof. In some embodiments, the viral genome may have an ITR that comprises ITR1. In some embodiments, the viral genome may have an ITR that comprises ITR2. In some embodiments, the viral genome may have an ITR that comprises ITR3. In some embodiments, the viral genome may have an ITR that comprises ITR4.

[0331] In some embodiments, the ITR comprises the nucleotide sequence of any one of SEQ ID NOs: 1035-1038, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 1035 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 1036 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 1037 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 1038 or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto.

[0332] In some embodiments, the viral genome may have two ITRs. As a non-limiting example, the two ITRs are ITR1 and ITR3. As a non-limiting example, the two ITRs are ITR1

and ITR4. As a non-limiting example, the two ITRs are ITR2 and ITR3. As a non-limiting example, the two ITRs are ITR2 and ITR4.

Viral Genome Component: Promoters

[0333] In some embodiments, the viral genome may comprise an element to enhance the transgene target specificity and/or expression (See *e.g.*, Powell et al. Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy, 2015; the contents of which are herein incorporated by reference in its entirety). In some embodiments, the AAV particle viral genome may comprise an element to enhance the transgene target specificity and/or expression comprise a promoter, an enhancer, *e.g.*, a CMV enhancer, or both. In some embodiments, the AAV particle viral genome comprises a promoter operably linked to a transgene encoded by a nucleic acid molecule encoding a payload, *e.g.*, antibody molecule (*e.g.*, an anti-tau antibody molecule). In some embodiments, the AAV particle viral genome comprises an enhancer, *e.g.*, a CMV enhancer. In some embodiment, the AAV particle viral genome comprises at least two promoters.

[0334] In some embodiments, the viral genome comprises a promoter that is species specific, inducible, tissue-specific, and/or cell cycle-specific (*e.g.*, as described in Parr et al., *Nat. Med.* 3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety). In some embodiments, the viral genome comprises a promoter that is sufficient for expression, *e.g.*, in a target cell, of a payload (*e.g.*, an antibody molecule, *e.g.*, an anti-tau antibody) encoded by a transgene.

[0335] In some embodiments, the promoter results in expression of the payload, *e.g.*, an antibody molecule (*e.g.*, an anti-tau antibody) for a sufficient period of time in a cell, tissue, and/or organ. In some embodiments, the promoter results in expression of the payload for at least 1 hour to 24 hours, *e.g.*, 1-5 hours, 1-10 hours, 1-15 hours, 1-20 hours, 2-5 hours, 2-10 hours, 2-15 hours, 2-20 hours, or 2-24 hours, 3-5 hours, 3-15 hours, 3-20 hours, 3-24 hours, 4-5 hours, 4-15 hours, 4-20 hours, 4-24 hours, 5-15 hours, 5-20 hours, 5-23 hours, 6-15 hours, 6-20 hours 6-24 hours, 7-15 hours, 7-20 hours, 7-24 hours, 8-10 hours, 8-15 hours, 8-20 hours, 8-24 hours, 9-10 hours, 9-15 hours, 9-20 hours, 9-24 hours, 10-15 hours, 10-20 hours, 10-23 hours, 11-15 hours, 11-20 hours 11-24 hours, 12-15 hours, 12-20 hours, 12-24 hours, 13-15 hours, 13-20 hours, 13-24 hours, 14-15 hours, 14-20 hours, 14-23 hours, 15-20 hours, 15-24 hours, 16-20 hours, 16-24 hours, 17-20 hours, 17-24 hours, 18-20 hours, 18-24 hours, 19-20 hours, 19-24 hours, 20-24 hours, 21-24 hours, 22-24 hours, or 23-24 hours, *e.g.*, 1 hour, 5 hours, 10 hours, 12 hours, 14 hours, 18 hours, 20 hours, or 24 hours. In some embodiments, the promoter results in expression of the payload for at least 1-7 days, *e.g.*, 1-6 days, 1-5 days, 1-4 days, 1-3 days, 1-2 days, 2-7

days, 2-6 days, 2-5 days, 2-4 days, 2-3 days, 3-7 days, 3-6 days, 3-5 days, 3-4 days, 4-7 days, 4-6 days, 4-5 days, 5-7 days, 5-6 days, or 6-7 days, *e.g.*, 1 day, 5 days, or 7 days. In some embodiments, the promoter results in expression of the payload for 1 week to 4 weeks, *e.g.*, 1-3 weeks, 1-2 weeks, 2-4 weeks, 2-3 weeks, or 3-4 weeks. In some embodiments, the promoter results in expression of the payload for at least 1-12 months, at least 10-24 months, or at least 1-10 years, *e.g.*, at least 1 year, at least 5 years, at least 10 years, or more than 10 years.

[0336] In some embodiments, the promoter may be a naturally occurring promoter, or a non-naturally occurring promoter. In some embodiments, the promoter is from a naturally expressed protein. In some embodiments, the promoter is an engineered promoter. In some embodiments, the promoter comprises a viral promoter, plant promoter, and/or a mammalian promoter. In some embodiments, the promoter may be a human promoter. In some embodiments, the promoter may be truncated. In some embodiments, the promoter is not a cell specific promoter.

[0337] In some embodiments, the promoter results in expression in one or more, *e.g.*, multiple, cells and/or tissues, *e.g.*, a ubiquitous promoter. In some embodiments, a promoter that results in expression in one or more tissues includes but is not limited to a human elongation factor 1 α -subunit (EF1 α) promoter, a cytomegalovirus (CMV) immediate-early enhancer and/or promoter, a chicken β -actin (CBA) promoter and its derivative CAG, a β glucuronidase (GUSB) promoter, or ubiquitin C (UBC) promoter. In some embodiments, a tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes. In some embodiments, the promoter is a ubiquitous promoter as described in Yu et al. (Molecular Pain 2011, 7:63), Soderblom et al. (E. Neuro 2015), Gill et al., (Gene Therapy 2001, Vol. 8, 1539-1546), and Husain et al. (Gene Therapy 2009), each of which are incorporated by reference in their entirety. In some embodiments, the promoter is a ubiquitous promoter chosen from CMV, CBA (including derivatives CAG, CB6, CBh, *etc.*), EF-1 α , PGK, UBC, GUSB (hGBp), or UCOE (promoter of HNRPA2B1-CBX3).

[0338] In some embodiments, the promoter is a muscle-specific promoter, *e.g.*, a promoter that results in expression in a muscle cell. In some embodiments, a muscle-specific promoter includes but is not limited to a mammalian muscle creatine kinase (MCK) promoter, a mammalian desmin (DES) promoter, a mammalian troponin I (TNNI2) promoter, a synthetic C5-12 promoter, and a mammalian skeletal alpha-actin (ASKA) promoter (see, *e.g.* U.S. Patent Publication US20110212529, the contents of which are herein incorporated by reference in their entirety).

[0339] In some embodiments, the promoter is a nervous system specific promoter, *e.g.*, a promoter that results in expression of a payload in a neuron, an astrocyte, and/or an oligodendrocyte. In some embodiments, a nervous system specific promoter that results in expression in neurons includes but is not limited to a neuron-specific enolase (NSE) promoter, a platelet-derived growth factor (PDGF) promoter, a platelet-derived growth factor B-chain (PDGF- β) promoter, a synapsin (Syn) promoter, a methyl-CpG binding protein 2 (MeCP2) promoter, a Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) promoter, a metabotropic glutamate receptor 2 (mGluR2) promoter, a neurofilament light (NFL) or heavy (NFH) promoter, a β -globin minigene n β 2 promoter, a preproenkephalin (PPE) promoter, an enkephalin (Enk) promoter, and an excitatory amino acid transporter 2 (EAAT2) promoter. In some embodiments, a nervous system specific promoter that results in expression in astrocytes includes but is not limited to a glial fibrillary acidic protein (GFAP) promoter and a EAAT2 promoter. In some embodiments, a nervous system specific promoter that results in expression in oligodendrocytes includes but is not limited to a myelin basic protein (MBP) promoter. In some embodiments, the viral genome comprises a nervous system specific promoter as described in Husain et al. (Gene Therapy 2009), Passini and Wolfe (J. Virol. 2001, 12382-12392), Xu et al. (Gene Therapy 2001, 8, 1323-1332), Drews et al. (Mamm Genome (2007) 18:723-731), and Raymond et al. (Journal of Biological Chemistry (2004) 279(44) 46234-46241), each of which are incorporated by reference in their entirety.

[0340] In some embodiments, the promoter is a liver promoter, *e.g.* a promoter that results in expression a liver cell. In some embodiments, the liver promoter is chosen from human α -1-antitrypsin (hAAT) or thyroxine binding globulin (TBG). In some embodiments, the viral genome comprises an RNA pol III promoter. In some embodiments, the RNA pol III promoter is chosen from U6 or H1.

[0341] In some embodiments, the viral genome comprises two promoters. As a non-limiting example, the promoters are an EF1 α promoter and a CMV promoter.

[0342] In some embodiments, the promoter is a ubiquitin c (UBC) promoter. The UBC promoter may have a size of 300-350 nucleotides. As a non-limiting example, the UBC promoter is 332 nucleotides. In some embodiments, the promoter is a β -glucuronidase (GUSB) promoter. The GUSB promoter may have a size of 350-400 nucleotides. As a non-limiting example, the GUSB promoter is 378 nucleotides. In some embodiments, the promoter is a neurofilament light (NFL) promoter. The NFL promoter may have a size of 600-700 nucleotides. As a non-limiting example, the NFL promoter is 650 nucleotides. In some embodiments, the promoter is a neurofilament heavy (NFH) promoter. The NFH promoter may have a size of 900-950 nucleotides. As a non-limiting example, the NFH promoter is 920 nucleotides. In some

embodiments, the promoter is a *scn8a* promoter. The *scn8a* promoter may have a size of 450-500 nucleotides. As a non-limiting example, the *scn8a* promoter is 470 nucleotides. In some embodiments, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.

[0343] In some embodiments, the promoter is chosen from a CAG promoter, a CBA promoter (*e.g.*, a minimal CBA promoter), a CB promoter, a CMV(IE) promoter and/or enhancer, a GFAP promoter, a synapsin promoter, or a functional variant thereof.

[0344] In some embodiments, the viral genome comprises an enhancer element, a promoter and/or a 5'UTR intron. The enhancer element, also referred to herein as an "enhancer," may be, but is not limited to, a CMV enhancer, the promoter may be, but is not limited to, a CMV, CBA, UBC, GUSB, NSE, Synapsin, MeCP2, and GFAP promoter and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. As a non-limiting example, the enhancer, promoter and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV 40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter; and (9) GFAP promoter.

[0345] In some embodiments, the viral genome comprises a promoter that has a length between about 100-2000 nucleotides. In some embodiments, the promoter has a length between about 100-700 nucleotides, *e.g.*, between about 100-600 nucleotides, 100-500 nucleotides, 100-400 nucleotides, 100-300 nucleotides, 100-200 nucleotides, 200-700 nucleotides, 200-600 nucleotides, 200-500 nucleotides, 200-400 nucleotides, 200-300 nucleotides, 300-700 nucleotides, 300-600 nucleotides, 300-500 nucleotides, 300-400 nucleotides, 400-700 nucleotides, 400-600 nucleotides, 400-500 nucleotides, 500-700 nucleotides, 500-600 nucleotides, or 600-700 nucleotides. In some embodiments, the promoter has a length between about 900-2000 nucleotides, *e.g.*, between about 900-1000 nucleotides, 900-1500 nucleotides, 1000-1500 nucleotides, 1000-2000 nucleotides, or 1500-2000 nucleotides. In some embodiments, the promoter has a length between about 1500 to about 1800 nucleotides, *e.g.*, about 1715 nucleotides. In some embodiments, the promoter has a length of about 500 to about 750 nucleotides, *e.g.*, about 557 nucleotides or about 699 nucleotides. In some embodiments, the promoter has a length of about 200 to about 450 nucleotides, *e.g.*, about 260 nucleotides, about 283 nucleotides, about 299 nucleotides, about 380 nucleotides, or about 399 nucleotides..

[0346] In some embodiments, the viral genome comprises a promoter provided in Table 11. In some embodiments, the promoter is chosen from any one of Promoter 1 - Promoter 12, or a functional variant thereof.

Table 11. Promoter Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
Promoter 1	1715	1039
Promoter 2	299	1040
Promoter 3	283	1041
Promoter 4	260	1042
Promoter 5	654	1043
Promoter 6	699	1044
Promoter 7	557	1045
Promoter 8	382	1046
Promoter 9	1736	1047
Promoter 10	365	1048
Promoter 11	1714	1049
Promoter 12	380	1050

[0347] In some embodiments, the viral genome comprises a promoter provided in Table 11. In some embodiments, the promoter is chosen from any one of Promoter 1- Promoter 12, or a functional variant thereof. In some embodiments, the promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 1039-1050, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1039 or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1040, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1041, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1042, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1043, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1044, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 1050, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto.

[0348] In some embodiments, the viral genome comprises one promoter sequence region. In some embodiments, the promoter sequence region is Promoter 1. In some embodiments, the promoter sequence region is Promoter 2. In some embodiments, the promoter sequence region is Promoter 3. In some embodiments, the promoter sequence region is Promoter 4. In some embodiments, the promoter sequence region is Promoter 5. In some embodiments, the promoter sequence region is Promoter 6. In some embodiments, the promoter sequence region is Promoter 7. In some embodiments, the promoter sequence region is Promoter 8. In some embodiments, the promoter sequence region is Promoter 9. In some embodiments, the promoter sequence region is Promoter 10. In some embodiments, the promoter sequence region is Promoter 11. In some embodiments, the promoter sequence region is Promoter 12.

[0349] In some embodiments, the promoter sequence region further comprises at least one promoter sub-region. As a non-limiting example, the promoter sequence is Promoter 1, further comprising Promoter 2 and Promoter 3 sub-regions. In some embodiments, the viral genome comprises at least 2 or more promoters. In some embodiments, the viral genome comprises Promoter 12 and Promoter 4.

[0350] In some embodiments, the CAG promoter comprises the nucleotide sequence of SEQ ID NO: 1039 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the CBA promoter (*e.g.*, a minimal CBA promoter) comprises the nucleotide sequence of SEQ ID NO: 1041 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the CB promoter comprises the nucleotide sequence of SEQ ID NO: 1042 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the GFAP promoter comprises the nucleotide sequence of SEQ ID NO: 1044 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the synapsin promoter comprises the nucleotide sequence of SEQ ID NO: 1045 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the CMV(IE) promoter comprises the nucleotide sequence of SEQ ID NO: 1050 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the CMV(ie) enhancer comprises a nucleotide sequence of SEQ ID NO: 1040 or nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

[0351] In some embodiments, the viral genome comprises more than one promoter sequence region. In some embodiments, the viral genome comprises two promoter sequence regions. In some embodiments, the viral genome comprises three promoter sequence regions.

Viral genome Component: Untranslated Regions (UTRs)

[0352] In some embodiments, the viral genome comprises an untranslated region (UTR). In some embodiments, a wild type UTR of a gene are transcribed but not translated. In some embodiments, the 5' UTR starts at the transcription start site and ends at the start codon and the 3' UTR starts immediately following the stop codon and continues until the termination signal for transcription.

[0353] In some embodiments, a UTR comprises a feature found in abundantly expressed genes of specific target organs to enhance the stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the liver (*e.g.*, albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII) may be used in the viral genome of an AAV particle described herein to enhance expression in hepatic cell lines or liver.

[0354] In some embodiments, the viral genome comprises a 5'UTR, *e.g.*, a wild-type (*e.g.*, naturally occurring) 5'UTR or a recombinant (*e.g.*, non-naturally occurring) 5'UTR. In some embodiments, a 5' UTR comprises a feature which plays a role in translation initiation. In some embodiments, a UTR, *e.g.*, a 5' UTR, comprises a Kozak sequence. In some embodiments, a Kozak sequence is involved in the process by which the ribosome initiates translation of many genes. In some embodiments, a Kozak sequence has the consensus sequence of CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (ATG), which is followed by another 'G'. In some embodiments, a Kozak sequence comprises the nucleotide sequence of GAGGAGCCACC (SEQ ID NO: 1089) or a nucleotide sequence with at least 95-99% sequence identity thereto. In some embodiments, a Kozak sequence comprises the nucleotide sequence of GCCGCCACCATG (SEQ ID NO: 1079), or a nucleotide sequence with at least 95-99% sequence identity thereto. In some embodiments, a viral genome comprises a 5'UTR comprising a Kozak sequence. In some embodiments, a viral genome comprises a 5'UTR that does not comprise a Kozak sequence.

[0355] In some embodiments, the viral genome comprises a 3'UTR, *e.g.*, a wild-type (*e.g.*, naturally occurring) 3'UTR or a recombinant (*e.g.*, non-naturally occurring) 3'UTR. In some embodiments, a 3' UTR comprises an element that modulates, *e.g.*, increases or decreases, stability of a nucleic acid. In some embodiments, a 3' UTR comprises stretches of Adenosines and Uridines embedded therein, *e.g.*, an AU rich signature. These AU rich signatures are generally prevalent in genes with high rates of turnover and are described, *e.g.*, in Chen et al, 1995, the contents of which are herein incorporated by reference in its entirety. In some embodiments, an AR rich signature comprises an AU rich element (ARE). In some embodiments, a 3'UTR comprises an ARE chosen from a class I ARE (*e.g.*, c-Myc and MyoD), a

class II ARE (*e.g.*, GM-CSF and TNF- α), a class III ARE (*e.g.*, c-Jun and Myogenin), or combination thereto. In some embodiments, a class I ARE comprises several dispersed copies of an AUUUA motif within U-rich regions. In some embodiments, a class II ARE comprises two or more overlapping UUAUUUA(U/A)(U/A) nonamers. In some embodiments, a class III ARE comprises U rich regions and/or do not contain an AUUUA motif. In some embodiments, an ARE destabilizes the messenger.

[0356] In some embodiments, a 3'UTR comprises a binding site for a protein member of the ELAV family. In some embodiments, a 3' UTR comprises a binding site for an HuR protein. In some embodiments, an HuR protein binds to an ARE of any one of classes I-III and/or increases the stability of mRNA. Without wishing to be bound by theory, it is believed in some embodiments, that a 3'UTR comprising an HuR specific binding sites will lead to HuR binding and, stabilization of a message *in vivo*.

[0357] In some embodiments, the 3' UTR of the viral genome comprises an oligo(dT) sequence for templated addition of a poly-A tail.

[0358] In some embodiments, the viral genome comprises a miRNA seed, binding site and/or full sequence. Generally, microRNAs (or miRNA or miR) are 19-25 nucleotide noncoding RNAs that bind to the sites of nucleic acid targets and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. In some embodiments, the microRNA sequence comprises a seed region, *e.g.*, a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence of the nucleic acid. In some embodiments, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, sequence, or seed region.

[0359] In some embodiments, a UTR from any gene known in the art may be incorporated into the AAV particle viral genome described herein. These UTRs, or portions thereof, may be placed in the same orientation as in the gene from which they were selected, or they may be altered in orientation or location. In some embodiments, the UTR used in the viral genome may be inverted, shortened, lengthened, made with one or more other 5' UTRs or 3' UTRs known in the art. In some embodiments, an altered UTR, comprises a UTR has been changed in some way in relation to a reference sequence. For example, a 3' or 5' UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides. In some embodiments, the viral genome comprises an artificial UTR, *e.g.*, a UTR that is not a variant of a wild-type, *e.g.*, a naturally occurring, UTR. In some embodiments, the viral genome comprises a UTR selected from a family of transcripts whose proteins share a common function, structure, feature or property.

Viral Genome Component: miR Binding Site

[0360] Tissue- or cell-specific expression of the AAV viral particles of the invention can be enhanced by introducing tissue- or cell-specific regulatory sequences, *e.g.*, promoters, enhancers, microRNA binding sites, *e.g.*, a detargeting site. Without wishing to be bound by theory, it is believed that an encoded miR binding site can modulate, *e.g.*, prevent, suppress, or otherwise inhibit, the expression of a gene of interest on the viral genome of the invention, based on the expression of the corresponding endogenous microRNA (miRNA) or a corresponding controlled exogenous miRNA in a tissue or cell, *e.g.*, a non-targeting cell or tissue. In some embodiments, a miR binding site modulates, *e.g.*, reduces, expression of the payload encoded by a viral genome of an AAV particle described herein in a cell or tissue where the corresponding mRNA is expressed.

[0361] In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a microRNA binding site, *e.g.*, a detargeting site. In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a miR binding site, a microRNA binding site series (miR BSs), or a reverse complement thereof.

[0362] In some embodiments, the nucleotide sequence encoding the miR binding site series or the miR binding site is located in the 3'-UTR region of the viral genome (*e.g.*, 3' relative to the nucleic acid sequence encoding a payload), *e.g.*, before the polyA sequence, 5'-UTR region of the viral genome (*e.g.*, 5' relative to the nucleic acid sequence encoding a payload), or both.

[0363] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, *e.g.*, at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, all copies are identical, *e.g.*, comprise the same miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, *e.g.*, a non-coding sequence. In some embodiments, the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, nucleotides in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0364] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, *e.g.*, at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, at least 1, 2, 3, 4, 5, or all of the copies are different, *e.g.*, comprise a different miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR

binding sites within an encoded miR binding site series are separated by a spacer, *e.g.*, a non-coding sequence. In some embodiments, the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0365] In some embodiments, the encoded miR binding site is substantially identical (*e.g.*, at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical), to the miR in the host cell. In some embodiments, the encoded miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the encoded miR binding site is 100% identical to the miR in the host cell.

[0366] In some embodiments, the nucleotide sequence encoding the miR binding site is substantially complimentary (*e.g.*, at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical), to the miR in the host cell. In some embodiments, to complementary sequence of the nucleotide sequence encoding the miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the encoded miR binding site is 100% identical to the miR in the host cell.

[0367] In some embodiments, an encoded miR binding site or sequence region is at least about 10 to about 125 nucleotides in length, *e.g.*, at least about 10 to 50 nucleotides, 10 to 100 nucleotides, 50 to 100 nucleotides, 50 to 125 nucleotides, or 100 to 125 nucleotides in length. In some embodiments, an encoded miR binding site or sequence region is at least about 7 to about 28 nucleotides in length, *e.g.*, at least about 8-28 nucleotides, 7-28 nucleotides, 8-18 nucleotides, 12-28 nucleotides, 20-26 nucleotides, 22 nucleotides, 24 nucleotides, or 26 nucleotides in length, and optionally comprises at least one consecutive region (*e.g.*, 7 or 8 nucleotides) complementary to the seed sequence of a miRNA (*e.g.*, a miR122, a miR142, a miR183).

[0368] In some embodiments, the encoded miR binding site is complementary to a miR expressed in liver or hepatocytes, such as miR122. In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR122 binding site sequence. In

some embodiments, the encoded miR122 binding site comprises the nucleotide sequence of ACAAACACCATTGTCACACTCCA (SEQ ID NO: 1029), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1029, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR122 binding site, *e.g.*, an encoded miR122 binding site series, optionally wherein the encoded miR122 binding site series comprises the nucleotide sequence of:

ACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCA (SEQ ID NO: 1030), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1030, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, at least two of the encoded miR122 binding sites are connected directly, *e.g.*, without a spacer. In other embodiments, at least two of the encoded miR122 binding sites are separated by a spacer, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR122 binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8, in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a miR122 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length.

[0369] In some embodiments, the encoded miR binding site is complementary to a miR expressed in hematopoietic lineage, including immune cells (*e.g.*, antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes). In some embodiments, the encoded miR binding site complementary to a miR expressed in hematopoietic lineage comprises a nucleotide sequence disclosed, *e.g.*, in US 2018/0066279, the contents of which are incorporated by reference herein in its entirety.

[0370] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR-142-3p binding site sequence. In some embodiments, the encoded miR-142-3p binding site comprises the nucleotide sequence of TCCATAAAGTAGGAAACACTACA (SEQ ID NO: 1031), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%,

80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1031, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR-142-3p binding site, *e.g.*, an encoded miR-142-3p binding site series. In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a miR-142-3p binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length.

[0371] In some embodiments, the encoded miR binding site is complementary to a miR expressed in a DRG (dorsal root ganglion) neuron, *e.g.*, a miR183, a miR182, and/or miR96 binding site. In some embodiments, the encoded miR binding site complementary to a miR expressed in a DRG neuron comprises a nucleotide sequence disclosed, *e.g.*, in WO2020/132455, the contents of which are incorporated by reference herein in its entirety.

[0372] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR183 binding site sequence. In some embodiments, the encoded miR183 binding site comprises the nucleotide sequence of AGTGAATTCTACCAGTGCCATA (SEQ ID NO: 1032), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1032, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the sequence complementary to the seed sequence corresponds to the double underlined of the encoded miR-183 binding site sequence. In some embodiments, the viral genome comprises at least comprises at least 3, 4, or 5 copies of the encoded miR183 binding site, *e.g.* an encoded miR183 binding site. In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a miR183 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length.

[0373] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR182 binding site sequence. In some embodiments, the encoded miR182 binding site comprises, the nucleotide sequence of AGTGTGAGTTCTACCATTGCCAAA (SEQ ID NO: 1033), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1033, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5

copies of the encoded miR182 binding site, *e.g.*, an encoded miR182 binding site series. In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a miR182 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length.

[0374] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR96 binding site sequence. In some embodiments, the encoded miR96 binding site comprises the nucleotide sequence of AGCAAAAATGTGCTAGTGCCAAA (SEQ ID NO: 1034), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1034, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR96 binding site, *e.g.*, an encoded miR96 binding site series. In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a miR96 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8, in length.

[0375] In some embodiments, the encoded miR binding site series comprises a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, the encoded miR binding site series comprises at least 3, 4, or 5 copies of a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, at least two of the encoded miR binding sites are connected directly, *e.g.*, without a spacer. In other embodiments, at least two of the encoded miR binding sites are separated by a spacer, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a combination of at least two, three, four, five, or all of a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR96 binding site, with or without a spacer, wherein the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, in length.

Viral Genome Component: Exon Sequence Region

[0376] In some embodiments, the viral genome may comprise at least one exon sequence region. In some embodiments, the viral genome comprises at least 2, at least 3, at least 4, or at least 5 exon regions. In some embodiments, the viral genome comprises two Exon sequence regions. In some embodiments, the viral genome comprises three Exon sequence regions. In some embodiments, the viral genome comprises four Exon sequence regions. In some embodiments, the viral genome comprises more than four Exon sequence regions.

[0377] In some embodiments, the exon region(s) may, independently, have a length such as, but not limited to, about 50-150 nucleotides in length, *e.g.*, about 50-140 nucleotides, about 50-130 nucleotides, about 50-120 nucleotides, about 50-110 nucleotides, about 50-100 nucleotides, about 50-90 nucleotides, about 50-80 nucleotides, about 50-80 nucleotides, about 50-70 nucleotides, about 50-60 nucleotides, about 60-150 nucleotides, about 60-140 nucleotides, about 60-130 nucleotides, about 60-120 nucleotides, about 60-110 nucleotides, about 60-100 nucleotides, about 60-90 nucleotides, about 60-80 nucleotides, about 60-80 nucleotides, about 60-70 nucleotides, about 70-150 nucleotides, about 70-140 nucleotides, about 70-130 nucleotides, about 70-120 nucleotides, about 70-110 nucleotides, about 70-100 nucleotides, about 70-90 nucleotides, about 70-80 nucleotides, about 80-150 nucleotides, about 80-140 nucleotides, about 80-130 nucleotides, about 80-120 nucleotides, about 80-110 nucleotides, about 80-100 nucleotides, about 80-90 nucleotides, about 90-150 nucleotides, about 90-140 nucleotides, about 90-130 nucleotides, about 90-120 nucleotides, about 90-110 nucleotides, about 90-100 nucleotides, about 100-150 nucleotides, about 100-140 nucleotides, about 100-130 nucleotides, about 100-120 nucleotides, about 100-110 nucleotides, about 110-150 nucleotides, about 110-140 nucleotides, about 110-130 nucleotides, about 110-120 nucleotides, about 120-150 nucleotides, about 120-140 nucleotides, about 120-130 nucleotides, about 130-150 nucleotides, about 130-140 nucleotides, or about 140-150 nucleotides. In some embodiments, the exon region comprises about 120 nucleotides to about 140 nucleotides in length, *e.g.*, about 134 nucleotides. In some embodiments, the exon region comprises about 40 nucleotides to about 60 nucleotides in length, *e.g.*, about 53 nucleotides.

[0378] In some embodiments, the exon region is provided in Table 12.

Table 12. Exon Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
Exon1	134	1051
Exon2	102	1052
Exon3	59	1053

Exon4	53	1054
Exon5	54	1055

[0379] In some embodiments, the viral genome comprises an exon region chosen from Exon1, Exon2, Exon3, Exon4, or a function variant thereof. In some embodiments, the exon region comprises the nucleotide sequence of any one of SEQ ID NOs: 1051-1055, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

[0380] In some embodiments, the viral genome comprises one Exon sequence region. In some embodiments, the Exon sequence region is the Exon1 sequence region. In some embodiments, the Exon sequence region is the Exon2 sequence region. In some embodiments, the Exon sequence region is the Exon3 sequence region. In some embodiments, the Exon sequence region is the Exon4 sequence region. In some embodiments, the Exon sequence region is the Exon5 sequence region.

Viral Genome Component: Intron Sequence Region

[0381] In some embodiments, the viral genome comprises at least one element to enhance the expression of a transgene encoding a payload. In some embodiments, an element that enhances expression of a transgene comprises an introns or functional variant thereof. In some embodiments, the viral genome comprises an intron or functional variant thereof. In some embodiments, the viral genome comprises at least two intron regions, *e.g.*, at least 2 intron regions, at least 3 intron regions, at least 4 intron regions, or 5 or more intron regions.

[0382] In some embodiments, the viral genome comprises an intron chosen from a MVM intron (67-97 bps), an F.IX truncated intron 1 (300 bps), an β -globin SD/immunoglobulin heavy chain splice acceptor intron (250 bps), an adenovirus splice donor/immunoglobulin splice acceptor intron (500 bps), SV40 late splice donor/splice acceptor intron (19S/16S) (180 bps), or a hybrid adenovirus splice donor/IgG splice acceptor intron (230 bps). In some embodiments, the viral genome comprises a human beta-globin intron region.

[0383] In some embodiments, the viral genome comprises an intron region comprising about 10 nucleotides to about 1200 nucleotides in length. In some embodiments, the intron region comprises about 10-100 nucleotides in length, *e.g.*, about 10-90 nucleotides, about 10-80 nucleotides, about 10-70 nucleotides, about 10-60 nucleotides, about 10-50 nucleotides, about 10-40 nucleotides, about 10-30 nucleotides, about 10-20 nucleotides, about 20-100 nucleotides, about 20-90 nucleotides, about 20-80 nucleotides, about 20-70 nucleotides, about 20-60 nucleotides, about 20-50 nucleotides, about 20-40 nucleotides, about 20-30 nucleotides, about 30-100 nucleotides, about 30-90 nucleotides, about 30-80 nucleotides, about 30-70 nucleotides, about 30-60 nucleotides, about 30-50 nucleotides, about 30-40 nucleotides, about 40-100

nucleotides, about 40-90 nucleotides, about 40-80 nucleotides, about 40-70 nucleotides, about 40-60 nucleotides, about 40-50 nucleotides, about 50-100, about 50-90 nucleotides, about 50-80 nucleotides, about 50-70 nucleotides, about 50-60 nucleotides, about 60-100 nucleotides, about 60-90 nucleotides, about 60-80 nucleotides, about 60-70 nucleotides, about 70-100 nucleotides, about 70-90 nucleotides, about 70-80 nucleotides, about 80-100 nucleotides, about 80-90 nucleotides, or about 90-100 nucleotides in length. In some embodiments, the intron region comprises about 100-600 nucleotides in length, *e.g.*, about 100-500 nucleotides, about 100-400 nucleotides, about 100-300 nucleotides, about 100-200 nucleotides, about 200-600 nucleotides, about 200-500 nucleotides, about 200-400 nucleotides, about 200-300 nucleotides, about 300-600 nucleotides, about 300-500 nucleotides, about 300-400 nucleotides, about 400-600 nucleotides, about 400-500 nucleotides, or about 500-600 nucleotides in length. In some embodiments, the intron region comprises about 900-1200 nucleotides in length, *e.g.*, about 900-1100 nucleotides, about 900-1000 nucleotides, about 1000-1200 nucleotides, about 1000-1100 nucleotides, or about 1100-1200 nucleotides.

[0384] In some embodiments, the intron region comprises about 20 to about 40 nucleotides in length, *e.g.*, about 32 nucleotides. In some embodiments, the intron region comprises about 340 to about 360 nucleotides in length, *e.g.*, about 347 nucleotides. In some embodiments, the intron region comprises about 550 to about 570 nucleotides in length, *e.g.*, about 566 nucleotides.

[0385] As a non-limiting example, the viral genome comprises an intron region that is about 15 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 32 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 41 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 53 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 73 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 168 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 172 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 292 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 347 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 387 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 491 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 566 nucleotides in length. As a non-limiting example, the viral genome comprises an intron region that is about 1074 nucleotides in length.

[0386] In some embodiments, the viral genome comprises an intron region provided in Table 13.

Table 13. Intron Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
Intron1	32	1056
Intron2	15	1057
Intron3	347	1058
Intron4	168	1059
Intron5	73	1060
Intron6	73	1061
Intron7	73	1062
Intron8	53	1063
Intron9	172	1064
Intron10	1074	1065
Intron11	41	1066
Intron12	566	1067
Intron13	491	1068
Intron14	387	1069
Intron15	292	1070

[0387] In some embodiments, the viral genome comprises an intron region chosen from any one of Intron1 to Intron15, or a functional variant thereof. In some embodiments, the viral genome comprises Intron1. In some embodiments, the viral genome comprises Intron3. In some embodiments, the viral genome comprises Intron12. In some embodiments, the viral genome comprises Intron12 and Intron3. In some embodiments, the viral genome comprises Intron1 and Intron12. In some embodiments, the viral genome comprises an intron region of any one of SEQ ID NOs: 1056-1070, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

[0388] In some embodiments, the viral genome comprises one intron sequence region. In some embodiments, the intron sequence region is the Intron 1 sequence region. In some embodiments, the intron sequence region is the Intron 2 sequence region. In some embodiments, the intron sequence region is the Intron3 sequence region. In some embodiments, the intron sequence region is the Intron4 sequence region. In some embodiments, the intron sequence region

is the Intron5 sequence region. In some embodiments, the intron sequence region is the Intron6 sequence region. In some embodiments, the intron sequence region is the Intron7 sequence region. In some embodiments, the intron sequence region is the Intron8 sequence region. In some embodiments, the intron sequence region is the Intron9 sequence region. In some embodiments, the intron sequence region is the Intron10 sequence region. In some embodiments, the intron sequence region is the Intron11 sequence region. In some embodiments, the intron sequence region is the Intron12 sequence region. In some embodiments, the intron sequence region is the Intron13 sequence region. In some embodiments, the intron sequence region is the Intron14 sequence region. In some embodiments, the intron sequence region is the Intron15 sequence region.

[0389] In some embodiments, the viral genome comprises two intron sequence regions. In some embodiments, the viral genome comprises three intron sequence regions. In some embodiments, the viral genome comprises more than three intron sequence regions.

Viral Genome Component: Signal Sequence Region

[0390] In some embodiments, the viral genome comprises a nucleotide sequence encoding a signal sequence region (*e.g.*, one, two, or three signal sequence region(s)). In some embodiments, the nucleic acid sequence encoding the signal sequence is located 5' relative to the nucleic acid sequence encoding the VH and/or the heavy chain. In some embodiments, the nucleotide sequence encoding the signal sequence is located 5' relative to the nucleic acid sequence encoding the VL and/or the light chain. In some embodiments, the encoded VH, VL, heavy chain, and/or light chain of the encoded antibody molecule comprises a signal sequence at the N-terminus, wherein the signal sequence is optionally cleaved during cellular processing and/or localization of the antibody molecule.

[0391] In some embodiments, the signal sequence is derived from an antibody, variant or fragment thereof. In another embodiment, the signal sequence region may not be derived from an antibody. In some embodiments, the signal sequence is derived from the same antibody as the heavy and light chain. In some embodiments, the signal sequence is derived from the same antibody as one of the heavy or light chain sequences. In some embodiments, the signal sequence is derived from a different antibody than either the heavy or light chain sequences.

[0392] As a non-limiting example, a signal sequence or the nucleotide sequence encoding the signal sequence may be derived from the heavy chain or the light chain of an anti-tau antibody, such as, but not limited to, IPN002, PHF1 and/or MC1. While not wishing to be bound by theory, the first approximately 57 nucleotides of an antibody heavy chain or light chain sequence may be

considered a signal sequence. Non-limiting examples of antibody derived signal sequences include Signal13-Signal18 (SEQ ID NO: 1083-1088, respectively).

[0393] In some embodiments, the signal sequence region may signal for transcription. In some embodiments, the signal sequence region may signal for translation. In some embodiments, the signal sequence region directs the payload out of the nucleus or out of the cell. In some embodiments, the signal sequence region directs the payload to a particular target, wherein the target may be an organ, tissue, cell, cellular compartment, cellular organelle or a component of any of the above.

[0394] The signal sequence region(s) may, independently, have a length such as, but not limited to, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, or more than 150 nucleotides. The length of the signal region in the viral genome may be 10-15, 15-25, 25-35, 25-50, 35-45, 45-55, 50-75, 55-65, 65-75, 75-85, 75-100, 85-95, 95-105, 100-125, 105-115, 115-125, 125-135, 125-150, 135-145, 145-155, 150-175, 155-165, 165-175, 175-185, 175-200, 185-195, 195-205, 200-225, 205-215, 215-225, 225-235, 225-250, 235-245, 245-255, 250-275, 255-265, 265-275, 275-285, 275-300, 285-295, 295-305, 300-325, 305-315, 315-325, 325-335, 325-350, 335-345, and 345-500 nucleotides.

[0395] In some embodiments, the viral genome comprises at least one signal sequence region. Non-limiting examples of signal sequence regions are listed in Table 14.

Table 14. Signal Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
Signal1	84	1071
Signal2	93	1072
Signal3	96	1073
Signal4	66	1074
Signal5	72	1075
Signal6	93	1076
Signal7	69	1077

Signal8	81	1078
Signal9	12	1079
Signal10	81	1080
Signal11	66	1081
Signal12	78	1082
Signal13	57	1083
Signal14	57	1084
Signal15	57	1085
Signal16	411	1086
Signal17	57	1087
Signal18	72	1088
Signal19	11	1089

[0396] In some embodiments, the viral genome comprises one signal sequence region. In some embodiments, the viral genome comprises two signal sequence regions. In some embodiments, the viral genome comprises three signal sequence regions. In some embodiments, the viral genome comprises more than three signal sequence regions. In some embodiments, the signal sequences of a viral genome comprising more than one signal sequence, are the same. In another embodiment, the signal sequences of a viral genome comprising more than one signal sequence, are not the same.

[0397] In some embodiments, the viral genome comprises one signal sequence region. In some embodiments, the signal sequence region is the Signal1 sequence region. In some embodiments, the signal sequence region is the Signal2 sequence region. In some embodiments, the signal sequence region is the Signal3 sequence region. In some embodiments, the signal sequence region is the Signal4 sequence region. In some embodiments, the signal sequence region is the Signal5 sequence region. In some embodiments, the signal sequence region is the Signal6 sequence region. In some embodiments, the signal sequence region is the Signal7 sequence region. In some embodiments, the signal sequence region is the Signal8 sequence region. In some embodiments, the signal sequence region is the Signal9 sequence region. In some embodiments, the signal sequence region is the Signal10 sequence region. In some embodiments, the signal sequence region is the Signal11 sequence region. In some embodiments, the signal sequence region is the Signal12 sequence region. In some embodiments, the signal sequence region is the Signal13 sequence region. In some embodiments, the signal sequence region is the Signal14 sequence region. In some embodiments, the signal sequence region is the Signal15

sequence region. In some embodiments, the signal sequence region is the Signal16 sequence region. In some embodiments, the signal sequence region is the Signal17 sequence region. In some embodiments, the signal sequence region is the Signal18 sequence region. In some embodiments, the signal sequence region is the Signal19 sequence region.

[0398] In some embodiments, the signal sequence comprises any one of the signal sequences provided in Table 14 or a functional variant thereof. In some embodiments, the encoded signal sequence comprises an amino acid sequence encoded by any one of the nucleotide sequences provided in Table 14, or an amino acid sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the nucleic acid sequence encoding the signal sequence comprises any one of the nucleotide sequences provided in Table 14, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

Viral Genome Component: Linkers

[0399] In some embodiments, the viral genome comprises or encodes a linker region or linker. In some embodiments, the linker connects two antibody sequence regions of the viral genome (*e.g.*, a VH-linker-VL, VL-linker-VH heavy chain-linker-light chain or light chain-linker-heavy chain).

[0400] In some cases, the linker may be a peptide linker that may be used to connect the polypeptides encoded by the payload region (*e.g.*, light and heavy antibody chains during expression). Some peptide linkers may be cleaved after expression to separate heavy and light chain domains, allowing assembly of mature antibodies or antibody fragments. Linker cleavage may be enzymatic. In some cases, linkers comprise an enzymatic cleavage site to facilitate intracellular or extracellular cleavage. Some payload regions encode linkers that interrupt polypeptide synthesis during translation of the linker sequence from an mRNA transcript. Such linkers may facilitate the translation of separate protein domains (*e.g.*, heavy and light chain antibody domains) from a single transcript. In some cases, two or more linkers are encoded by a payload region of the viral genome.

[0401] In some embodiments, the encoded linker comprises a linker provided in Table 15.. For those sequences described by their amino acid composition (*e.g.*, G4S; SEQ ID NO: 1097) the SEQ ID NO: provided in parentheses represents the amino acid sequence while the SEQ ID NO: column lists DNA SEQ ID NO.

Table 15. Linkers

Linker ID	Description	Length	Nucleotide SEQ ID NO:
Linker1	Furin	12	1090
Linker2	Furin	12	1091
Linker3	T2A	54	1092
Linker4	F2A	75	1093
Linker5	P2A	66	1094
Linker6	IRES	609	1095
Linker7	IRES-2	623	1096
Linker8	G4S (SEQ ID NO:1097)	15	1098
Linker9	SG4S (SEQ ID NO: 1099)	18	1100
Linker10	(G4S)2 (SEQ ID NO: 1101)	30	1102
Linker11	(G4S)3 (SEQ ID NO: 1103)	45	1104
Linker12	(G4S)3 (SEQ ID NO: 1103)	45	1105
Linker13	(G4S)4 (SEQ ID NO: 1106)	60	1107
Linker14	(G4S)4 (SEQ ID NO: 1106)	60	1108
Linker15	(G4S)5 (SEQ ID NO: 1109)	75	1110
Linker16	(G4S)5 (SEQ ID NO: 1109)	75	1111
Linker17	(G4S)5 (SEQ ID NO: 1109)	75	1112
Linker18	(G4S)6 (SEQ ID NO: 1113)	90	1114
Linker19	(G4S)6 (SEQ ID NO: 1113)	90	1115
Linker20	(G4S)8 (SEQ ID NO: 1116)	120	1117

Linker21	(G4S)8 (SEQ ID NO:1116)	120	1118
Linker22	nxG4S, where n=1-10 (SEQ ID NO: 1119)	50	-
Linker23	hIgG2 hinge	54	1120
Linker24	hIgG3 hinge	108	1121
Linker25	hIgG3-2 hinge	153	1122
Linker26	hIgG3-3 hinge	198	1123
Linker27	msiGG-1 hinge	45	1124
Linker28	msiGG1 hinge	18	1125
Linker29	HigG3 hinge	198	1126

[0402] In some embodiments, the encoded linker comprises an amino acid sequence encoded by any one of the nucleotide sequences provided in Table 15, or an amino acid sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the nucleic acid sequence encoding the linker comprises any one of the nucleotide sequences provided in Table 15, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

[0403] In some embodiments, the encoded linker comprises an enzymatic cleavage site, *e.g.*, for intracellular and/or extracellular cleavage. In some embodiments, the linker is cleaved to separate the VH and the VL of the antigen binding domain and/or the heavy chain and light chain of the antibody molecule (*e.g.*, an anti-tau antibody).

[0404] In some embodiments, the encoded linker comprises a furin linker (furin cleavage sites) or a functional variant. In some embodiments, furin cleaves proteins just downstream of a basic amino acid target sequence (Arg-X-(Arg/Lys)-Arg). In some embodiments, the nucleotide sequence encoding the furin linker comprises the nucleotide sequence of SEQ ID NO: 1090 or 1091, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, furin cleaves proteins downstream of a basic amino acid target sequence (*e.g.*, Arg-X-(Arg/Lys)-Arg) (*e.g.*, as described in Thomas, G., 2002. Nature Reviews Molecular Cell Biology 3(10): 753-66; the contents of which are herein incorporated by reference in its entirety).

[0405] In some embodiments, the encoded linker comprises a 2A self-cleaving peptide (*e.g.*, a 2A peptide derived from foot-and-mouth disease virus (F2A), porcine teschovirus-1 (P2A), *Thoseaasigna* virus (T2A), or equine rhinitis A virus (E2A)). The 2A designation refers specifically to a region of picornavirus polyproteins that lead to a ribosomal skip at the glycyl-

prolyl bond in the C-terminus of the 2A peptide (Kim, J.H. *et al.*, 2011. PLoS One 6(4): e18556; the contents of which are herein incorporated by reference in its entirety). This skip results in a cleavage between the 2A peptide and its immediate downstream peptide. Without wishing to be bound by theory, it is believed in some embodiments, that 2A peptides generate stoichiometric expression of proteins flanking the 2A peptide and their shorter length can be advantageous in generating viral expression vectors.

[0406] In some embodiments, the encoded linker comprises a T2A self-cleaving peptide linker. In some embodiments, the nucleotide sequence encoding the T2A linker comprises the nucleotide sequence of SEQ ID NO: 1092, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the nucleic acid encoding the payload encodes a furin linker and a T2A linker.

[0407] In some embodiments, the encoded linker comprises an internal ribosomal entry site (IRES) is a nucleotide sequence (>500 nucleotides) for initiation of translation in the middle of a nucleotide sequence, *e.g.*, an mRNA sequence (Kim, J.H. *et al.*, 2011. PLoS One 6(4): e18556; the contents of which are herein incorporated by reference in its entirety), which can be used, for example, to modulate expression of one or more transgenes. Use of an IRES sequence ensures co-expression of genes before and after the IRES, though the sequence following the IRES may be transcribed and translated at lower levels than the sequence preceding the IRES sequence.

[0408] In some embodiments, the encoded linker comprises a small and unbranched serine-rich peptide linker, such as those described by Huston *et al.* in US Patent No. US5525491, the contents of which are herein incorporated in their entirety. In some embodiments, polypeptides comprising a serine-rich linker has increased solubility. In some embodiments, the encoded linker comprises an artificial linker, such as those described by Whitlow and Filpula in US Patent No. US5856456 and Ladner *et al.* in US Patent No. US 4946778, the contents of each of which are herein incorporated by their entirety.

[0409] In some embodiments, the viral genome comprises one or more linkers such as, but not limited to, cathepsin, matrix metalloproteinases or legumain cleavage sites. Such linkers are described *e.g.* by Cizeau and Macdonald in International Publication No. WO2008052322, the contents of which are herein incorporated in their entirety.

[0410] In some embodiments, the viral genome may encode linkers that are not cleaved. In some embodiments, any of the antibody molecules described herein can have a flexible polypeptide linker, of varying lengths, connecting the variable domains (*e.g.*, the VH and the VL) of the antigen binding domain of the antibody molecule. For example, a (Gly4-Ser)*n* linker, wherein *n* is 0, 1, 2, 3, 4, 5, 6, 7, or 8 can be used (*e.g.*, any one of SEQ ID NOs: 1098, 1100, 1102, 1104-1105, 1107-1108, 1110-1112, 1114-1115, 1117-1119). In some embodiments, such

linkers may include a simple amino acid sequence, such as a glycine rich sequence. In some cases, the linkers comprise glycine and serine residues. In some embodiments, the linker may comprise flexible peptide linkers of different lengths, *e.g.* nxG4S, where n=1-10 (SEQ ID NO: 1119), and the length of the encoded linker varies between 5 and 50 amino acids. In a non-limiting example, the linker may be 5xG4S (SEQ ID NO: 1109). Without wishing to be bound by theory, it is believed in some embodiments, that these flexible linkers are small and without side chains so they tend not to influence secondary protein structure while providing a flexible linker between antibody segments (George, R.A., *et al.*, 2002. Protein Engineering 15(11): 871-9; Huston, J.S. *et al.*, 1988. PNAS 85:5879-83; and Shan, D. *et al.*, 1999. Journal of Immunology. 162(11):6589-95; the contents of each of which are herein incorporated by reference in their entirety). Furthermore, the polarity of the serine residues improves solubility and prevents aggregation problems.

[0411] In some embodiments, the viral genome encodes at least one G4S3 linker (“G4S3” disclosed as SEQ ID NO: 1103). In some embodiments, the viral genome encodes at least one G4S linker (“G4S” disclosed as SEQ ID NO: 1097). In some embodiments, the viral genome encodes at least one furin site. In some embodiments, the viral genome encodes at least one G4S5 linker (“G4S5” disclosed as SEQ ID NO: 1109). In some embodiments, the viral genome encodes at least one T2A linker. In some embodiments, the viral genome encodes at least one F2A linker. In some embodiments, the viral genome encodes at least one P2A linker. In some embodiments, the viral genome encodes at least one furin and one 2A linker. As non-limiting examples, the viral genome may comprise furin and T2A linkers or furin and F2A linkers.

[0412] In some embodiments, the AAV particle viral genome encodes at least one IRES sequence. In some embodiments, the viral genome encodes at least one hinge region. As a non-limiting example, the hinge is an IgG hinge.

[0413] In some embodiments, the nucleic acid sequence encoding the linker comprises about 10 to about 700 nucleotides in length, *e.g.*, about 10 to about 700 nucleotides, *e.g.* about 10 to about 100, *e.g.*, about 50-200 nucleotides, about 150-300 nucleotides, about 250-400 nucleotides, about 350-500 nucleotides, about 450-600 nucleotides, about 550-700 nucleotides, about 650-700 nucleotides. In some embodiments, the nucleic acid sequence encoding the linker comprises about 5 to about 20 nucleotides in length, *e.g.*, about 12 nucleotides in length. In some embodiments, the nucleic acid sequence encoding the linker comprises about 40 to about 60 nucleotides in length, *e.g.*, about 54 nucleotides in length.

[0414] In some embodiments, the linker region may be 1-50, 1-100, 50-100, 50-150, 100-150, 100-200, 150-200, 150-250, 200-250, 200-300, 250-300, 250-350, 300-350, 300-400, 350-400, 350-450, 400-450, 400-500, 450-500, 450-550, 500-550, 500-600, 550-600, 550-650, or 600-650

nucleotides in length. The linker region may have a length of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 115, 120, 125, 130, 135, 140, 145, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 165, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 185, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 640, 650 or greater than 650. In some embodiments, the linker region may be 12 nucleotides in length. In some embodiments, the linker region may be 15 nucleotides in length, In some embodiments, the linker region may be 18 nucleotides in length. In some embodiments, the linker region may be 30 nucleotides in length. In some embodiments, the linker region may be 45 nucleotides in length. In some embodiments, the linker region may be 54 nucleotides in length. In some embodiments, the linker region may be 60 nucleotides in length. In some embodiments, the linker region may be 66 nucleotides in length. In some embodiments, the linker region may be 75 nucleotides in length. In some embodiments, the linker region may be 78 nucleotides in length. In some embodiments, the linker region may be 87 nucleotides in length. In some embodiments, the linker region may be 108 nucleotides in length. In some embodiments, the linker region may be 120 nucleotides in length. In some embodiments, the linker region may be 153 nucleotides in length. In some embodiments, the linker region may be 198 nucleotides in length. In some embodiments, the linker region may be 609 nucleotides in length. In some embodiments, the linker region may be 623 nucleotides in length.

Viral Genome Component: Tag

[0415] In some embodiments, the viral genome may comprise a tag polypeptide (*e.g.*, a tag sequence or tag sequence region herein). As used herein, the term “tag” indicates a polynucleotide sequence appended to the payload, that once expressed may be used to identify the expressed payload. Alternatively, the term “tag” may indicate a polynucleotide sequence appended to the payload that signals for retention of the expressed payload in a particular region of the cell (*e.g.*, endoplasmic reticulum).

[0416] In some embodiments, the nucleotide sequence encoding the tag polypeptide comprises about 10-50 nucleotides in length, *e.g.*, about 10-40 nucleotides, about 10-30

nucleotides, about 10-20 nucleotides, about 20-50 nucleotides, about 20-40 nucleotides, about 20-30 nucleotides, about 30-50 nucleotides, about 30-40 nucleotides, or about 40 to 50 nucleotides. In some embodiments, the nucleotide sequence encoding the tag polypeptide comprises about 10 nucleotides to about 30 nucleotides, *e.g.*, about 18 nucleotides or about 21 nucleotides. In some embodiments, the nucleotide sequence encoding the tag polypeptide comprises about 20 nucleotides to about 40 nucleotides, *e.g.*, about 27 nucleotides..

Table 16. Tag Sequence Regions

Sequence Region Name	Sequenc e Length	SEQ ID NO
Tag1	27	1127
Tag2	21	1128
Tag3	18	1129
Tag4	18	1130
Tag5	18	1131
Tag6	4	1132
Tag7	6	1133

[0417] In some embodiments, the viral genome comprises a tag sequence provided in Table 16. In some embodiments, the viral genome comprises any one of Tag1-Tag7 or a functional variant thereof. In some embodiments, the tag sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 1127-1133, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto. In some embodiments, the encoded tag polypeptide comprises an amino acid sequence encoded by of any one of SEQ ID NOs: 1127-1133, or an amino acid sequence with at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity thereto.

[0418] In some embodiments, the viral genome comprises one tag sequence region. In some embodiments, the tag sequence region is the Tag1 sequence region. In some embodiments, the tag sequence region is the Tag2 sequence region. In some embodiments, the tag sequence region is the Tag3 sequence region. In some embodiments, the tag sequence region is the Tag4 sequence region. In some embodiments, the tag sequence region is the Tag5 sequence region. In some embodiments, the encoded tag sequence region is the Tag6 sequence region. In some embodiments, the encoded tag sequence region is the Tag7 sequence region.

[0419] In some embodiments, the viral genome comprises more than one tag sequence region. In some embodiments, the viral genome comprises two tag sequence regions. In some

embodiments, the viral genome comprises three tag sequence regions. In some embodiments, the viral genome comprises more than three tag sequence regions.

Viral Genome Component: Polyadenylation Sequence Region

[0420] In some embodiments, the viral genome may comprise at least one polyadenylation sequence region. In some embodiments, the viral genome comprises a polyadenylation (referred to herein as poly A, polyA, or poly-A) sequence between the 3' end of the transgene encoding the payload and the 5' end of the 3'ITR. In some embodiments, the viral genome comprises two or more polyA sequences. In some embodiments, the viral genome does not comprise a polyA sequence.

[0421] In some embodiments, the polyA signal region comprises a length of about 100-600 nucleotides, *e.g.*, about 100-500 nucleotides, about 100-400 nucleotides, about 100-300 nucleotides, about 100-200 nucleotides, about 200-600 nucleotides, about 200-500 nucleotides, about 200-400 nucleotides, about 200-300 nucleotides, about 300-600 nucleotides, about 300-500 nucleotides, about 300-400 nucleotides, about 400-600 nucleotides, about 400-500 nucleotides, or about 500-600 nucleotides. In some embodiments, the polyA signal region comprises a length of about 100 to 150 nucleotides, *e.g.*, about 127 nucleotides.

Table 17. Poly-A Signal Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
PolyA1	127	1134
PolyA2	477	1135
PolyA3	552	1136

[0422] In some embodiments, the polyA signal region is provided in Table 17. In some embodiments, viral genome comprises a polyA sequence region chosen from polyA1, polyA2, polyA3, or a functional variant thereof. In some embodiments, the polyA signal region comprises the nucleotide sequence of any one of SEQ ID NOs: 1134-1136, or a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

[0423] In some embodiments, the viral genome comprises one polyA sequence region. In some embodiments, the polyA sequence region is the PolyA1 sequence. In some embodiments, the polyA sequence region is the PolyA2 sequence. In some embodiments, the polyA sequence region is the PolyA3 sequence.

[0424] In some embodiments, the viral genome comprises more than one polyA sequence region.

Viral Genome Component: Filler Sequence Region

[0425] In some embodiments, the viral genome may comprise at least one or multiple filler sequence regions.

[0426] In some embodiments, the filler sequence comprises about 100-2000, about 200 to 1900, about 300 to 1800, about 400 to 1700, about 500 to 1600, about 600 to 1500, about 700 to 1500, about 800 to 1500, about 900 to 1500, about 1000-1500 nucleotides in length, *e.g.*, about 1000-1400 nucleotides, about 1000-1300 nucleotides, about 1000-1200 nucleotides, about 1200-1500 nucleotides, about 1200-1400 nucleotides, about 1200-1300 nucleotides, about 1300-1500 nucleotides, about 1300-1400 nucleotides, or about 1400-1500 nucleotides. In some embodiments, the filler sequence comprises about 1140 nucleotides to about 1160 nucleotides in length, *e.g.*, about 1153 nucleotides. In some embodiments, the filler sequence comprises about 1230 nucleotides to about 1250 nucleotides in length, *e.g.*, about 1240 nucleotides. As a non-limiting example, the viral genome comprises a filler region that is about 1153 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1240 nucleotides in length.

[0427] In some embodiments, the A viral genome comprises at least one filler sequence region. Non-limiting examples of filler sequence regions are described in Table 18.

Table 18. Filler Sequence Regions

Sequence Region Name	Sequence Length	SEQ ID NO
FILLER1	1153	1137
FILLER2	1240	1138

[0428] In some embodiments, the viral genome comprises two or more filler sequences. A filler sequence is provided in Table 18. In some embodiments, the viral genome comprises FILLER1, FILLER2, or a functional variant thereof. In some embodiments, the viral genome comprises FILLER 1 and FILLER2. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1137, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% sequence identity thereto. In some embodiments, the filler sequence comprises the nucleotide sequence of SEQ ID NO: 1138, or a nucleotide sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% sequence identity thereto.

[0429] In some embodiments, the viral genome does not comprise a filler sequence region.

Viral Genome Component: Payload

[0430] The viral genomes of the present disclosure comprise at least one payload region. As used herein, “payload” or “payload region” refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome, or an expression product of such polynucleotide or polynucleotide region, *e.g.*, a transgene, a polynucleotide encoding a

polypeptide or multi-polypeptide or a modulatory nucleic acid or regulatory nucleic acid.

Payloads of the present disclosure typically encode polypeptides (*e.g.*, antibodies or antibody-based compositions) or fragments or variants thereof.

[0431] The payload region may be constructed in such a way as to reflect a region similar to or mirroring the natural organization of an mRNA.

[0432] The payload region may comprise a combination of coding and non-coding nucleic acid sequences.

[0433] In some embodiments, the AAV payload region may encode a coding or non-coding RNA.

[0434] In some embodiments, the AAV particle comprises a viral genome with a payload region comprising nucleic acid sequences encoding more than one polypeptide of interest (*e.g.*, heavy and light chains of an antibody). In such an embodiment, a viral genome encoding more than one polypeptide may be replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising more than one polypeptides may express each of the polypeptides in a single cell.

[0435] In some embodiments, an AAV particle comprises a viral genome with a payload region comprising a nucleic acid sequence encoding a heavy chain and a light chain of an antibody, or fragments thereof. The heavy chain and light chain are expressed and assembled to form a functional antibody, which may then be secreted.

[0436] In some embodiments, the payload region may comprise at least one inverted terminal repeat (ITR), a promoter region, an intron region, and a coding region. In some embodiments, the coding region comprises a heavy chain region and/or a light chain region of an antibody, or a fragment thereof, and any two components may be separated by a linker region.

[0437] In some embodiments, the coding region may comprise a payload region with a heavy chain and light chain sequence separated by a linker and/or a cleavage site. In some embodiments, the heavy and light chain sequence is separated by an IRES sequence. In some embodiments, the heavy and light chain sequence is separated by a foot and mouth virus sequence. In some embodiments, the heavy and light chain sequence is separated by a foot and mouth virus sequence and a furin cleavage site. In some embodiments, the heavy and light chain sequence is separated by a porcine teschovirus-1 virus sequence. In some embodiments, the heavy and light chain sequence is separated by a porcine teschovirus-1 virus and a furin cleavage site. In some embodiments, the heavy and light chain sequence is separated by a 5xG4S sequence (“5xG4S” disclosed as SEQ ID NO: 1109).

[0438] In some embodiments, the payload region comprises one or more nucleic acid sequences encoding anti-tau antibodies, variants or fragments thereof. In some embodiments, the

variant is a humanized variant, such as a humanized variant comprising any one or more (*e.g.*, all 6) CDR regions of any one of the antibodies in any one of the Tables 1, 6, 2A-2C, 4 and 5.

[0439] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide or polypeptides comprising a heavy chain variable region (VH) and/or a light chain variable region (VL) sequences each listed in any of Tables 3 or 4, or variants or fragments thereof; optionally the polypeptide(s) further comprises a heavy chain constant region and/or a light chain constant region, such as those listed in Table X. The polypeptide may constitute a full-length antibody (*e.g.*, comprising a VH and a heavy chain constant region, such as those listed in Table X; and a VL and a light chain constant region, such as those listed in Table X), or an antibody fragment thereof, such as Fab, F(ab')₂, scFv, *etc.* The payload region may also comprise a linker between the heavy and light chain sequences. In certain embodiments, the coding sequence for the heavy chain or VH is 5' to the coding sequence for the light chain or VL, or vice versa.

[0440] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide comprising a heavy chain variable region and a light chain variable region sequences listed in Table 3 or 4, or variants or fragments thereof, where the heavy chain variable region sequence is from a different antibody than the light chain variable region sequence. In certain embodiments, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide comprising a heavy chain variable region and a light chain variable region sequences listed in Table 3 or 4, or variants or fragments thereof, where the VH and VL sequences are from the same antibody. The payload region may also comprise a linker between the heavy and light chain variable region sequences.

[0441] In some embodiments, the payload region comprises, in the 5' to 3' direction, an antibody light chain sequence, a linker and a heavy chain sequence (*e.g.*, light-linker-heavy or L.Linker.H or LH). In another embodiment, the linker is not used or absent.

[0442] In some embodiments, the payload region comprises a nucleic acid sequence encoding, in the 5' to 3' direction, an antibody light chain sequence from Tables 3 or 4 (for VL sequence) and X (for constant region sequence), a linker and a heavy chain sequence from Tables 3 or 4 (for VH sequence) and X (for constant region sequence).

[0443] In some embodiments, the payload region comprises, in the 5' to 3' direction, an antibody heavy chain sequence, a linker region (may comprise one or more linkers) and a light chain sequence (*i.e.*, heavy-linker-light or H.Linker.L or HL). In another embodiment, the linker is not used or absent.

[0444] In some embodiments, the payload region comprises a nucleic acid sequence encoding, in the 5' to 3' direction, an antibody heavy chain sequence from Tables 3 or 4 (for VH

sequence) and X (for constant region sequence), one or more linkers, and a light chain sequence from Tables 3 or 4 (for VL sequence) and X (for constant region sequence).

[0445] In some embodiments, the payload region comprises a nucleic acid sequence encoding a single heavy chain. As a non-limiting example, the heavy chain comprises one or more amino acid sequences or fragments thereof described in Tables 3 (for VH), 2A-2C & 6 (for CDRH1-CDRH3), 7 (for FRH1-FRH4), 4 (for CDRH1-CDRH3 or VH), 5 (for CDRH1-CDRH3), and/or X (for heavy chain constant region).

[0446] In some embodiments, the payload region may further comprise a nucleic acid sequence encoding a light chain. As a non-limiting example, the light chain comprises one or more amino acid sequences or fragments thereof described in Tables 3 (for VL), 2A-2C & 6 (for CDRL1-CDRL3), 7 (for FRL1-FRL4), 4 (for CDRL1-CDRL3 or VL), 5 (for CDRL1-CDRL3), and/or X (for light chain constant region).

[0447] Shown in Tables 1, 3, 6, 7, X, 2A-2C, 4, and 5 are a listing of antibody components and their polynucleotides and/or polypeptides sequences. These sequences may be encoded by or included in the viral genomes of the present disclosure. Variants or fragments of the antibody sequences described in Tables 1, 3, 6, 7, X, 2A-2C, 4, and 5 may be utilized in the viral genomes of the present disclosure.

[0448] In some embodiments, the payload region of the AAV particle comprises one or more nucleic acid sequences encoding one or more of the payload antibody polypeptides listed in Tables 1, 3, 6, 7, 2A-2C, 4, and 5, or variants or fragments thereof. As used herein, “antibody polynucleotide” refers to a nucleic acid sequence encoding an antibody polypeptide.

[0449] In some embodiments, the payload region of the AAV particle comprises one or more nucleic acid sequences listed in Table 3, X or 4, or variants or fragments thereof.

[0450] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence encoding a payload antibody with at least 50% identity to one or more payload antibody polypeptides or fragments thereof including framework region, constant region and antigen-binding fragments thereof (such as VH/VL, and CDRs) listed in any of Tables 1, 3, 6, 7, X, 2A-2C, 4, and 5. The encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload antibody polypeptides or fragments thereof listed in Tables 1, 3, 6, 7, X, 2A-2C, 4, and 5, or variants or fragments thereof.

[0451] In some embodiments, the variable region sequence(s) (*e.g.*, heavy or light chain) of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%,

59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload antibody polypeptides listed in Table 3 or 4, or variants or fragments thereof.

[0452] In some embodiments, any one or more of the CDR regions of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity, or contains at least or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 changes (*e.g.*, substitutions including conservative substitutions, deletions, and/or insertions) compared to the CDRs of one or more of the payload antibody polypeptides listed in any of Tables 1, 2A-2C, 6, 4, and 5, or variants or fragments thereof.

[0453] In some embodiments, the framework region of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity, or contains at least or no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 changes (*e.g.*, substitutions including conservative substitutions, deletions, and/or insertions) compared to the framework sequences of one or more of the payload antibody polypeptides listed in Table 7 or 4, or variants or fragments thereof.

[0454] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 90% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3, 6, 7, X, 4, and/or 5, or variants or fragments thereof.

[0455] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 91% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0456] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 92% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a

VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0457] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 93% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0458] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 94% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0459] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 95% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0460] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 96% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0461] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 97% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0462] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 98% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0463] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 99% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a

VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0464] In some embodiments, the payload antibody (*e.g.*, a full length heavy chain or a full-length light chain; or a VH or a VL thereof comprising the HC CDR1-3 or LC CDR1-3) has 100% identity to one or more of the antibody polypeptides (*e.g.*, full-length antibody comprising a VH/VL region and a CH/CL region) listed in Tables 1, 2A-2C, 3-7, and/or X, or variants or fragments thereof.

[0465] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence with at least 50% identity to one or more nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof. The payload nucleic acid sequence may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0466] In some embodiments, the payload nucleic acid sequence has 90% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0467] In some embodiments, the payload nucleic acid sequence has 91% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0468] In some embodiments, the payload nucleic acid sequence has 92% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0469] In some embodiments, the payload nucleic acid sequence has 93% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0470] In some embodiments, the payload nucleic acid sequence has 94% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0471] In some embodiments, the payload nucleic acid sequence has 95% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0472] In some embodiments, the payload nucleic acid sequence has 96% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0473] In some embodiments, the payload nucleic acid sequence has 97% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0474] In some embodiments, the payload nucleic acid sequence has 98% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0475] In some embodiments, the payload nucleic acid sequence has 99% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

[0476] In some embodiments, the payload nucleic acid sequence has 100% identity to one or more of the nucleic acid sequences listed in Table 3 or 4, or variants or fragments thereof.

In some embodiments, the viral genome may comprise one or more components which have been codon-optimized. Codon-optimization may be achieved by any method known to one with skill in the art such as, but not limited to, by a method according to Genscript, EMBOSS, Bioinformatics, NUS, NUS2, Geneinfinity, IDT, NUS3, GregThatcher, Insilico, Molbio, N2P, Snapgene, and/or VectorNTI. Antibody heavy and/or light chain sequences within the same viral genome may be codon-optimized according to the same or according to different methods.

[0477] In some embodiments, the viral genome may comprise any combination of the components described herein, or generally known in the art. In some embodiments, the viral genome may comprise any combination of the following components, including, but not limited to, a 5' ITR, a promoter region (may comprise one or more component pieces), an exon region, an intronic region, a Kozak sequence, one or more signal sequences (antibody signal sequences or signal sequence derived from another protein), one or more furin cleavage sites, one or more linker sequences, one or more antibody light chain variable regions, one or more antibody light chain constant regions, one or more antibody heavy chain variable regions, one or more antibody heavy chain constant regions, a polyadenylation sequence, and/or a filler sequence.

[0478] In some embodiments, the AAV viral genome comprises, when read in the 5' to 3' direction, a 5' ITR, a promoter region, an optional intronic region, a signal sequence, an antibody light chain region, a linker region, a signal sequence, an antibody heavy chain region, a polyadenylation sequence, an optional filler sequence, and a 3' ITR. In some embodiments, the AAV viral genome comprises, when read in the 5' to 3' direction, an antibody construct in a light-linker-heavy format.

[0479] In some embodiments, the AAV viral genome comprises, when read in the 5' to 3' direction, a 5' ITR, a promoter region, an optional intronic region, a signal sequence, an antibody heavy chain region, a linker region, a signal sequence, an antibody light chain region, a polyadenylation sequence, an optional filler sequence, and a 3' ITR. In some embodiments, the AAV viral genome comprises, when read in the 5' to 3' direction, an antibody construct in a heavy-linker-light format.

[0480] The viral genome may encode an antibody fragment, such as, but not limited to Fab, F(ab')² or scFv fragments. In some embodiments, the viral genome encodes a Fab antibody fragment. In another embodiment, the viral genome encodes an F(ab')₂ antibody fragment. In some embodiments, the viral genome encodes an scFv.

[0481] In some embodiments, a viral genome described herein, or a fragment thereof, is packaged in a capsid having a serotype selected from Table 9 or described herein to generate an AAV particle. For example, the capsid serotype may be VOY101, VOY201, AAVPHP.B, AAVPHP.N, AAV1, AAV2, AAV2 variant, AAV3, AAV2/3 variant, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV9 K449R, AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAVDJ, or AAVDJ8, or any variant thereof. In some embodiments, the capsid serotype is AAVPHP.B, AAV9, AAV6, AAVrh10, and/or AAVDJ.

[0482] This disclosure also provides in some embodiments, nucleic acids, cells, AAV vectors, and AAV particles comprising the above viral genome.

AAV Production

[0483] The present disclosure provides methods for the generation of parvoviral particles, *e.g.* AAV particles, by viral genome replication in a viral replication cell.

[0484] In accordance with the disclosure, the viral genome comprising a payload region encoding an antibody, an antibody-based composition or fragment thereof, will be incorporated into the AAV particle produced in the viral replication cell. Methods of making AAV particles are well known in the art and are described in *e.g.*, United States Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353, and WO2001023597; *Methods In Molecular Biology*, ed. Richard, Humana Press, NJ (1995); O'Reilly *et al.*, *Baculovirus Expression Vectors*, A Laboratory Manual, Oxford Univ. Press (1994); Samulski *et al.*, *J. Vir.* 63:3822-8 (1989); Kajigaya *et al.*, *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing *et al.*, *J. Vir.* 66:6922-30 (1992); Kimbauer *et al.*, *Vir.*, 219:37-44 (1996); Zhao *et al.*, *Vir.* 272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the AAV particles are made using the methods described in WO2015191508, the contents of which are herein incorporated by reference in their entirety.

[0485] Viral replication cells commonly used for production of recombinant AAV viral vectors include but are not limited to 293 cells, COS cells, HeLa cells, KB cells, and other mammalian cell lines as described in U.S. Pat. Nos. US6156303, US5387484, US5741683, US5691176, and US5688676; U.S. patent publication No. 2002/0081721, and International Patent Publication Nos. WO 00/47757, WO 00/24916, and WO 96/17947, the contents of each of which are herein incorporated by reference in their entireties.

[0486] In some embodiments, the AAV particles of the present disclosure may be produced in insect cells (*e.g.*, Sf9 cells).

[0487] In some embodiments, the AAV particles of the present disclosure may be produced using triple transfection.

[0488] In some embodiments, the AAV particles of the present disclosure may be produced in mammalian cells.

[0489] In some embodiments, the AAV particles of the present disclosure may be produced by triple transfection in mammalian cells.

[0490] In some embodiments, the AAV particles of the present disclosure may be produced by triple transfection in HEK293 cells.

[0491] The present disclosure provides a method for producing an AAV particle comprising the steps of: 1) co-transfecting competent bacterial cells with a bacmid vector and either a viral construct vector and/or AAV payload construct vector, 2) isolating the resultant viral construct expression vector and AAV payload construct expression vector and separately transfecting viral replication cells, 3) isolating and purifying resultant payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, 4) co-infecting a viral replication cell with both the AAV payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, 5) harvesting and purifying the viral particle comprising a parvoviral genome.

[0492] In some embodiments, the present disclosure provides a method for producing an AAV particle comprising the steps of 1) simultaneously co-transfecting mammalian cells, such as, but not limited to HEK293 cells, with a payload region, a construct expressing rep and cap genes and a helper construct, 2) harvesting and purifying the AAV particle comprising a viral genome.

[0493] In some embodiments, the viral construct vector(s) used for AAV production may contain a nucleotide sequence encoding the AAV capsid proteins where the initiation codon of the AAV VP1 capsid protein is a non-ATG, *i.e.*, a suboptimal initiation codon, allowing the expression of a modified ratio of the viral capsid proteins in the production system, to provide improved infectivity of the host cell. In a non-limiting example, a viral construct vector may contain a nucleic acid construct comprising a nucleotide sequence encoding AAV VP1, VP2, and VP3 capsid proteins, wherein the initiation codon for translation of the AAV VP1 capsid protein is CTG, TTG, or GTG, as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in its entirety.

[0494] In some embodiments, the viral construct vector(s) used for AAV production may contain a nucleotide sequence encoding the AAV rep proteins where the initiation codon of the

AAV rep protein or proteins is a non-ATG. In some embodiments, a single coding sequence is used for the Rep78 and Rep52 proteins, wherein initiation codon for translation of the Rep78 protein is a suboptimal initiation codon, selected from the group consisting of ACG, TTG, CTG and GTG, that effects partial exon skipping upon expression in insect cells, as described in US Patent No. 8,512,981, the contents of which is herein incorporated by reference in its entirety, for example to promote less abundant expression of Rep78 as compared to Rep52, which may be advantageous in that it promotes high vector yields.

[0495] In some embodiments, the viral genome of the AAV particle optionally encodes a selectable marker. The selectable marker may comprise a cell-surface marker, such as any protein expressed on the surface of the cell including, but not limited to receptors, CD markers, lectins, integrins, or truncated versions thereof.

[0496] In some embodiments, selectable marker reporter genes are selected from those described in International Application No. WO 96/23810; Heim *et al.*, Current Biology 2:178-182 (1996); Heim *et al.*, Proc. Natl. Acad. Sci. USA (1995); or Heim *et al.*, Science 373:663-664 (1995); WO 96/30540, the contents of each of which are incorporated herein by reference in their entireties).

[0497] The AAV viral genomes encoding an anti-tau antibody payload described herein may be useful in the fields of human disease, veterinary applications and a variety of *in vivo* and *in vitro* settings. The AAV particles of the present disclosure may be useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders. In some embodiments, the AAV particles are used for the prevention and/or treatment of a tauopathy.

[0498] Various embodiments herein provide a pharmaceutical composition comprising the AAV particles described herein and a pharmaceutically acceptable excipient.

[0499] Various embodiments herein provide a method of treating a subject in need thereof comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition described herein.

[0500] Certain embodiments of the method provide that the subject is treated by a route of administration of the pharmaceutical composition selected from the group consisting of intravenous, intracerebroventricular, intraparenchymal, intrathecal, subpial and intramuscular, or a combination thereof. Certain embodiments of the method provide that the subject is treated for a tauopathy and/or other neurological disorder. In one aspect of the method, a pathological feature of the tauopathy or other neurological disorder is alleviated and/or the progression of the tauopathy or other neurological disorder is halted, slowed, ameliorated or reversed.

[0501] Various embodiments herein describe a method of decreasing the level of soluble tau in the central nervous system of a subject in need thereof comprising administering to said subject an effective amount of the pharmaceutical composition described herein.

[0502] Also described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of AAV particles. In some embodiments, payloads, such as but not limited to anti-tau antibodies, may be encoded by payload constructs or contained within plasmids or vectors or recombinant adeno-associated viruses (AAVs).

[0503] The present disclosure also provides administration and/or delivery methods for vectors and viral particles, *e.g.*, AAV particles, for the treatment or amelioration of neurological disease, such as, but not limited to tauopathy.

III. FORMULATION AND DELIVERY

Pharmaceutical Compositions

[0504] Compounds and AAV particles disclosed herein may be prepared as pharmaceutical compositions. As used herein the term “pharmaceutical composition” refers to compositions including at least one active ingredient and, most often, a pharmaceutically acceptable excipient.

[0505] Relative amounts of the active ingredient (*e.g.* an antibody), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may include between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may include between 0.1% and 100%, *e.g.*, between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0506] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, *e.g.*, to non-human animals, *e.g.* non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats,

dogs, mice, rats, birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[0507] In some embodiments, compositions are administered to humans, human patients, or subjects.

Formulations

[0508] Compounds and AAV particles of the present disclosure can be formulated using one or more excipients to: (1) increase stability; (2) increase cell permeability; (3) permit the sustained or delayed release (*e.g.*, from a sustained release formulation); and/or (4) alter the biodistribution (*e.g.*, target an antibody to specific tissues or cell types). In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, formulations of the present disclosure can include, without limitation, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, transfected cells (*e.g.*, for transplantation into a subject) and combinations thereof.

[0509] Pharmaceutical compositions described herein may be prepared by methods known or hereafter developed in the art of pharmacology. Such preparatory methods may include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[0510] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” refers to a discrete amount of the pharmaceutical composition including a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0511] In some embodiments, the AAV particles may be formulated in phosphate buffered saline (PBS), in combination with an ethylene oxide/propylene oxide copolymer (also known as Pluronic or poloxamer).

[0512] In some embodiments, the AAV particles may be formulated in PBS with 0.001% Pluronic acid (F-68) (poloxamer 188) at a pH of about 7.0.

[0513] In some embodiments, the AAV particles may be formulated in PBS with 0.001% Pluronic acid (F-68) (poloxamer 188) at a pH of about 7.3.

[0514] In some embodiments, the AAV particles may be formulated in PBS with 0.001% Pluronic acid (F-68) (poloxamer 188) at a pH of about 7.4.

[0515] In some embodiments, the AAV particles may be formulated in a solution comprising sodium chloride, sodium phosphate and an ethylene oxide/propylene oxide copolymer.

[0516] In some embodiments, the AAV particles may be formulated in a solution comprising sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic and poloxamer 188/Pluronic acid (F-68).

[0517] In some embodiments, the AAV particles may be formulated in a solution comprising about 180mM sodium chloride, about 10mM sodium phosphate and about 0.001% poloxamer 188. In some embodiments, this formulation may be at a pH of about 7.3. The concentration of sodium chloride in the final solution may be 150mM-200mM. As non-limiting examples, the concentration of sodium chloride in the final solution may be 150mM, 160mM, 170mM, 180mM, 190mM or 200mM. The concentration of sodium phosphate in the final solution may be 1mM-50mM. As non-limiting examples, the concentration of sodium phosphate in the final solution may be 1mM, 2mM, 3mM, 4mM, 5mM, 6mM, 7mM, 8mM, 9mM, 10mM, 15mM, 20mM, 25mM, 30mM, 40mM, or 50mM. The concentration of poloxamer 188 (Pluronic acid (F-68)) may be 0.0001%-1%. As non-limiting examples, the concentration of poloxamer 188 (Pluronic acid (F-68)) may be 0.0001%, 0.0005%, 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, or 1%. The final solution may have a pH of 6.8-7.7. Non-limiting examples for the pH of the final solution include a pH of 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, or 7.7.

[0518] In some embodiments, the AAV particles of the invention may be formulated in a solution comprising about 1.05% sodium chloride, about 0.212% sodium phosphate dibasic, heptahydrate, about 0.025% sodium phosphate monobasic, monohydrate, and 0.001% poloxamer 188, at a pH of about 7.4. As a non-limiting example, the concentration of AAV particle in this formulated solution may be about 0.001%. The concentration of sodium chloride in the final solution may be 0.1-2.0%, with non-limiting examples of 0.1%, 0.25%, 0.5%, 0.75%, 0.95%, 0.96%, 0.97%, 0.98%, 0.99%, 1.00%, 1.01%, 1.02%, 1.03%, 1.04%, 1.05%, 1.06%, 1.07%, 1.08%, 1.09%, 1.10%, 1.25%, 1.5%, 1.75%, or 2%. The concentration of sodium phosphate dibasic in the final solution may be 0.100-0.300% with non-limiting examples including 0.100%, 0.125%, 0.150%, 0.175%, 0.200%, 0.210%, 0.211%, 0.212%, 0.213%, 0.214%, 0.215%, 0.225%, 0.250%, 0.275%, 0.300%. The concentration of sodium phosphate monobasic in the final solution may be 0.010-0.050%, with non-limiting examples of 0.010%, 0.015%, 0.020%, 0.021%, 0.022%, 0.023%, 0.024%, 0.025%, 0.026%, 0.027%, 0.028%, 0.029%, 0.030%, 0.035%, 0.040%, 0.045%, or 0.050%. The concentration of poloxamer 188 (Pluronic acid (F-68)) may be 0.0001%-1%. As non-limiting examples, the concentration of poloxamer 188 (Pluronic acid (F-68)) may be 0.0001%, 0.0005%, 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, or 1%. The final solution may

have a pH of 6.8-7.7. Non-limiting examples for the pH of the final solution include a pH of 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, or 7.7.

[0519] Relative amounts of active ingredient (*e.g.* antibody), pharmaceutically acceptable excipients, and/or any additional ingredients in pharmaceutical compositions in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of subjects being treated and further depending upon route of administration. For example, compositions may include between 0.1% and 99% (w/w) of active ingredient. By way of example, compositions may include between 0.1% and 100%, *e.g.*, between 0.5 and 50%, between 1-30%, between 5-80%, or at least 80% (w/w) active ingredient.

[0520] According to the present disclosure, compounds may be formulated for CNS delivery. Agents that cross the brain blood barrier may be used. For example, some cell penetrating peptides that can target molecules to the brain blood barrier endothelium may be used for formulation (*e.g.*, Mathupala, *Expert Opin Ther Pat.*, 2009, 19, 137-140; the content of which is incorporated herein by reference in its entirety).

Excipients and Diluents

[0521] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by the United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0522] Excipients, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparation are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of conventional excipient media may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient media may be incompatible with certain substances or their derivatives, such as by producing any undesirable biological effects or otherwise interacting in a deleterious manner with any other component(s) of pharmaceutical compositions of the present disclosure.

[0523] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

Inactive Ingredients

[0524] In some embodiments, formulations of the present disclosure may include at least one inactive ingredient. As used herein, the term “inactive ingredient” refers to an agent that does not contribute to the activity of a pharmaceutical composition. In some embodiments, all, none or some of the inactive ingredients which may be used in formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0525] Formulations disclosed herein may include cations or anions. Formulations may include Zn^{2+} , Ca^{2+} , Cu^{2+} , Mn^{2+} , Mg^{+} , or combinations thereof. As a non-limiting example, formulations may include polymers and complexes with metal cations (*See e.g.*, U.S. Pat. Nos. 6265389 and 6555525, each of which is herein incorporated by reference in its entirety).

IV. ADMINISTRATION AND DOSING

Administration

[0526] Compounds and compositions (*e.g.*, AAV particles) of the present disclosure may be administered by any delivery route which results in a therapeutically effective outcome. These include, but are not limited to, enteral (into the intestine), gastroenteral, epidural (into the dura mater), oral (by way of the mouth), transdermal, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraparenchymal (into the substance of a tissue, *e.g.*, brain tissue), intraperitoneal (infusion or injection into the peritoneum), intravesical infusion, intravitreal (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis,

infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracoronaral, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis, and spinal.

[0527] In some embodiments, compositions may be administered in a way which allows them to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. Compounds and compositions of the present disclosure may be administered in any suitable form, including, but

not limited to, as a liquid solution, as a suspension, or as a solid form suitable for liquid solution or suspension in a liquid solution.

[0528] In some embodiments, delivery to a subject may be via a single route administration.

In some embodiments, delivery to a subject may be via multi-site route of administration.

Administration may include a bolus infusion. Administration may include sustained delivery over a period of minutes, hours, or days. Administration by infusion may include an infusion rate that may be changed depending on the subject, distribution, formulation, or other delivery parameter.

Administration may be by more than one route of administration. As non-limiting examples, combination administrations may include intrathecal and intracerebroventricular administration, or intravenous and intraparenchymal administration.

Intravenous administration

[0529] Compounds and compositions of the present disclosure may be administered to a subject by systemic administration. In some embodiments, systemic administration may include intravenous administration. Systemic administration may include intraarterial administration.

[0530] Compounds and compositions of the present disclosure may be administered to a subject by intravenous administration. In some embodiments, intravenous administration may be achieved by subcutaneous delivery. In some embodiments, the AAV particle is administered to the subject via focused ultrasound (FUS), *e.g.*, coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration, *e.g.*, as described in Terstappen *et al.* (Nat Rev Drug Discovery, <https://doi.org/10.1038/s41573-021-00139-y> (2021)), Burgess *et al.* (Expert Rev Neurother. 15(5): 477–491 (2015)), and/or Hsu *et al.* (PLOS One 8(2): 1-8), the contents of which are incorporated herein by reference in its entirety. In some embodiments, the AAV particle is administered to the subject intravenously. Intravenous administration may be achieved by a tail vein injection (*e.g.*, in a mouse model). Intravenous administration may be achieved by retro-orbital injection.

Administration to the CNS

[0531] Compounds and compositions of the present disclosure may be administered to a subject by direct injection into the brain. As a non-limiting example, the brain delivery may be by intrahippocampal administration. Administration may be by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to tissue of the central nervous system. Administration may be by intracranial delivery (See, *e.g.*, US Pat. No. 8119611; the content of which is incorporated herein by reference in its entirety). Administration may be by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular (*e.g.*, intracisternal magna – ICM) administration.

Administration to the brain may be by systemic delivery. As a non-limiting example, the systemic delivery may be by intravascular administration. As a non-limiting example, the systemic or intravascular administration may be intravenous. Administration may be by intraocular delivery route. A non-limiting example of intraocular administration includes an intravitreal injection.

Intramuscular administration

[0532] In some embodiments, the AAV particles may be delivered by intramuscular administration. Whilst not wishing to be bound by theory, the multi-nucleated nature of muscle cells provides an advantage to gene transduction subsequent to AAV delivery. Cells of the muscle are capable of expressing recombinant proteins with the appropriate post-translational modifications. The enrichment of muscle tissue with vascular structures allows for transfer to the blood stream and whole-body delivery. Examples of intramuscular administration include systemic (*e.g.*, intravenous), subcutaneous or directly into the muscle. In some embodiments, more than one injection is administered.

[0533] In some embodiments, the AAV particles of the present disclosure may be delivered by intramuscular delivery route. (See, *e.g.*, U. S. Pat. No. 6506379; the content of which is incorporated herein by reference in its entirety). Non-limiting examples of intramuscular administration include an intravenous injection or a subcutaneous injection.

[0534] In some embodiments, the AAV particles of the present disclosure are administered to a subject and transduce muscle of a subject. As a non-limiting example, the AAV particles are administered by intramuscular administration.

[0535] In some embodiments, the AAV particles of the present disclosure may be administered to a subject by subcutaneous administration.

[0536] In some embodiments, the intramuscular administration is via systemic delivery.

[0537] In some embodiments, the intramuscular administration is via intravenous delivery.

[0538] In some embodiments, the intramuscular administration is via direct injection to the muscle.

[0539] In some embodiments, the muscle is transduced by administration, and this is referred to as intramuscular administration.

[0540] In some embodiments, the intramuscular delivery comprises administration at one site.

[0541] In some embodiments, the intramuscular delivery comprises administration at more than one site. In some embodiments, the intramuscular delivery comprises administration at two sites. In some embodiments, the intramuscular delivery comprises administration at three sites. In some embodiments, the intramuscular delivery comprises administration at four sites. In some embodiments, the intramuscular delivery comprises administration at more than four sites.

[0542] In some embodiments, intramuscular delivery is combined with at least one other method of administration.

[0543] In some embodiments, the AAV particles that may be administered to a subject by peripheral injections. Non-limiting examples of peripheral injections include intraperitoneal, intramuscular, intravenous, conjunctival, or joint injection. It was disclosed in the art that the peripheral administration of AAV vectors can be transported to the central nervous system, for example, to the motor neurons (*e.g.*, U. S. Patent Publication Nos. US20100240739 and US20100130594; the content of each of which is incorporated herein by reference in their entirety).

[0544] In some embodiments, the AAV particles of the present disclosure may be administered to a subject by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to muscle tissue.

[0545] In some embodiments, the AAV particles of the present disclosure are delivered as described in Bright et al 2015 (Neurobiol Aging. 36(2):693-709), the contents of which are herein incorporated by reference in their entirety.

[0546] In some embodiments, the AAV particles of the present disclosure are administered to the gastrocnemius muscle of a subject.

[0547] In some embodiments, the AAV particles of the present disclosure are administered to the bicep femorii of the subject.

[0548] In some embodiments, the AAV particles of the present disclosure are administered to the tibialis anterior muscles.

[0549] In some embodiments, the AAV particles of the present disclosure are administered to the soleus muscle.

Depot administration

[0550] As described herein, in some embodiments, pharmaceutical compositions, AAV particles of the present disclosure are formulated in depots for extended release. Generally, specific organs or tissues (“target tissues”) are targeted for administration.

[0551] In some aspects, pharmaceutical compositions, AAV particles of the present disclosure are spatially retained within or proximal to target tissues. Provided are methods of providing pharmaceutical compositions, AAV particles, to target tissues of mammalian subjects by contacting target tissues (which comprise one or more target cells) with pharmaceutical compositions, AAV particles, under conditions such that they are substantially retained in target tissues, meaning that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissues. Advantageously,

retention is determined by measuring the amount of pharmaceutical compositions, AAV particles, that enter one or more target cells. For example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99%, or greater than 99.99% of pharmaceutical compositions, AAV particles, administered to subjects are present intracellularly at a period of time following administration. For example, intramuscular injection to mammalian subjects may be performed using aqueous compositions comprising pharmaceutical compositions, AAV particles of the present disclosure and one or more transfection reagents, and retention is determined by measuring the amount of pharmaceutical compositions, AAV particles, present in muscle cells.

[0552] Certain aspects are directed to methods of providing pharmaceutical compositions, AAV particles of the present disclosure to a target tissues of mammalian subjects, by contacting target tissues (comprising one or more target cells) with pharmaceutical compositions, AAV particles under conditions such that they are substantially retained in such target tissues. Pharmaceutical compositions, AAV particles comprise enough active ingredient such that the effect of interest is produced in at least one target cell. In some embodiments, pharmaceutical compositions, AAV particles generally comprise one or more cell penetration agents, although “naked” formulations (such as without cell penetration agents or other agents) are also contemplated, with or without pharmaceutically acceptable carriers.

Dose and Regimen

[0553] The present disclosure provides methods of administering compounds and compositions in accordance with the disclosure to a subject in need thereof. Administration may be in any amount and by any route of administration effective for preventing, treating, managing, or diagnosing diseases, disorders, and/or conditions. The exact amount required may vary from subject to subject, depending on species, age, general condition of the subject, severity of disease, particular composition, mode of administration, mode of activity, and the like. Subjects may be, but are not limited to, humans, mammals, or animals. Compositions may be formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of compositions of the present disclosure may be decided by an attending physician within the scope of sound medical judgment. Specific therapeutically effective, prophylactically effective, or appropriate diagnostic dose levels for any particular individual may vary depending upon a variety of factors including the disorder being treated and severity of the disorder; the activity of specific payloads employed; specific compositions employed; age, body weight, general health, sex, and diet of patients; time of administration, route of administration, and rate of excretion of compounds and compositions employed; duration

of treatment; drugs used in combination or coincidental with compounds and compositions employed; and like factors well known in the medical arts.

[0554] In some embodiments, compounds and compositions in accordance with the present disclosure may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, or prophylactic, effect.

[0555] In some embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, or more than four administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a “split dose” is the division of “single unit dose” or total daily dose into two or more doses, *e.g.*, two or more administrations of the “single unit dose”. As used herein, a “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, *i.e.*, single administration event.

[0556] Compounds and compositions of the present disclosure may be administered as a “pulse dose” or as a “continuous flow.” As used herein, a “pulse dose” is a series of single unit doses of any therapeutic agent administered with a set frequency over a period of time. As used herein, a “continuous flow” is a dose of therapeutic agent administered continuously for a period of time in a single route/single point of contact, *i.e.*, continuous administration event. A total daily dose, an amount given or prescribed in a 24-hour period, may be administered by any of these methods, or as a combination of these methods, or by any other methods suitable for pharmaceutical administration.

[0557] In some embodiments, delivery of AAV particles may comprise a total dose between about 1×10^6 VG and about 1×10^{16} VG. In some embodiments, delivery may comprise a total dose of about 1×10^6 , 2×10^6 , 3×10^6 , 4×10^6 , 5×10^6 , 6×10^6 , 7×10^6 , 8×10^6 , 9×10^6 , 1×10^7 , 2×10^7 , 3×10^7 , 4×10^7 , 5×10^7 , 6×10^7 , 7×10^7 , 8×10^7 , 9×10^7 , 1×10^8 , 2×10^8 , 3×10^8 , 4×10^8 , 5×10^8 , 6×10^8 , 7×10^8 , 8×10^8 , 9×10^8 , 1×10^9 , 2×10^9 , 3×10^9 , 4×10^9 , 5×10^9 , 6×10^9 , 7×10^9 , 8×10^9 , 9×10^9 , 1×10^{10} , 1.9×10^{10} , 2×10^{10} , 3×10^{10} , 3.73×10^{10} , 4×10^{10} , 5×10^{10} , 6×10^{10} , 7×10^{10} , 8×10^{10} , 9×10^{10} , 1×10^{11} , 2×10^{11} , 2.5×10^{11} , 3×10^{11} , 4×10^{11} , 5×10^{11} , 6×10^{11} , 7×10^{11} , 8×10^{11} , 9×10^{11} , 1×10^{12} , 2×10^{12} , 3×10^{12} , 4×10^{12} , 5×10^{12} , 6×10^{12} , 7×10^{12} , 8×10^{12} , 9×10^{12} , 1×10^{13} , 2×10^{13} , 3×10^{13} , 4×10^{13} , 5×10^{13} , 6×10^{13} , 7×10^{13} , 8×10^{13} , 9×10^{13} , 1×10^{14} , 2×10^{14} , 3×10^{14} , 4×10^{14} , 5×10^{14} , 6×10^{14} , 7×10^{14} , 8×10^{14} , 9×10^{14} , 1×10^{15} , 2×10^{15} , 3×10^{15} , 4×10^{15} , 5×10^{15} , 6×10^{15} , 7×10^{15} , 8×10^{15} , 9×10^{15} , or 1×10^{16} VG. As a non-limiting

example, the total dose is 1×10^{13} VG. As another non-limiting example, the total dose is 2.1×10^{12} VG.

[0558] In some embodiments, delivery of AAV particles may comprise a composition concentration between about 1×10^6 VG/mL and about 1×10^{16} VG/mL. In some embodiments, delivery may comprise a composition concentration of about 1×10^6 , 2×10^6 , 3×10^6 , 4×10^6 , 5×10^6 , 6×10^6 , 7×10^6 , 8×10^6 , 9×10^6 , 1×10^7 , 2×10^7 , 3×10^7 , 4×10^7 , 5×10^7 , 6×10^7 , 7×10^7 , 8×10^7 , 9×10^7 , 1×10^8 , 2×10^8 , 3×10^8 , 4×10^8 , 5×10^8 , 6×10^8 , 7×10^8 , 8×10^8 , 9×10^8 , 1×10^9 , 2×10^9 , 3×10^9 , 4×10^9 , 5×10^9 , 6×10^9 , 7×10^9 , 8×10^9 , 9×10^9 , 1×10^{10} , 2×10^{10} , 3×10^{10} , 4×10^{10} , 5×10^{10} , 6×10^{10} , 7×10^{10} , 8×10^{10} , 9×10^{10} , 1×10^{11} , 2×10^{11} , 3×10^{11} , 4×10^{11} , 5×10^{11} , 6×10^{11} , 7×10^{11} , 8×10^{11} , 9×10^{11} , 1×10^{12} , 2×10^{12} , 3×10^{12} , 4×10^{12} , 5×10^{12} , 6×10^{12} , 7×10^{12} , 8×10^{12} , 9×10^{12} , 1×10^{13} , 2×10^{13} , 3×10^{13} , 4×10^{13} , 5×10^{13} , 6×10^{13} , 7×10^{13} , 8×10^{13} , 9×10^{13} , 1×10^{14} , 2×10^{14} , 3×10^{14} , 4×10^{14} , 5×10^{14} , 6×10^{14} , 7×10^{14} , 8×10^{14} , 9×10^{14} , 1×10^{15} , 2×10^{15} , 3×10^{15} , 4×10^{15} , 5×10^{15} , 6×10^{15} , 7×10^{15} , 8×10^{15} , 9×10^{15} , or 1×10^{16} VG/mL. In some embodiments, the delivery comprises a composition concentration of 1×10^{13} VG/mL. In some embodiments, the delivery comprises a composition concentration of 2.1×10^{12} VG/mL.

Combinations

[0559] Compounds and compositions of the present disclosure may be used in combination with one or more other therapeutic, prophylactic, research or diagnostic agents. By “in combination with,” it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, research, or diagnostic compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

V. METHODS AND USES OF THE COMPOSITIONS

[0560] In some embodiments, the present disclosure provides methods related to using and evaluating compounds and compositions for therapeutic and diagnostic applications.

Therapeutic applications

[0561] In some embodiments, methods of the present disclosure include methods of treating therapeutic indications using compounds and/or compositions disclosed herein. As used herein, the term “therapeutic indication” refers to any symptom, condition, disorder, or disease that may be alleviated, stabilized, improved, cured, or otherwise addressed by some form of treatment or

other therapeutic intervention. In some embodiments, methods of the present disclosure include treating therapeutic indications by administering antibodies disclosed herein.

[0562] As used herein the terms “treat,” “treatment,” and the like, refer to relief from or alleviation of pathological processes. In the context of the present disclosure insofar as it relates to any of the other conditions recited herein below, the terms “treat,” “treatment,” and the like mean to relieve or alleviate at least one symptom associated with such condition, or to slow or reverse the progression or anticipated progression of such condition.

[0563] By “lower” or “reduce” in the context of a disease marker or symptom is meant a significant decrease in such a level, often statistically significant. The decrease may be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably down to a level accepted as within the range of normal for an individual without such a disorder.

[0564] By “increase” or “raise” in the context of a disease marker or symptom is meant a significant rise in such level, often statistically significant. The increase may be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably up to a level accepted as within the range of normal for an individual without such disorder.

[0565] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of a compound or composition described herein, “effective against” a disease or disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in protein aggregation, reduction in neurofibrillary tangles, reduction in neurodegeneration, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of disease or disorder.

[0566] A treatment or preventive effect is evident when there is a significant improvement, often statistically significant, in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more may be indicative of effective treatment. Efficacy for a given compound or composition may also be judged using an experimental animal model for the given

disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant modulation in a marker or symptom is observed.

[0567] Compounds of the present disclosure and additional therapeutic agents can be administered in combination. Such combinations may be in the same composition, or the additional therapeutic agents can be administered as part of a separate composition or by another method described herein.

[0568] In some embodiments, therapeutic indications that may be addressed by methods of the present disclosure include neurological indications. As used herein, a “neurological indication” refers to any therapeutic indication relating to the central nervous system (CNS). Methods of treating neurological indications according to the present disclosure may include administering compounds (*e.g.*, antibodies) and/or compositions described herein. Neurological indications may include neurological diseases and/or disorders involving irregular expression or aggregation of tau. Such indications may include, but are not limited to neurodegenerative disease, Alzheimer’s disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down’s syndrome, Pick’s disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.

[0569] In some embodiments, methods of treating neurological diseases and/or disorders in a subject in need thereof may include one or more of the steps of: (1) deriving, generating, and/or selecting an anti-tau antibody or fragment or composition thereof; and (2) administering the anti-tau antibody or fragment or composition thereof to the subject. Administration to the subject may slow, stop, or reverse disease progression. As a non-limiting example, disease progression may be measured by cognitive tests such as, but not limited to, the Mini-Mental State Exam (MMSE) or other similar diagnostic tool(s), known to those skilled in the art. As another non-limiting example, disease progression may be measured by change in the pathological features of the brain, CSF or other tissues of the subject, such as, but not limited to a decrease in levels of tau (either soluble or insoluble). In some embodiments, levels of insoluble hyperphosphorylated tau are decreased. In some embodiments, levels of soluble tau are decreased. In some embodiments, both soluble and insoluble tau are decreased. In some embodiments, levels of insoluble hyperphosphorylated tau are increased. In some embodiments, levels of soluble tau are increased. In some embodiments, both insoluble and soluble tau levels are increased. In some embodiments, neurofibrillary tangles are decreased in size, number, density, or combination

thereof. In another embodiment, neurofibrillary tangles are increased in size, number, density or combination thereof.

Neurodegeneration

[0570] Neurodegenerative disease refers to a group of conditions characterized by progressive loss of neuronal structure and function, ultimately leading to neuronal cell death. Neurons are the building blocks of the nervous system(s) and are generally not able to reproduce and/or be replaced, and therefore neuron damage and/or death is especially devastating. Other, non-degenerating diseases that lead to neuronal cell loss, such as stroke, have similarly debilitating outcomes. Targeting molecules that contribute to deteriorating cell structure or function may prove beneficial generally for treatment of neurological indications, including neurodegenerative disease and stroke.

[0571] Certain molecules are believed to have inhibitory effects on neurite outgrowth, contributing to the limited ability of the central nervous system to repair damage. Such molecules include, but are not limited to, myelin associated proteins, such as, but not limited to, RGM (Repulsive guidance molecule), NOGO (Neurite outgrowth inhibitor), NOGO receptor, MAG (myelin associated glycoprotein), and MAI (myelin associated inhibitor). In some embodiments, anti-tau antibodies of the present disclosure may be utilized to target the aforementioned antigens (*e.g.*, neurite outgrowth inhibitors).

[0572] Many neurodegenerative diseases are associated with aggregation of misfolded proteins, including, but not limited to, alpha synuclein, tau (as in tauopathies), amyloid β , prion proteins, TDP-43, and huntingtin (see, *e.g.* De Genst *et al.*, 2014, *Biochim Biophys Acta*;1844(11):1907-1919, and Yu *et al.*, 2013, *Neurotherapeutics.*; 10(3): 459–472, references therein, all of which are herein incorporated by reference in their entirety). The aggregation results from disease-specific conversion of soluble proteins to an insoluble, highly ordered fibrillary deposit. This conversion is thought to prevent the proper disposal or degradation of misfolded proteins, thereby leading to further aggregation. Conditions associated with alpha synuclein misfolding and aggregation are referred to as “synucleinopathies.” In some embodiments, anti-tau antibodies of the present disclosure may be utilized to target misfolded or aggregated proteins.

Alzheimer's disease

[0573] Alzheimer Disease (AD) is a debilitating neurodegenerative disease currently afflicting more than 35 million people worldwide, with that number expected to double in coming decades. Symptomatic treatments have been available for many years but these treatments do not

address the underlying pathophysiology. Recent clinical trials using these and other treatments have largely failed and, to date, no known cure has been identified.

[0574] The AD brain is characterized by the presence of two forms of pathological aggregates, the extracellular plaques composed of β -amyloid ($A\beta$) and the intracellular neurofibrillary tangles (NFT) comprised of hyperphosphorylated microtubule associated protein tau. Based on early genetic findings, β -amyloid alterations were thought to initiate disease, with changes in tau considered downstream. Thus, most clinical trials have been $A\beta$ -centric. Although no mutations of the tau gene have been linked to AD, such alterations have been shown to result in a family of dementias known as tauopathies, demonstrating that changes in tau can contribute to neurodegenerative processes. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly activity. In tauopathies, the tau becomes hyperphosphorylated, misfolds and aggregates as NFT of paired helical filaments (PHF), twisted ribbons or straight filaments. In AD, NFT pathology, rather than plaque pathology, correlates more closely with neuropathological markers such as neuronal loss, synaptic deficits, severity of disease and cognitive decline. NFT pathology marches through the brain in a stereotyped manner and animal studies suggest a trans-cellular propagation mechanism along neuronal connections.

[0575] Several approaches have been proposed for therapeutically interfering with progression of tau pathology and preventing the subsequent molecular and cellular consequences. Given that NFT are composed of a hyperphosphorylated, misfolded and aggregated form of tau, interference at each of these stages has yielded the most avidly pursued set of targets. Introducing agents that limit phosphorylation, block misfolding or prevent aggregation have all generated promising results. Passive and active immunization with late stage anti-phospho-tau antibodies in mouse models have led to dramatic decreases in tau aggregation and improvements in cognitive parameters. It has also been suggested that introduction of anti-tau antibodies can prevent the trans-neuronal spread of tau pathology.

[0576] In some embodiments, anti-tau antibodies of the present disclosure may be used according to methods presented herein to treat subjects suffering from AD and other tauopathies. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing AD or other tauopathies.

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

[0577] Although Alzheimer's disease is, in part, characterized by the presence of tau pathology, no known mutations in the tau gene have been causally linked to the disease.

Mutations in the tau gene have been shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) and demonstrate that alterations in tau can lead to neurodegenerative changes in the brain. Mutations in the tau gene that lead to FTDP-17 are thought to influence splicing patterns, thereby leading to an elevated proportion of tau with four microtubule binding domains (rather than three). These molecules are considered to be more amyloidogenic, meaning they are more likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. *et al.*, 1998, Nature 393(6686):702-5, the contents of which are herein incorporated by reference in their entirety). Although physically and behaviorally, FTDP-17 patients can appear quite similar to Alzheimer's disease patients, at autopsy FTDP-17 brains lack the prominent A β plaque pathology of an AD brain (Gotz, J. *et al.*, 2012, British Journal of Pharmacology 165(5):1246-59, the contents of which are herein incorporated by reference in their entirety). Therapeutically targeting the aggregates of tau protein may ameliorate and prevent degenerative changes in the brain and potentially lead to improved cognitive ability.

[0578] As of today, there is no treatment to prevent, slow the progression, or cure FTDP-17. Medication may be prescribed to reduce aggressive, agitated or dangerous behavior. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[0579] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from FTDP-17. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing FTDP-17.

Chronic traumatic encephalopathy

[0580] Unlike the genetically linked tauopathies, chronic traumatic encephalopathy is a degenerative tauopathy linked to repeated head injuries. The disease was first described in boxers whom behaved “punch drunk” and has since been identified primarily in athletes that play American football, ice hockey, wrestling and other contact sports. The brains of those suffering from CTE are characterized by distinctive patterns of brain atrophy accompanied by accumulation of hyperphosphorylated species of aggregated tau in NFT. In CTE, pathological changes in tau are accompanied by a number of other pathobiological processes, such as inflammation (Daneshvar, D.H. *et al.*, 2015 Mol Cell Neurosci 66(Pt B): 81-90, the contents of which are herein incorporated by reference in their entirety). Targeting the tau aggregates may provide reprieve from the progression of the disease and may allow cognitive improvement.

[0581] As of today, there is no medical therapy to treat or cure CTE. The condition is only diagnosed after death, due to lack of *in vivo* techniques to identify CTE specific biomarkers.

There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[0582] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from CTE. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing CTE.

Prion diseases

[0583] Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare progressive conditions affecting the nervous system. The related conditions are rare and are typically caused by mutations in the PRNP gene which enables production of the prion protein. Gene mutations lead to an abnormally structured prion protein. Alternatively, the abnormal prion may be acquired by exposure from an outside source, *e.g.* by consumption of beef products containing the abnormal prion protein. Abnormal prions are misfolded, causing the brain tissue to degenerate rapidly. Prion diseases include, but are not limited to, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnia (FFI), variably protease-sensitive prionopathy (VPSPr), and kuru. Prion diseases are rare. Approximately 350 cases of prion diseases are diagnosed in the US annually.

[0584] CJD is a degenerative brain disorder characterized by problems with muscular coordination, personality changes including mental impairment, impaired vision, involuntary muscle jerks, weakness and eventually coma. The most common categories of CJD are sporadic, hereditary due to a genetic mutation, and acquired. Sporadic CJD is the most common form affecting people with no known risk factors for the disease. The acquired form of CJD is transmitted by exposure of the brain and nervous system tissue to the prion. As an example, variant CJD (vCDJ) is linked to a bovine spongiform encephalopathy (BSE), also known as a ‘mad cow’ disease. CJD is fatal and patients typically die within one year of diagnosis.

[0585] Prion diseases are associated with an infectious agent consisting of an alternative conformational isoform of the prion protein, PrP^{Sc}. PrP^{Sc} replication is considered to occur through an induction of the infectious prion in the normal prion protein (PrP^C). The replication occurs without a nucleic acid.

[0586] As of today, there is no therapy to manage or cure CJD, or other prion diseases. Typically, treatment is aimed at alleviating symptoms and increasing comfort of the patient, *e.g.* with pain relievers. There remains a need for therapy affecting the underlying pathophysiology.

[0587] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from a prion disease. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing a prion disease.

Diagnostic applications

[0588] In some embodiments, compounds (*e.g.*, antibodies) and compositions of the present disclosure may be used as diagnostics. Anti-tau antibodies may be used to identify, label, or stain cells, tissues, organs, *etc.* expressing tau proteins. Anti-tau antibodies may be used to identify tau proteins present in tissue sections (*e.g.*, histological tissue sections), including tissue known or suspected of having tau protein aggregates. Such antibodies may in some cases be used to identify subjects with neurological diseases and/or disorders. Tissue sections may be from CNS tissue.

[0589] In some embodiments, diagnostic methods of the present disclosure may include the analysis of one or more cells or tissues using immunohistochemical techniques. Such methods may include the use of one or more of any of the anti-tau antibodies described herein. Immunohistochemical methods may include staining tissue sections to determine the presence and/or level of one or more tau proteins or other markers. Tissue sections may be derived from subject CNS tissue (*e.g.*, patient CNS, animal CNS, and CNS from animal models of disease). Tissue sections may come from formalin-fixed or unfixed fresh frozen tissues. In some cases, tissue sections come from formalin fixed paraffin-embedded (FFPE) tissues. Anti-tau antibodies described herein may be used as primary antibodies. Primary antibodies are used to contact tissue sections directly and bind to target epitopes. Primary antibodies may be directly conjugated with a detectable label or may be detected through the use of a detection agent such as a secondary antibody. In some embodiments, primary antibodies or detection agents include an enzyme that can be used to react with a substrate to generate a visible product (*e.g.*, precipitate). Such enzymes may include, but are not limited to horse radish peroxidase, alkaline phosphatase, beta-galactosidase, and catalase.

[0590] Anti-tau antibodies described herein may be used according to immunohistochemical methods of the present disclosure to detect tau proteins in tissues or cells. In some cases, these antibodies are used to detect and/or determine the level of tau proteins in tissues. Levels of anti-tau antibodies used in immunohistochemical staining techniques may be varied to increase visible staining or to decrease background levels of staining. In some embodiments, antibody concentrations of from about 0.01 µg/ml to about 50 µg/ml are used. For example, antibody concentrations of from about 0.01 µg/ml to about 1 µg/ml, from about 0.05 µg/ml to about 5 µg/ml, from about 0.1 µg/ml to about 3 µg/ml, from about 1 µg/ml to about 10 µg/ml, from about 2 µg/ml to about 20 µg/ml, from about 3 µg/ml to about 25 µg/ml, from about 4 µg/ml to about 30 µg/ml, or from about 5 µg/ml to about 50 µg/ml may be used.

[0591] Levels and/or identities of tau proteins may be determined according to any methods known in the art for identifying proteins and/or quantitating protein levels. In some embodiments,

such methods may include, but are not limited to mass spectrometry, array analysis (*e.g.*, antibody array or protein array), Western blotting, flow cytometry, immunoprecipitation, surface plasmon resonance analysis, and ELISA. Tau proteins may in some cases be immunoprecipitated from samples prior to analysis. Such immunoprecipitation may be carried out using anti-tau antibodies disclosed herein. In some embodiments, tau proteins are immunoprecipitated from biological samples using anti-tau antibodies and then identified and/or quantitated using mass spectrometry.

[0592] In some embodiments, treatments are informed by diagnostic information generated using anti-tau antibodies. Accordingly, the present disclosure provides methods of treating neurological diseases and/or disorders that include obtaining a sample from a subject, diagnosing one or more neurological diseases and/or disorders using an anti-tau antibody, and administering a treatment selected based on the diagnosis. Such treatments may include treatment with anti-tau antibodies. Anti-tau antibodies administered according to such methods may include any of those described herein.

[0593] In some embodiments, the present disclosure provides methods of detecting and/or quantifying tau proteins in samples through the use of capture and detection antibodies. As used herein, a “capture antibody” is an antibody that binds an analyte in a way that it may be isolated or detected. Capture antibodies may be associated with surfaces or other carriers (*e.g.*, beads). Detection antibodies are antibodies that facilitate observation of the presence or absence of an analyte. According to some methods of detecting and/or quantifying tau proteins, both capture antibodies and detection antibodies bind to tau proteins. Capture and detection antibodies may bind to different epitopes or regions of tau proteins to avoid competition for binding. In some embodiments, detection antibodies may be conjugated with a detectable label for direct detection. In some embodiments, binding of detection antibodies may be assessed using a secondary antibody that binds to a constant domain of the detection antibody or to a detectable label of the detection antibody. Capture, detection, and/or secondary antibodies may be derived from different species. This may prevent secondary antibodies from binding to both capture and detection antibodies.

VI. KITS AND DEVICES

Kits

[0594] In some embodiments, compounds and composition of the present disclosure may be included in a kit. Such compounds and compositions may include anti-tau antibodies disclosed herein. In a non-limiting example, kits may include reagents for generating anti-tau antibodies, including tau protein antigens. Kits may include additional reagents and/or instructions for use,

e.g., for creating or synthesizing anti-tau antibodies. Kits may include one or more buffers. Kits may include additional components, for example, solid supports or substrates for antibody or antigen attachment.

[0595] In some embodiments, the present disclosure includes kits for screening, monitoring, and/or diagnosis of a subject that include one or more anti-tau antibodies. Such kits may be used alone or in combination with one or more other methods of screening, monitoring, and/or diagnosis. Kits may include one or more of a buffer, a biological standard, a secondary antibody, a detection reagent, and a composition for sample pre-treatment (*e.g.*, for antigen retrieval, blocking, *etc.*).

[0596] Kit components may be packaged. In some embodiments, kit components are packaged in aqueous media or in lyophilized form. Packaging may include one or more vial, test tube, flask, bottle, syringe or other container into which a component may be placed and/or suitably aliquoted. Where there are multiple kit components (labeling reagent and label may be packaged together), kits may include second, third or other additional containers into which additional components may be separately placed.

[0597] When kit components are provided in one and/or more liquid solutions, liquid solutions may be aqueous. Liquid solutions may be provided sterile. Kit components may be provided as dried powder(s). Dried powder components may be provided for reconstitution by kit users, *e.g.*, by addition of suitable solvent. Solvents may also be provided in kits in one or more separate containers. In some embodiments, labeling dyes are provided in dried powder format.

[0598] Kits may include instructions for employing kit components as well other reagents not included in the kit. Instructions may include variations that can be implemented.

Devices

[0599] Any of the compounds and compositions described herein may be combined with, coated onto, or embedded in, or delivered by a device. Devices may include, but are not limited to, implants, stents, bone replacements, artificial joints, valves, pacemakers, or other implantable therapeutic devices.

VII. DEFINITIONS

[0600] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub combination of the members of such groups and ranges.

[0601] *About:* As used herein, the term “about” means +/- 10% of the recited value.

[0602] *Activity*: As used herein, the term “activity” refers to the condition in which things are happening or being done. Compositions may have activity and this activity may involve one or more biological events.

[0603] *Adeno-associated virus*: The term “adeno-associated virus” or “AAV” as used herein refers to members of the dependovirus genus comprising any particle, sequence, gene, protein, or component derived therefrom.

[0604] *AAV Particle*: As used herein, an “AAV particle” is a virus which comprises a viral genome with at least one payload region and at least one ITR region. AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. AAV particles may be derived from any serotype, described herein or known in the art, including combinations of serotypes (*i.e.*, “pseudotyped” AAV) or from various genomes (*e.g.*, single stranded or self-complementary). In addition, the AAV particle may be replication defective and/or targeted.

[0605] *Administered in combination*: As used herein, the term “administered in combination” or “combined administration” means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[0606] *Amelioration*: As used herein, the term “amelioration” or “ameliorating” refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[0607] *Animal*: As used herein, the term “animal” refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans at any stage of development. In some embodiments, “animal” refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[0608] *Approximately*: As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference

value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0609] *Associated with:* As used herein, the terms “associated with,” “conjugated,” “linked,” “attached,” and “tethered,” when used with respect to two or more entities, means that the entities are physically associated or connected with one another, either directly or via a linker, to form a structure that is sufficiently stable so that the entities remain physically associated, *e.g.*, under working conditions, *e.g.*, under physiological conditions. An “association” need not be through covalent chemical bonding and may include other forms of association or bonding sufficiently stable such that the “associated” entities remain physically associated, *e.g.*, ionic bonding, hydrostatic bonding, hydrophobic bonding, hydrogen bonding, or hybridization-based connectivity.

[0610] *Bifunctional:* As used herein, the term “bifunctional” refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may affect the same outcome or a different outcome. The structure that produces the function may be the same or different.

[0611] *Biocompatible:* As used herein, the term “biocompatible” means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[0612] *Biodegradable:* As used herein, the term “biodegradable” means capable of being broken down into innocuous products by the action of living things.

[0613] *Biologically active:* As used herein, the phrase “biologically active” refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active.

[0614] *Capsid:* As used herein, the term “capsid” refers to the protein shell of a virus particle. In some embodiments, the term capsid may refer to the nucleic acid encoding the protein shell of the virus particle.

[0615] *Chimeric antigen receptor (CAR):* As used herein, the term “chimeric antigen receptor” or “CAR” refers to an artificial chimeric protein comprising at least one antigen specific targeting region (ASTR), a transmembrane domain and an intracellular signaling domain, wherein the antigen specific targeting region comprises a full-length antibody or a fragment thereof. As a non-limiting example, the ASTR of a CAR may be any of the antibodies presented herein or fragments thereof. Any molecule that is capable of binding a target antigen with high affinity can be used in the ASTR of a CAR. The CAR may optionally have an extracellular

spacer domain and/or a co-stimulatory domain. A CAR may also be used to generate a cytotoxic cell carrying the CAR.

[0616] *Compound*: Compounds of the present disclosure include all of the isotopes of the atoms occurring in the intermediate or final compounds. “Isotopes” refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[0617] The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

[0618] *Comprehensive Positional Evolution (CPETM)*: As used herein, the term “comprehensive positional evolution” refers to an antibody evolution technology that allows for mapping of the effects of amino acid changes at every position along an antibody variable domain’s sequence. This comprehensive mutagenesis technology can be used to enhance one or more antibody properties or characteristics.

[0619] *Comprehensive Protein Synthesis (CPSTM)*: As used herein, the term “comprehensive protein synthesis” refers to a combinatorial protein synthesis technology that can be used to optimize antibody properties or characteristics by combining the best properties into a new, high-performance antibody.

[0620] *Conditionally active*: As used herein, the term “conditionally active” refers to a mutant or variant of a wild-type polypeptide, wherein the mutant or variant is more or less active at physiological conditions than the parent polypeptide. Further, the conditionally active polypeptide may have increased or decreased activity at aberrant conditions as compared to the parent polypeptide. A conditionally active polypeptide may be reversibly or irreversibly inactivated at normal physiological conditions or aberrant conditions.

[0621] *Conserved*: As used herein, the term “conserved” refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[0622] In some embodiments, two or more sequences are said to be “completely conserved” if they are 100% identical to one another. In some embodiments, two or more sequences are said to be “highly conserved” if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be “highly conserved” if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be “conserved” if they are at least 30% identical, at least 40%

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

[0623] *Control Elements:* As used herein, “control elements”, “regulatory control elements”, or “regulatory sequences” refers to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites (“IRES”), enhancers, and the like, which provide for the replication, transcription and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present as long as the selected coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell.

[0624] *Cytotoxic:* As used herein, “cytotoxic” refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[0625] *Delivery:* As used herein, “delivery” refers to the act or manner of providing a compound, substance, entity, moiety, cargo, or payload to a subject or destination.

[0626] *Detectable label:* As used herein, “detectable label” refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity, which markers, signals or moieties are readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include, but are not limited to, radioisotopes, fluorophores, chemiluminescent compounds, chromophores, enzymes, enzyme co-factors, dyes, metal ions, ligands, biotin, avidin, streptavidin, haptens, quantum dots, and the like. Detectable labels may be located at any position in or on an entity with which they are conjugated or otherwise attached, incorporated, or associated. For example, when conjugated or otherwise attached, incorporated, or associated with a peptide or protein, detectable labels may be on, within, or between amino acids or may be attached or associated with the N- or C- termini.

[0627] *Digest:* As used herein, the term “digest” means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[0628] *Distal:* As used herein, the term “distal” means situated away from the center or away from a point or region of interest.

[0629] *Dosing regimen*: As used herein, a “dosing regimen” is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[0630] *Encapsulate*: As used herein, the term “encapsulate” means to enclose, surround or encase.

[0631] *Engineered*: As used herein, embodiments are “engineered” when they are designed to have a feature or property, whether structural or chemical, that varies from a starting compound, material or molecule (*e.g.*, from a wild type or native molecule).

[0632] *Effective Amount*: As used herein, the term “effective amount” of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment of a therapeutic indication as compared to the response obtained without administration of the agent.

[0633] *Epitope*: As used herein, an “epitope” refers to a surface or region on one or more entities that is capable of interacting with an antibody or other binding biomolecule. For example, a protein epitope may contain one or more amino acids and/or post-translational modifications (*e.g.*, phosphorylated residues) which interact with an antibody. In some embodiments, an epitope may be a “conformational epitope,” which refers to an epitope involving a specific three-dimensional arrangement of the entity(ies) having or forming the epitope. For example, conformational epitopes of proteins may include combinations of amino acids and/or post-translational modifications from folded, non-linear stretches of amino acid chains.

[0634] *EvoMap™*: As used herein, an EvoMap™ refers to a map of a polypeptide, wherein detailed informatics are presented about the effects of single amino acid mutations within the length of the polypeptide and their influence on the properties and characteristics of that polypeptide.

[0635] *Expression*: As used herein, “expression” of a gene, nucleic acid, or protein refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0636] *Feature*: As used herein, a “feature” refers to a characteristic, a property, or a distinctive element.

[0637] *Formulation*: As used herein, a “formulation” refers to a material or mixture prepared according to a formula. Formulations may include a compound (*e.g.*, an antibody) or substance combined with a carrier or excipient.

[0638] *Fragment*: A “fragment,” as used herein, refers to a portion. For example, fragments of proteins may include polypeptides obtained by digesting full-length protein isolated from cultured cells.

[0639] *Functional*: As used herein, a “functional” biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized. For example, a “functional” antibody may include an antibody that binds a specific target or that activates or inhibits a specific biological process.

[0640] *Half maximal effective concentration*: As used herein, the term “half maximal effective concentration” or “EC50” refers to the concentration of a substance necessary to increase a given reaction, activity or process by half. For example, when measuring binding of an antibody in a sample to a target using a binding assay (*e.g.*, an ELISA assay), the EC50 is the concentration of antibody in the sample needed to yield 50% of the maximum binding that can be observed with that assay. Similarly, the term “half maximal inhibitory concentration” or “IC50” refers to a concentration necessary to reduce a given reaction or process by half. For example, the IC50 for an antibody capable of inhibiting a biological process is the concentration of antibody necessary in a sample to reduce the biological process by 50%. EC50 and IC50 values may be differ under specific time constraints and/or conditions.

[0641] *Homology*: As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0642] *Heterologous Region*: As used herein the term “heterologous region” refers to a region which would not be considered a homologous region.

[0643] *Homologous Region*: As used herein the term “homologous region” refers to a region which is similar in position, structure, evolution origin, character, form or function.

[0644] *Identity*: As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H. and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package,

Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)). *In vitro*: As used herein, the term “*in vitro*” refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[0645] *In vivo*: As used herein, the term “*in vivo*” refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[0646] *Isolated*: As used herein, the term “isolated” refers to a substance or entity that is altered or removed from the natural state, *e.g.*, altered or removed from at least some of component with which it is associated in the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature. In some embodiments, an isolated nucleic acid is recombinant, *e.g.*, incorporated into a vector.

[0647] *Linker*: As used herein “linker” refers to a molecule or group of molecules which connects two molecules. In some embodiments, linkers may be cleavable (*e.g.*, through contact with an enzyme, change in pH, or change in temperature).

[0648] *MicroRNA (miRNA or miR) binding site*: As used herein, a “miR binding site” comprises a nucleic acid sequence (whether RNA or DNA, *e.g.*, differ by “U” of RNA or “T” in DNA) that is capable of binding, or binds, in whole or in part to a microRNA (miR) through complete or partial hybridization. Typically, such binding occurs between the miR and the miR binding site in the reverse complement orientation. In some embodiments, the miR binding site is transcribed from the AAV vector genome encoding the miR binding site.

[0649] In some embodiments, a miR binding site may be encoded or transcribed in series. Such a “miR binding site series” or “miRBSs” may include two or more miR binding sites having the same or different nucleic acid sequence.

[0650] *Modified*: As used herein “modified” refers to a changed state or structure of a molecule. Molecules may be modified in many ways including chemically, structurally, and functionally.

[0651] *Naturally occurring*: As used herein, “naturally occurring” or “wild-type” means existing in nature without artificial aid, or involvement of the hand of man.

[0652] *Non-human vertebrate*: As used herein, a “non-human vertebrate” includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, primate, rabbit, reindeer, sheep, water buffalo, and yak.

[0653] *Off-target*: As used herein, “off-target” refers to unintended activity or binding to an entity other than an expected target.

[0654] *Operably linked*: As used herein, the phrase “operably linked” refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[0655] *Particle*: As used herein, a “particle” is a virus comprised of at least two components, a protein capsid and a polynucleotide sequence enclosed within the capsid (*e.g.*, viral genome).

[0656] *Patient*: As used herein, “patient” refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[0657] *Payload*: As used herein, “payload” refers to any substance being delivered by an agent. For example, payloads may include therapeutic agents conjugated to antibodies for delivery to a cell, tissue, or region harboring an epitope of the antibody.

[0658] *Peptide*: As used herein, “peptide” is less than or equal to 50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0659] *Pharmaceutically acceptable*: The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0660] *Pharmaceutically acceptable excipients*: The phrase “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspension or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl

methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0661] *Pharmaceutically acceptable salts:* The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (*e.g.*, by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge *et al.*, *Journal of*

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

[0662] *Pharmaceutically acceptable solvate*: The term “pharmaceutically acceptable solvate,” as used herein, means a compound wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a “hydrate.”

[0663] *Pharmacokinetic*: As used herein, “pharmacokinetic” refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[0664] *Physicochemical*: As used herein, “physicochemical” means of or relating to a physical and/or chemical property.

[0665] *Preventing*: As used herein, the term “preventing” refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0666] *Proliferate*: As used herein, the term “proliferate” means to grow, expand or increase or cause to grow, expand or increase rapidly. “Proliferative” means having the ability to

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

[0667] *Prophylactic*: As used herein, “prophylactic” refers to a therapeutic or course of action used to prevent the spread of disease.

[0668] *Prophylaxis*: As used herein, a “prophylaxis” refers to a measure taken to maintain health and prevent the spread of disease.

[0669] *Protein of interest*: As used herein, the terms “proteins of interest” or “desired proteins” include those provided herein and fragments, mutants, variants, and alterations thereof.

[0670] *Proximal*: As used herein, the term “proximal” means situated nearer to the center or to a point or region of interest.

[0671] *Purified*: As used herein, “purify,” “purified,” “purification” means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection. “Purified” refers to the state of being pure. “Purification” refers to the process of making pure.

[0672] *Region*: As used herein, the term “region” refers to a zone or general area. In some embodiments, when referring to a polypeptide or protein, a region may include a linear sequence of amino acids along the polypeptide or protein or may include a three-dimensional area, an epitope, or a cluster of epitopes. When referring to a polynucleotide, a region may include a linear sequence of nucleic acids along the polynucleotide or may include a three-dimensional area, secondary structure, or tertiary structure. Regions may include terminal regions. As used herein, the term “terminal region” refers to a region located at the end or “terminus” of a given entity. When referring to polypeptides, terminal regions may include N- and/or C-termini. N-terminus refers to the end of a polypeptide with a free amino acid amino group. C-terminus refers to the end of a polypeptide with a free amino acid carboxyl group. N- and/or C-terminal regions may refer to a single terminal functional group, single amino acid, or multiple amino acids located at either terminus. When referring to polynucleotides, terminal regions may include 5’ and 3’ termini. The 5’ terminus refers to the end of a polynucleotide that includes a free nucleic acid phosphate group. The 3’ terminus refers to the end of a polynucleotide that includes a free nucleic acid hydroxyl group. Polynucleotide terminal regions may refer to a single terminal functional group, single nucleotide, or multiple nucleotides located at a terminus.

[0673] *RNA and DNA*: As used herein, the term “RNA” or “RNA molecule” or “ribonucleic acid molecule” refers to a polymer of ribonucleotides; the term “DNA” or “DNA molecule” or “deoxyribonucleic acid molecule” refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, *e.g.*, by DNA replication and transcription of DNA, respectively; or be chemically synthesized. RNA and DNA can be single-stranded (*i.e.*, ssRNA or ssDNA,

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

[0674] *Sample:* As used herein, the term “sample” refers to a portion or subset of larger entity. A sample from a biological organism or material is referred to herein as a “biological sample” and may include, but is not limited to, tissues, cells, and body fluids (*e.g.*, blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid, and semen). Samples may further include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, and organs. Samples may further include a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecules.

[0675] *Signal Sequences:* As used herein, the phrase “signal sequences” refers to a sequence which can direct the transport or localization of a protein.

[0676] *Single unit dose:* As used herein, a “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, *i.e.*, single administration event. In some embodiments, a single unit dose is provided as a discrete dosage form (*e.g.*, a tablet, capsule, patch, loaded syringe, vial, *etc.*).

[0677] *Spacer:* As used here, a “spacer” is generally any selected nucleic acid sequence of, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. Spacers may also be more than 10 nucleotides in length, *e.g.*, 20, 30, 40, or 50 or more than 50 nucleotides.

[0678] *Split dose:* As used herein, a “split dose” is the division of single unit dose or total daily dose into two or more doses.

[0679] *Stable:* As used herein “stable” refers to a state of an entity that is sufficiently robust to survive a certain degree of perturbation. For example, a stable compound or protein may remain intact during isolation to a useful degree of purity from a reaction mixture.

[0680] *Stabilized:* As used herein, the term “stabilize” or “stabilized” means to make or become stable.

[0681] *Subject:* As used herein, the term “subject” refers to any organism to which a compound, composition, method, kit, or device according to the present disclosure may be administered or applied, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Subjects can include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human

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

[0682] *Substantially:* As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0683] *Suffering from:* An individual who is “suffering from” a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[0684] *Susceptible to:* An individual who is “susceptible to” a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, neurodegenerative disease) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity or dysfunction of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0685] *Sustained release:* As used herein, the term “sustained release” refers to release of a compound or agent over a specific period of time, typically at a relatively controlled or consistent rate.

[0686] *Synthetic:* The term “synthetic” means produced, prepared, and/or manufactured by the hand of man. Synthetic polynucleotides, polypeptides, or other molecules of the present disclosure may be prepared using chemical or enzymatic processes.

[0687] *Target:* As used herein, the term “target” refers to an entity of interest or attention, which may include a subject, an organ, a tissue, a cell, a protein, a nucleic acid, biomolecule, or a group, complex, or portion of any of the foregoing. In some embodiments, a target may be a

protein or epitope thereof for which an antibody has affinity or for which an antibody is desired, designed, or developed to have affinity for. As used herein, the term “target” may also be used to refer to an activity of an agent that is directed to a particular object. For example, an antibody that has affinity for a specific protein “X” may be said to *target* protein X or may be referred to as an antibody *targeting* protein X or referred to as a protein X-*targeting* antibody. Similarly, an object that is the subject of an agent’s activity may be referred to as a “targeted” object. For example, where an antibody has affinity for a specific protein “X,” protein X may be referred to as being *targeted* by the antibody.

[0688] *Therapeutic Agent:* The term “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect. Therapeutic agents capable of producing a biological effect in living organisms are referred to herein as “drugs.”

[0689] *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” means an amount of an agent (*e.g.*, antibody or other therapeutic agent) to be delivered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, that when delivered or administered in that amount is sufficient to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen that includes a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to include a therapeutically effective amount of a particular agent or entity if it includes an amount that is effective when administered as part of such a dosage regimen.

[0690] *Therapeutically effective outcome:* As used herein, the term “therapeutically effective outcome” means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0691] *Total daily dose:* As used herein, a “total daily dose” is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

[0692] *Treating:* As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, “treating” neurodegenerative disease in a subject may refer to inhibiting neurodegeneration; promoting the health of neuronal cells; reversing, preventing, or reducing the formation of plaques or tangles in

the brain; and/or reversing, preventing, or reducing memory loss or loss of other neurological functions or activities of the subject. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0693] *Unmodified:* As used herein, “unmodified” refers to any substance, compound or molecule prior to being changed in any way. Unmodified may refer to the wild type or native form of a biomolecule. Molecules may undergo a series of modifications whereby each modified molecule may serve as the “unmodified” starting molecule for a subsequent modification.

[0694] *Vector:* As used herein, a “vector” is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. Vectors of the present disclosure may be produced recombinantly.

[0695] *Viral genome:* As used herein, a “viral genome” or “vector genome” is a polynucleotide comprising at least one inverted terminal repeat (ITR) and at least one encoded payload. A viral genome encodes at least one copy of the payload.

VIII. EQUIVALENTS AND SCOPE

[0696] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0697] In the claims, articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0698] It is also noted that the term “comprising” is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term “comprising” is used herein, the term “consisting of” is thus also encompassed and disclosed.

[0699] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of

ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0700] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (*e.g.*, any nucleic acid or protein encoded thereby; any method of production; any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0701] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[0702] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Antigen preparation

[0703] Antigen preparation was carried out to support mouse immunization and generation and characterization of anti-human tau antibodies. Enriched paired helical filament (ePHF; sarkosyl insoluble tau) including human microtubule-associated protein tau, isoform 2 (SEQ ID NO: 920) was prepared along with several tau protein antigens with different phosphorylated residues corresponding to pathological tau. Related sequences are presented in Table 19. Phosphorylated residues are double-underlined in the Table.

Table 19. Tau protein antigens

Antigen	Sequence	SEQ ID NO
human microtubule-associated protein tau, isoform 2	MAEPRQEFEFVMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESP LQTPTE ^u DGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPH TEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKK AKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEP PKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREP ^u KKVAVVRTPPKS PSSAKSRLQTAPVMPDLKNVSKIGSTENLKHQPGGGKVQIINKKL	920

	DLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSCGSLGNIH HKPGGGQVEVKSEKLDKDRVQSKIGSLDNITHVPGGGNKKIETHKL TFRENAKAKTDHGAEIVYKSPVVS ~~G~~ DTSPRHLSNVSS ~~T~~ GSIDMV ~~D~~ SP QLATLADEV ~~S~~ ASLAKQGL	
PT3 epitope peptide (pT212/pT217)	TPGSRSRTPSLPTPPPTREPK	921
Peptide 5 (pT212/pS214/pT217)	GTPGSRSRTPSLPTPPPTRE	922
Peptide 12 (pS396/pS404/pS409)	RENAKAKTDHGAEIVYKSPVVS ~~G~~ DTSPRHLSNVSS ~~T~~ G	923
Peptide 1 (AT120 epitope)	PTREPKKV	924

[0704] Tau protein antigens were conjugated with keyhole limpet hemocyanin (KLH) for immunization. For ePHF antigen preparation, ePHF was isolated from fractions of AD or non-AD frontal cortical tissue. Cortical tissue fractions were prepared according to methods described by Greenberg and Davies (1990) with minor modification (Liu *et al.*, J Neuroscience, 2016, the contents of which are herein incorporated by reference in their entirety). Briefly, brain tissue was homogenized with cold homogenization buffer (10 mM Tris/1 mM EDTA/0.8 M NaCl/10% sucrose, pH 7.4) with protease inhibitor (Roche Molecular Systems, Inc., Branchburg, NJ) and phosphatase inhibitors cocktail (ThermoFisher, Waltham, MA, catalog #78437) or 1 mM NaF/1 mM Na₃VO₄ in a Teflon glass homogenizer. Brain homogenate was then centrifuged at 27,000 x g for 30 min at 4°C. The resulting supernatant was subjected to extraction with 1% (w/v) N-lauroylsarcosine in the presence of 1% (v/v) 2-mercaptoethanol at 37°C for 2.5 h followed by centrifugation at 108,000 x g for 30 min at room temperature. The pellet recovered from this centrifugation was quickly rinsed one time with 0.5 mL of PBS/tube. The rinsed PBS was discarded. Another 0.5 mL of PBS was added to each tube to dissolve PHF. PHF from 6 tubes were pooled and the pooled PHF solution was sonicated. The resulting solution was concentrated to ~5X and further sonicated. PHF samples were then analyzed by HT7 western for qualitative and PT3 ELISA quantitative assessment. PHF samples were then stored at -80°C.

Example 2. Immunization

[0705] Wild type and tau knockout mouse cohorts were immunized with ePHF or KLH-conjugated tau protein antigens described in Example 1. Sera from immunized mice were screened by enzyme-linked immunosorbent assay (ELISA) for the presence of antibodies binding

to albumin-conjugated antigens. Immunized mice with sera testing positive for antigen-specific antibodies were used to prepare hybridoma cells. Supernatants from hybridoma cell culture medium were screened by direct ELISA to identify cells producing antigen-specific antibodies. Hybridoma clones producing antibodies with positive antigen binding were selected for subcloning and antibody sequence analysis.

[0706] Variable domain amino acid and nucleic acid sequences for selected clones are presented in Table 3, with each ID# corresponding to an antibody expressed by a selected hybridoma clone. Complementarity determining region (CDR) analysis was carried out to identify heavy chain CDRH1, CDRH2, and CDRH3 sequences and light chain CDRL1, CDRL2, and CDRL3 sequences. CDR amino acid sequences identified include those presented in Table 6.

Example 3. Tau binding

[0707] Variable domain nucleic acid sequences from antibodies obtained from immunizations described above were used to prepare recombinant mouse IgG antibodies. These candidate antibodies were analyzed for binding to ePHF and specificity for ePHF over wild type tau by direct ELISA.

[0708] For direct ePHF and wildtype tau ELISA, plates were first coated with ePHF or wild type tau. Antigen solutions were prepared in PBS and 50 μ L were pipetted into each well. Plates were covered and incubated for one hour at 37°C or overnight at 4°C. Plates were then washed and blocked by addition of 150 μ L of blocking buffer to each well and incubated one hour at room temperature. Plates were then washed before addition of serially diluted candidate antibody samples prepared in blocking buffer. Detection of candidate antibody binding was carried out by washing plates and adding a solution of enzyme-labeled secondary antibody in blocking buffer to each well. Secondary antibody binding was detected by addition of substrate and spectrophotometric analysis of resulting reaction product. Half maximal effective concentration (EC50) for antibody binding to ePHF and wild type tau are presented in Table 20.

Table 20. ELISA results

ID#	ePHF EC50 (nM)	Wild type Tau EC50 (nM)
V0009	0.038	No binding
V1004	0.069	No binding
V0037	0.073	No binding
V0004	0.083	No binding
V0047	0.118	No binding
V0024	0.125	No binding

V00010	0.134	No binding
V00011	0.171	No binding
V0044	0.209	No binding
V1003	0.234	No binding
V2001	0.237	No binding
V0020	0.351	No binding
V1005	0.480	No binding
V0021	0.571	No binding
V0043	0.581	No binding
V0045	0.618	No binding
V0007	0.740	No binding
V0006	0.861	No binding
V0042	0.869	No binding
V0008	1.541	No binding
V0058	2.452	No binding
V0003	2.833	No binding
V0027	3.509	No binding
V0026	5.610	No binding
V0036	6.426	No binding
V0031	8.800	No binding
V0032	14.300	No binding
V0050	17.950	No binding
V0025	0.098	Weak binding
V1001	0.401	Weak binding
V0035	0.315	0.169
V0034	0.351	0.140
V00018	0.718	0.238
V0049	0.053	Not determined
V0022	0.070	Not determined
V0023	0.110	Not determined
V0001	0.126	Not determined
V0028	Weak binding	No binding

V0029	Weak binding	No binding
V0046	Weak binding	No binding
V0053	Weak binding	No binding
V0054	Weak binding	No binding
V0055	Weak binding	No binding
V0059	Weak binding	No binding
V0060	Weak binding	No binding
V0062	Weak binding	No binding
V0064	Weak binding	No binding
V00019	Weak binding	0.285
V0052	Weak binding	Not determined
V0057	Weak binding	Not determined
V2003	Weak binding	Not determined
V00014	No binding	No binding
V0038	No binding	No binding
V0040	No binding	No binding
V1002	No binding	No binding
V2004	No binding	No binding
V0002	No binding	Not determined
V0030	No binding	Not determined
V00016	No binding	0.141
V0033	No binding	0.342

[0709] Follow up analysis of antibodies V0004, V0009, V0022, V0023, V0024, and V0052 indicated greater than 100-fold selectivity for ePHF over wild type tau. Further, these antibodies demonstrated low polyspecificity and good stability in solution at 1 mg/mL.

Example 4. Epitope binning by antibody competition

[0710] Variable domain nucleic acid sequences from antibodies obtained from immunizations described above were used to prepare recombinant mouse IgG antibodies for iPHF affinity measurement and epitope binding competition analysis. Studies were carried out by Octet (ForteBio, Menlo Park, CA) analysis.

[0711] For iPHF affinity analysis, candidate antibodies were immobilized on anti-mouse IgG Fc capture (AMC) biosensor tips (ForteBio, cat#18-5088) in kinetic buffer (ForteBio, cat#18-

1105). Biosensor tips were then washed before introduction of a solution of iPHF in kinetic buffer for analysis of iPHF association and dissociation with candidate antibodies. Affinity measurements were obtained using Data Analysis HT version 11.1 and corrected for background and high-frequency noise.

[0712] For epitope binding competition analysis, a process also referred to as “epitope binning,” candidate antibodies were analyzed using a sandwich assay format, wherein a first “capture” antibody is attached to the Octet biosensor before antigen and a second antibody are sequentially introduced and biosensor readings are used to determine whether one or both antibodies bind to each antigen. Antibodies demonstrating competitive epitope binding were placed into the same or similar characterization category or “bin.” Antibodies demonstrating simultaneous binding were placed into separate categories. PT3, IPN002, or C10.2 antibodies were used as capture antibodies and immobilized on AMC biosensor tips as described above. Biosensor tips were then washed and blocked in 10 µg/ml MOPC. After a further wash, biosensor capture antibodies were associated with iPHF. Candidate antibodies were then analyzed for binding to iPHF. MOPC (non antigen-specific control) and PT3, IPN002, or C10.2 antibodies (in each case matching the biosensor antibody) were used as directly competing controls. Results are shown in Table 21.

Table 21. Epitope binning results

ID#	Antibody response
V0009	Cross blocked by C10.2
V0030	Cross blocked by C10.2
V0004	Cross blocked by PT3
V1003	Cross blocked by PT3
V1004	Cross blocked by PT3
V0001	Cross blocked by PT3 and C10.2
V0003	Cross blocked by PT3 and C10.2
V0006	Cross blocked by PT3 and C10.2
V0008	Cross blocked by PT3 and C10.2
V00010	Cross blocked by PT3 and C10.2
V0034	Cross blocked by PT3 and C10.2
V0038	Cross blocked by PT3 and C10.2
V0039	Cross blocked by PT3 and C10.2
V0040	Cross blocked by PT3 and C10.2
V0041	Cross blocked by PT3 and C10.2

V0042	Cross blocked by PT3 and C10.2
V0044	Cross blocked by PT3 and C10.2
V0045	Cross blocked by PT3 and C10.2
V0046	Cross blocked by PT3 and C10.2
V0047	Cross blocked by PT3 and C10.2
V0059	Cross blocked by PT3 and C10.2
V0060	Cross blocked by PT3 and C10.2
V2004	Cross blocked by PT3 and C10.2
V0007	Not cross blocked by IPN002, PT3, or C10.2
V00011	Not cross blocked by IPN002, PT3, or C10.2
V00016	Not cross blocked by IPN002, PT3, or C10.2
V00018	Not cross blocked by IPN002, PT3, or C10.2
V00019	Not cross blocked by IPN002, PT3, or C10.2
V0020	Not cross blocked by IPN002, PT3, or C10.2
V0021	Not cross blocked by IPN002, PT3, or C10.2
V0022	Not cross blocked by IPN002, PT3, or C10.2
V0023	Not cross blocked by IPN002, PT3, or C10.2
V0024	Not cross blocked by IPN002, PT3, or C10.2
V0025	Not cross blocked by IPN002, PT3, or C10.2
V0026	Not cross blocked by IPN002, PT3, or C10.2
V0027	Not cross blocked by IPN002, PT3, or C10.2

V0031	Not cross blocked by IPN002, PT3, or C10.2
V0032	Not cross blocked by IPN002, PT3, or C10.2
V0035	Not cross blocked by IPN002, PT3, or C10.2
V0036	Not cross blocked by IPN002, PT3, or C10.2
V0049	Not cross blocked by IPN002, PT3, or C10.2
V0052	Not cross blocked by IPN002, PT3, or C10.2
V0054	Not cross blocked by IPN002, PT3, or C10.2
V0055	Not cross blocked by IPN002, PT3, or C10.2
V0057	Not cross blocked by IPN002, PT3, or C10.2
V0058	Not cross blocked by IPN002, PT3, or C10.2
V0002	No binding to iPHF
V00014	No binding to iPHF
V0028	No binding to iPHF
V0029	No binding to iPHF
V0033	No binding to iPHF
V0061	No binding to iPHF
V0062	No binding to iPHF
V0063	No binding to iPHF
V0064	No binding to iPHF

[0713] Candidate antibodies were identified that demonstrated cross blocking with PT3, C10.2, or both PT3 and C10.2. Further candidate antibodies were identified that did not demonstrate cross blocking with any of the antibodies tested or did not demonstrate binding to iPHF.

Example 5. Epitope binning by peptide antigen

[0714] Variable domain nucleic acid sequences from antibodies obtained from immunizations described above were used to prepare recombinant mouse IgG antibodies for PHF tau epitope binning analysis by sandwich ELISA. Anti-tau antibodies AT120 (directed to peptide 1), PT3 (directed to peptide 5), C10.2 (directed to peptide 12), PT76, 6C5, and UCB D were used as capture antibodies in the assay. Capture antibodies were diluted in PBS at a concentration of 1 µg/ml and 50 µl of the solution was used to coat each assay plate well. Plates were covered and incubated overnight at 4°C. Plates were then washed and blocked by addition of 150 µl of blocking buffer to each well and incubated one hour at room temperature. Plates were again washed before coating with ePHF or wild type tau in blocking buffer followed by incubation for 1 hour at room temperature. Plates were then washed before addition of serially diluted candidate antibody samples prepared in blocking buffer. Detection of candidate antibody binding was carried out by washing plates and adding a solution of enzyme-labeled secondary antibody in blocking buffer to each well. Secondary antibody binding was detected by addition of substrate and spectrophotometric analysis of resulting reaction product. Epitope “bins” were determined for each candidate antibody tested based on observed competition (epitope blocking) by each anti-tau capture antibody tested. Results are shown in Table 22.

Table 22. Epitope binning results

ID#	Epitope bin
V0036	C10.2 bin (Peptide 12)
V0049	C10.2 bin (Peptide 12)
V0054	C10.2 bin (Peptide 12)
V0055	C10.2 bin (Peptide 12)
V0057	C10.2 bin (Peptide 12)
V0058	C10.2 bin (Peptide 12)
V0050	C10.2 bin (Peptide 12); PT76-UCB D bin
V0004	PT3 bin (Peptide 5)
V1001	PT3 bin (Peptide 5)
V1003	PT3 bin (Peptide 5)
V1004	PT3 bin (Peptide 5)
V2001	PT3 bin (Peptide 5)
V1005	PT3 bin (Peptide 5); C10.2 bin (Peptide 12)
V00016	PT76-UCB D bin
V00018	PT76-UCB D bin

V00019	PT76-UCB D bin
V0024	PT76-UCB D bin
V0025	PT76-UCB D bin
V0026	PT76-UCB D bin
V0038	PT76-UCB D bin
V0047	PT76-UCB D bin
V00010	PT76-UCB D bin
V0059	Non-specific
V1002	No binding
V2003	No binding
V2004	No binding
V2005	No binding
V0001	No binding
V0002	No binding
V0003	No binding
V0006	No binding
V0007	No binding
V0008	No binding
V0009	No binding
V00011	No binding
V00014	No binding
V0020	No binding
V0021	No binding
V0022	No binding
V0023	No binding
V0027	No binding
V0028	No binding
V0029	No binding
V0030	No binding
V0031	No binding
V0032	No binding
V0033	No binding
V0034	No binding
V0035	No binding

V0037	No binding
V0039	No binding
V0040	No binding
V0041	No binding
V0042	No binding
V0043	No binding
V0044	No binding
V0045	No binding
V0046	No binding
V0051	No binding
V0052	No binding
V0053	No binding
V0060	No binding
V0061	No binding
V0062	No binding
V0063	No binding
V0064	No binding

[0715] Multiple antibodies competed for epitope binding with either C10.2 or PT3, with one antibody competing for epitope binding with both C10.2 and PT3. Multiple antibodies also competed for epitope binding with PT176 and UCB D, with one antibody competing for epitope binding with PT176, UCB D, and C10.2.

Example 6. Immunodepletion screening

[0716] Variable domain nucleic acid sequences from antibodies obtained from immunizations described above were used to prepare recombinant mouse IgG antibodies for immunodepletion assay screening. Immunodepletion assays analyze the ability of antibody candidates to deplete target antigens from solution by assessing altered properties associated with the depleted solution. Here, tau RD Biosensor cells were used to analyze tau aggregation induced by ePHF in supernatants obtained from solutions subjected to immunodepletion with candidate antibodies. RD Biosensor cells yield a fluorescent signal in response to tau aggregation. For the assay, 500 nM to 0.8 nM antibody solutions (5 dilutions tested in total) were incubated for 30 minutes at room temperature with 10 mg/ml solutions of Protein G Dynabeads to yield antibody-coated beads. 10 nM ePHF was diluted in phosphate buffered saline and sonicated prior to incubation with antibody-coated bead preparations for 90 minutes at room temperature. Supernatant was

then collected and diluted 1:5 before incubation at room temperature for 20 minutes with 1:1 lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA) in opti-mem (Thermo Fisher Scientific). 20 μ l of the resulting solution was added to biosensor cell cultures (150 μ l final medium volume). Cells were cultured for two days before fixation for fluorescence analysis. Nuclei were stained with Draq5 stain and nine 10X images per well (triplicate wells per condition) were captured by Cytation 5. Percentage of cells with tau aggregates was determined for each well and normalized against cells treated with MOPC-21 IgG control beads, which were used in parallel as a seeding control. Antibodies demonstrating tau aggregation inhibition in initial analyses were selected for dose response curve analysis to determine half maximal inhibitory concentration (IC₅₀) for inhibiting tau aggregation. Average IC₅₀ values (based on geometric mean) for each candidate antibody tested are shown in Table 23.

Table 23. Aggregation inhibition

ID#	Average IC₅₀ (nM)
V0020	1.9
V0052	3.0
V0058	4.1
V0021	4.7
V0009	4.8
V0031	5.8
V0055	5.8
V00016	6.1
V0057	6.1
V0054	6.3
V0032	8.0
V0050	9.0
V0026	9.1
V0027	9.3
V0023	16.5
V0022	18.2
V0024	18.6
V0036	20.4
V0004	26.3
V0053	26.4

[0717] Multiple antibodies demonstrated tau aggregation inhibition IC50 values of less than 30 nM, with 14 antibodies below 10 nM.

Example 7. Tissue staining

[0718] Variable domain nucleic acid sequences from antibodies obtained from immunizations described above were used to prepare recombinant mouse IgG antibodies and tested for ability to bind pathological tau in human brain tissue sections. Cryo-preserved human brain tissue sections from patients with or without Alzheimer's Disease (AD) were mounted on glass slides and washed with PBS. Endogenous peroxidase activity in tissue sections was quenched for 30 minutes at room temperature using a solution of 0.9% hydrogen peroxide and 0.02% Triton-X 100 in 1X PBS. Tissue sections were then washed with PBS and incubated for 1 hour at room temperature with a blocking solution of 10% normal goat serum in PBS with 0.02% Triton-X 100. Candidate antibody solutions were prepared by 1:500 dilution in PBS with protein diluent. Tissue sections were incubated in candidate antibody solutions for 1 hour at room temperature before washing in PBS to remove unbound antibody. Tissue sections were then treated with solutions of biotinylated goat-anti mouse IgG in PBS with protein diluent and incubated for 1 hour at room temperature. Tissue sections were again washed in PBS and treated with a solution of avidin-peroxidase conjugate before incubation for 30 minutes at room temperature. Tissue sections were again washed in PBS prior to treatment with a 3,3' diaminobenzidine tetrahydrochloride (DAB) substrate solution to yield a brown enzymatic precipitate at sites of candidate antibody binding and peroxidase immunocomplex formation. Enzymatic reactions were allowed to proceed for about 1 minute before being halted by rinsing in PBS wash solution. Tissue sections were then mounted for microscopic evaluation of immunostaining (indicating candidate antibody binding). Immunostained tissue sections were ranked based on degree of staining observed. Results are shown in Table 24. In the Table, "-" indicates no staining, and "+," "+/++," "++," "++/+++" and "+++" indicate levels of positive staining from low to high. "+/-" indicates no staining, with the exception of some staining observed in non-disease tissue. Antibodies yielding stained cell nuclei are indicated.

Table 24. Tissue staining results

ID#	Staining level in AD tissue	Staining level in non-AD tissue
V1003	+++	-
V0034	+++	-
V00016	+++	-
V0024	+++	-

V1001	+++	-
V1002	+++	-
V0009	+++	-/+
V0004	+++	-/+
V0007	+++	-/+
V00018	+++	-/+
V0022	+++	-/+
V0023	+++	-/+
V0025	+++	-/+
V0033	+++	-/+
V2001	+++	-/+
V2003	+++	-/+
V1005	+++	+ (nuclear)
V1004	+++	+/-
V0037	+++	++
V0020	++	+ (nuclear)
V0021	++	+ (nuclear)
V0026	++	++
V0053	++	++
V0031	+ /+++	+
V0032	+ /+++	+
V0052	+ /+++	+
V0058	+ /+++	+
V0030	+ /+++	+ /+++
V0057	+ /+++	+ /+++
V0050	+ /+++	+ /+++
V0027	+	+
V0036	+	+
V0054	+	+
V0055	+	+
V00010	+++	+++
V0051	++	+
V0043	++	++
V0008	+ /+++	+ /+++

V0061	+ /++	+ /++
V00014	+/-	+/-
V00019	+	-/+
V0063	+	-/+
V0064	+	-/+
V0001	+	+
V0003	+	+
V0006	+	+
V0039	+	+
V0040	+	+
V0041	+	+
V0042	+	+
V0044	+	+
V0045	+	+
V0046	+	+
V0047	+	+
V0059	+	+
V0060	+	+
V00011	+	+
V0035	+	+
V0049	+	+
V0002	+	+
V0028	+	+
V0029	+	+
V0062	+	+
V0038	+	+/-
V2005	-/+	-
V2004	-/+	-/+

[0719] Multiple antibodies yielded positive staining in AD brain tissue sections with little or no positive staining observed in brain tissue sections from non-AD brain tissue.

[0720] Similar results were obtained using fixed human brain tissues when assessing antibodies V0004, V0009, V0022, V0023, V0024, and V0052. Similar results were also obtained

for these antibodies when comparing brain tissue staining between wild type mice and FTD mutant tau transgenic mice carrying P301S tau mutations.

Example 8. iPHF affinity analysis

[0721] Anti-human tau antibodies were assessed for affinity for iPHF by Octet (ForteBio, Menlo Park, CA) analysis. Recombinant mouse IgG antibodies were prepared with clone-specific variable domain pairs selected from those presented in Table 3 and mouse IgG1 constant domains. Candidate antibodies were immobilized on biosensor tips (ForteBio) in kinetic buffer (ForteBio). Biosensor tips were then washed before introduction of a solution of iPHF in kinetic buffer for analysis of association and dissociation with candidate antibodies. Affinity measurements (K_D) were obtained using Data Analysis HT version 11.1 and corrected for background and high-frequency noise. Results are presented in Table 25.

Table 25. Affinity analysis results

ID#	iPHF K_D (nM)
V0009	0.2
V0022	0.3
V0050	0.4
V0052	0.6
V0026	0.7
V0058	1.0
V0055	1.3
V0024	2.8
V0023	4.0
V00016	5.5
V0027	10.5
V0021	15.1
V0057	17.4
V0032	17.5
V0004	20.0
V0020	32.7
V0031	57.7
V0054	105.0

[0722] The antibodies shown in Table 25 all demonstrated K_D values less than 150 nM, with antibodies V0009, V0022, V0050, V0052, V0026, V0058, V0055, V0024, V0023, and V00016 demonstrating K_D values less than 10 nM. Of the antibodies tested, all demonstrated weak or no affinity (greater than 200 nM K_D) for wild type tau, except for V00016, which demonstrated nearly equivalent affinity for wild type tau.

Example 9. Pepscan epitope analysis

[0723] Recombinant mouse IgG antibodies were prepared with clone-specific variable domain pairs selected from those presented in Table 3 and mouse IgG1 constant domains. Epitope analysis was carried out with different anti-tau antibodies using a peptide scanning approach (*e.g.*, see Verelst, J. *et al.* Front Mol Biosci. 2020 Mar 31;7:48). Libraries of overlapping synthetic biotinylated peptides corresponding to phosphorylated human tau (Pepscan, Lelystad, NL) were obtained and used to coat assay plate wells, each with individual library members. Recombinant mouse IgG antibodies were prepared with clone-specific variable domain pairs selected from those presented in Table 3 and mouse IgG1 constant domains. Antibody binding to peptides in each well was analyzed using colorimetric detection of peptide-antibody complexes with labeled secondary antibody or by associating biotinylated peptides with streptavidin coated biosensors in assay wells and assessing antibody binding by bio-layer interferometry (BLI)-based detection.

[0724] Results indicated binding of V0022, V0023, and V0024 antibodies close to the tau C-terminus with affinity for peptides corresponding with residues 409-436 of human tau (SEQ ID NO: 920). These antibodies demonstrated the highest affinity (V0022 $K_D=3.06 \times 10^{-10}$ M; V0023 $K_D=2.07 \times 10^{-10}$ M; V0024 $K_D=2.25 \times 10^{-10}$ M) for peptides corresponding with residues 413-430 of human tau (SEQ ID NO: 920).

[0725] Antibody V0052 demonstrated association with multiple regions of human tau indicating that the epitope on full length tau may be conformational (including multiple regions grouped together by protein folding). V0052 demonstrated affinity for peptides corresponding with residues 55-76, 159-194, 219-247, and 381-426 of human tau (SEQ ID NO: 920). Of these regions, V0052 affinity was greater for residues 57-72 ($K_D=1.40 \times 10^{-8}$ M), 175-191 ($K_D=7.24 \times 10^{-9}$ M), 223-238 ($K_D=2.08 \times 10^{-9}$ M), and 383-400 ($K_D=1.26 \times 10^{-8}$ M) of human tau (SEQ ID NO: 920), with the highest affinity for residues 223-238 of human tau (SEQ ID NO: 920) ($K_D=2.08 \times 10^{-9}$ M).

[0726] V0009 demonstrated greatest affinity around residues 32-49 and 185-200 of human tau (SEQ ID NO: 920).

Example 10. CDR sequence analysis

[0727] CDR amino acid sequences associated with antibodies described above were aligned and assessed for relationship between sequence structure. Multiple sequence alignment in the corresponding CDR regions is performed using the web-based T-coffee program (suitable for multi-sequence alignment of relatively small sequences) at the EMBL-EBI website. A number of antibody groups were identified with high levels of sequence identity among CDR sequences analyzed, in some cases correlating with specific epitope and/or binding affinity.

Alignment between antibodies V0020 and V0021

Alignment between antibodies V0020 and V0021 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0020	GYTFTSY (SEQ ID NO: 308)	NPNNSD (SEQ ID NO: 356)	ANYYGGSQFAY (SEQ ID NO: 409)
V0021	GYTFTSN (SEQ ID NO: 313)	NPNNSE (SEQ ID NO: 357)	ANYYGGSQFAY (SEQ ID NO: 409)

ID#	CDRL1	CDRL2	CDRL3
V0020	RSSQSLVHSNGKTYLH (SEQ ID NO: 472)	KVSNRFS (SEQ ID NO: 525)	SQSTHVPFT (SEQ ID NO: 570)
V0021	RSSQSLVHSNGKTYLH (SEQ ID NO: 472)	KVSNRFS (SEQ ID NO: 525)	SQSTHVPFT (SEQ ID NO: 570)

[0728] VH CDR sequence alignment yielded a CDRH1 consensus sequence of GYTFTS [Y/N] (SEQ ID NO: 927), or more generally GYTFTSX (SEQ ID NO: 928), where X may be any amino acid, *e.g.*, X is Y/F/N/Q; a CDRH2 consensus sequence of NPNNS [D/E] (SEQ ID NO: 929), or more generally NPNNSX (SEQ ID NO: 930), where X may be any amino acid, *e.g.*, an amino acid with a negatively charged side chain; and a CDRH3 consensus sequence of ANYYGGSQFAY (SEQ ID NO: 409), which was conserved among antibodies in this group.

[0729] VL CDR sequence alignment demonstrated that light chain CDR sequences are completely conserved among antibodies in this group.

Alignment between antibodies V0022-V0024

[0730] As described above, antibodies V0022-V0024 demonstrated binding near the C-terminus of human tau, with highest affinity for peptides corresponding to residues 413-430 of human tau (SEQ ID NO: 920). In view of this overlap, CDR sequence alignment between antibodies V0022-V0024 was carried out and used to identify consensus sequences.

[0731] Alignment between antibodies V0022-V0024 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0022	GFTFTRY (SEQ ID NO: 314)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)
V0023	GYTFTIF (SEQ ID NO: 315)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)
V0024	GYTFTRF (SEQ ID NO: 316)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)

ID#	CDRL1	CDRL2	CDRL3
V0022	RSSQSLVHNNGITYLY (SEQ ID NO: 1154)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0023	RSSQSLVHSNGITHLY (SEQ ID NO: 474)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0024	RSSQSLVHSNGNTHLY (SEQ ID NO: 475)	RVSSRFS (SEQ ID NO: 530)	FQGTHVPRT (SEQ ID NO: 571)

[0732] As described above, antibodies V0022-V0024 demonstrated binding near the C-terminus of human tau, with highest affinity for peptides corresponding to residues 413-430 of human tau (SEQ ID NO: 920).

[0733] VH CDR sequence alignment yielded a CDRH1 consensus sequence of G [F/Y] TFT [R/I] [Y/F] (SEQ ID NO: 931), or more generally G-X1-TFT-X2-X3 (SEQ ID NO: 932), where X1, X2, and X3 may be any amino acid, *e.g.*, X1 and/or X3 may be an amino acid with a hydrophobic and/or aromatic side chain, such as F or Y, and/or X2 may be a positively charged residue (such as R, K, H) or a residue with aliphatic side chain (such as A, V, I, or L); a CDRH2 consensus sequence of NPNNGG (SEQ ID NO: 341), which was conserved among antibodies in this group; and a CDRH3 consensus sequence of GTGTGAMDY (SEQ ID NO: 410), which was conserved among antibodies in this group.

[0734] VL CDR sequence alignment yielded a CDRL1 consensus sequence of RSSQSLVH [N/S] NG [I/N] T [H/Y] LY (SEQ ID NO: 933), or more generally RSSQSLVH-X1-NG-X2-T-X3-LY (SEQ ID NO: 934), where X1, X2, and X3 may be any amino acid, *e.g.*, X1 is Q/N/S/T and/or X2 is A/V/I/L/Q/N and/or X3 is H/R/K/Y/F; a CDRL2 consensus sequence of RVS [N/S] RFS (SEQ ID NO: 935), or more generally RVSEXRF (SEQ ID NO: 936), where X may be any

amino acid, *e.g.*, X is Q/N/S/T; and a CDRL3 consensus sequence of FQGTHVPRT (SEQ ID NO: 571), which was conserved among antibodies in this group.

Alignment between antibodies V0022-V0025

Alignment between antibodies V0022-V0025, and V0050 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0022	GFTFTRY (SEQ ID NO: 314)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)
V0023	GYTFTIF (SEQ ID NO: 315)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)
V0024	GYTFTRF (SEQ ID NO: 316)	NPNNGG (SEQ ID NO: 341)	GTGTGAMDY (SEQ ID NO: 410)
V0025	GFTFTRF (SEQ ID NO: 317)	NPNNGE (SEQ ID NO: 358)	GTGTGAMDY (SEQ ID NO: 410)
V0050	GYTFTDY (SEQ ID NO: 297)	NPNNGG (SEQ ID NO: 341)	GRGMGYALDY (SEQ ID NO: 433)

ID#	CDRL1	CDRL2	CDRL3
V0022	RSSQSLVHNNGITYLY (SEQ ID NO: 1154)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0023	RSSQSLVHSNGITHLY (SEQ ID NO: 474)	RVSNRFS (SEQ ID NO: 529)	FQGTHVPRT (SEQ ID NO: 571)
V0024	RSSQSLVHSNGNTHLY (SEQ ID NO: 475)	RVSSRFS (SEQ ID NO: 530)	FQGTHVPRT (SEQ ID NO: 571)
V0025	RSSQSLVHSTGNTYLY (SEQ ID NO: 476)	RVSTRFS (SEQ ID NO: 531)	FQGTHVPRT (SEQ ID NO: 571)
V0050	GASENVYGALN (SEQ ID NO: 494)	GATNLAD (SEQ ID NO: 539)	QNVLTIPWT (SEQ ID NO: 586)

[0735] VH CDR sequence alignment yielded a CDRH1 consensus sequence of G [F/Y] TFT [R/I/D] [Y/F] (SEQ ID NO: 937), or more generally G-X1-TFT-X2-X3 (SEQ ID NO: 938), where X1, X2 and X3 may be any amino acid, *e.g.*, X1 and X3 are each independently F/Y and/or X2 is any residue (such as R/K/H/D/E/G/A/I/L/V); a CDRH2 consensus sequence of NPNNG [G/E] (SEQ ID NO: 939), or more generally NPNNGX (SEQ ID NO: 940), where X may be any amino acid, *e.g.*, E/D/G/A/V/I/L; and a CDRH3 consensus sequence of G [T/R] G [T/M] G

[absent/Y] [absent/Y] A [M/L] DY (SEQ ID NO: 941), or more generally G-X1-G-X2-G-X3-X4-A-X5-DY (SEQ ID NO: 942), where each of X1-X5 may be any amino acid and/or where X3 and/or X4 may be absent, *e.g.*, X1 is S/T/R/K/H and/or X2 is S/T/V/L/A/I/M and/or X3 and X4 are each independently Y/F/absent and/or X5 is A/V/I/L/M.

[0736] VL CDR sequence alignment yielded a CDRL1 consensus sequence with from about 11 to about 17 amino acids with an amino acid sequence of [R/G] [S/A] S [Q/E] [S/N] [L/V] [V/Y] [H/G] [S/A/N] [N/T/L] [G/N] [I/N/absent] [T/absent] [H/Y/absent] [L/absent] [Y/absent], or more generally X1-X2-S-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15, where X1-X15 may be any amino acid and/or where X11, X12, X13, X14, and/or X15 may be absent, *e.g.*, X1 is R/K/H/G/A/V/I/L and/or X2 is S/T/A/V/I/L and/or X3 is Q/N/E/D and/or X4 is S/T/N/Q and/or X5 is L/V/A/I and/or X6 is A/V/I/L/Y/F and/or X7 is H/R/K/G/A and/or X8 is S/T/A/V/I/L/N/Q and/or X9 is N/Q/A/I/L/V/M/S/T and/or X10 is G/A/N/Q and/or X11 is Q/N/A/V/I/L/absent and/or X12 is T/S/absent and/or X13 is H/R/K/Y/F/absent and/or X14 is A/V/I/L/absent and/or X15 is Y/F/absent; a CDRL2 consensus sequence with from about 3 to about 7 amino acids with an amino acid sequence of [R/G][V/A][S/T][N/T/S][R/L][F/A][S/D], or more generally X1-X2-X3-X4-X5-X6-X7, where X1, X2, X3, X4, X5, X6, and X7 may be any amino acid, *e.g.*, X1 is R/K/H/G/A and/or X2 is V/A/I/L and/or X3 is S/T and/or X4 is N/Q/T/S and/or X5 is R/K/H/A/V/I/L and/or X6 is F/Y/A/V/I/L/G and/or X7 is S/T/D/E; and a CDRL3 consensus sequence with from about 9 amino acids with an amino acid sequence of [F/Q] [G/N] [G/V] [T/L] [H/T] [V/I] P [R/W] T (SEQ ID NO: 947), or more generally X1-X2-X3-X4-X5-X6-P-X7-T (SEQ ID NO: 948), where X1, X2, X3, X4, X5, X6, and X7 may be any amino acid, *e.g.*, X1 is F/Y/Q/N and/or X2 is G/A/Q/N and/or X3 is G/A/V/I/L and/or X4 is T/S/A/V/I/L and/or X5 is H/R/K/T/S and/or X6 is V/I/A/L and/or X7 is R/K/H/W/F/Y.

Alignment between antibodies V0026, V0027, and V0032

Alignment between antibodies V0026, V0027, and V0032 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0026	GYSFTDY (SEQ ID NO: 318)	FPGSDS (SEQ ID NO: 359)	PTVVARDYAMDY (SEQ ID NO: 411)
V0027	GYTFTEY (SEQ ID NO: 319)	FPGRGS (SEQ ID NO: 360)	PTIVARDYAMDY (SEQ ID NO: 412)
V0032	GYTFTDY (SEQ ID NO: 297)	YPGSGN (SEQ ID NO: 364)	PAYYSKDYAMEY (SEQ ID NO: 417)

ID#	CDRL1	CDRL2	CDRL3
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V0026	RSSQSIVYSNGNTYLE (SEQ ID NO: 477)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPYT (SEQ ID NO: 572)
V0027	RSSQSIVHRNGNTYLE (SEQ ID NO: 478)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPFT (SEQ ID NO: 573)
V0032	RSSQSIVYTNGNTYLE (SEQ ID NO: 481)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPYT (SEQ ID NO: 572)

[0737] VH CDR sequence alignment yielded a CDRH1 consensus sequence of GY [S/T] FT [D/E] Y (SEQ ID NO: 949), or more generally GY-X1-FT-X2-Y (SEQ ID NO: 950), where X1 and X2 may be any amino acid, *e.g.*, X1 is S/T and/or X2 is D/E/S/T; a CDRH2 consensus sequence of [F/Y] PG [S/R] [D/G] [S/N], or more generally X1-PG-X2-X3-X4, where X1-X4 may be any amino acid, *e.g.*, X1 is F/Y and/or X2 is S/T/R/K/H and/or X3 is D/E/G/A and/or X4 is S/T/N/Q; and a CDRH3 consensus sequence of P [T/A] [V/I/Y] [V/Y] [A/S] [R/K] DYAM [D/E] Y (SEQ ID NO: 953), or more generally P-X1-X2-X3-X4-X5-DYAM-X6-Y (SEQ ID NO: 954), where X1-X6 may be any amino acid, *e.g.*, X1 is T/S/A/V/I/L and/or X2 is V/I/A/L/Y/F and/or X3 is V/I/A/L/Y/F and/or X4 is A/V/I/L/S/T and/or X5 is R/K/H and/or X6 is D/E.

[0738] VL CDR sequence alignment yielded a CDRL1 consensus sequence of RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955), or more generally RSSQSIV-X1-X2-NGNTYLE (SEQ ID NO: 956), where X1 and X2 may be any amino acid, *e.g.*, X1 is Y/F/H/R/K and/or X2 is S/T/R/K/H; a CDRL2 consensus sequence of KVSNRFS (SEQ ID NO: 525), which was conserved among antibodies in this group; and a CDRL3 consensus sequence of FQGSHVP[Y/F]T (SEQ ID NO: 957), or more generally FQGSHVPXT (SEQ ID NO: 958), where X may be any amino acid, *e.g.*, Y, F.

Alignment between antibodies V0026, V0027, V0031, and V0032

[0739] Alignment between antibodies V0026, V0027, V0031, and V0032 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0026	GYSFTDY (SEQ ID NO: 318)	FPGSDS (SEQ ID NO: 359)	PTVVARDYAMDY (SEQ ID NO: 411)
V0027	GYTFTEY (SEQ ID NO: 319)	FPGRGS (SEQ ID NO: 360)	PTIVARDYAMDY (SEQ ID NO: 412)
V0031	GYTFTSY (SEQ ID NO: 308)	YPSNGG (SEQ ID NO: 363)	SSVVG RDYAMDY (SEQ ID NO: 416)
V0032	GYTFTDY (SEQ ID NO: 297)	YPGSGN (SEQ ID NO: 364)	PAYYSKDYAMEY (SEQ ID NO: 417)

ID#	CDRL1	CDRL2	CDRL3
V0026	RSSQSIVYSNGNTYLE (SEQ ID NO: 477)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPYT (SEQ ID NO: 572)
V0027	RSSQSIVHRNGNTYLE (SEQ ID NO: 478)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPFT (SEQ ID NO: 573)
V0031	RSSQSIVHSNGNTYLE (SEQ ID NO: 479)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPYT (SEQ ID NO: 572)
V0032	RSSQSIVYTNGNTYLE (SEQ ID NO: 481)	KVSNRFS (SEQ ID NO: 525)	FQGSHVPYT (SEQ ID NO: 572)

[0740] VH CDR sequence alignment yielded a CDRH1 consensus sequence of GY [S/T] FT [D/E/S] Y (SEQ ID NO: 959), or more generally GY-X1-FT-X2-Y (SEQ ID NO: 950), where X1 and X2 may be any amino acid, *e.g.*, X1 is S/T and/or X2 is E/D/S/T; a CDRH2 consensus sequence of [F/Y] P [G/S] [S/R/N] [D/G] [S/G/N], or more generally X1-P-X2-X3-X4-X5, where X1-X5 may be any amino acid, *e.g.*, X1 is F/Y and/or X2 is S/T/G/A/V/I/L and/or X3 is S/T/R/K/H/N/Q and/or X4 is D/E/G/A and/or X5 is S/T/N/Q/G/A; and a CDRH3 consensus sequence of [P/S] [T/A/S] [V/I/Y] [V/Y] [A/S/G] [R/K] DYAM [D/E] Y (SEQ ID NO: 962), or more generally X1-X2-X3-X4-X5-X6-DYAM-X7-Y (SEQ ID NO: 963), where X1-X7 may be any amino acid, *e.g.*, X1 is S/T/P/A/I/L/V and/or X2 is T/S/A/V/I/L and/or X3 is A/V/I/L/Y/F and/or X4 is A/V/I/L/Y/F and/or X5 is A/V/I/L/G/S/T and/or X6 is R/K/H and/or X7 is E/D.

[0741] VL CDR sequence alignment yielded a CDRL1 consensus sequence of RSSQSIV [Y/H] [S/R/T] NGNTYLE (SEQ ID NO: 955), or more generally RSSQSIV-X1-X2-NGNTYLE (SEQ ID NO: 956), where X1 and X2 may be any amino acid, *e.g.*, X1 is Y/F/H/R/K and/or X2 is S/T/R/K/H; a CDRL2 consensus sequence of KVSNRFS (SEQ ID NO: 525), which was conserved among antibodies in this group; and a CDRL3 consensus sequence of FQGSHVP[Y/F]T (SEQ ID NO: 957), or more generally FQGSHVPXT (SEQ ID NO: 958), where X may be any amino acid, *e.g.*, Y and F.

Alignment between antibodies V0052, V0054, V0055, V0057, and V0058

[0742] As described in the Pepscan epitope analysis presented above, V0052 demonstrated affinity for peptides corresponding with residues 55-76, 159-194, 219-247, and 381-426 of human tau (SEQ ID NO: 920). Of these regions, V0052 affinity was greater for residues 57-72, 175-191, 223-238, and 383-400 of human tau (SEQ ID NO: 920). Binding of antibodies V0054, V0055, V0057, and V0058 to ePHF was shown by ELISA analysis to be blocked when ePHF

was bound to plates coated with C10.2 capture antibody. C10.2 antibody is known to bind Peptide 12 (SEQ ID NO: 923) corresponding to amino acid residues 379-415 of human tau (SEQ ID NO: 920), which overlaps with residues involved in V0052 tau binding. In view of this overlap, CDR sequence alignment between antibodies V0052, V0054, V0055, V0057, and V0058 was carried out and used to identify consensus sequences.

[0743] Alignment between antibodies V0052, V0054, V0055, V0057, and V0058 is shown below.

ID#	CDRH1	CDRH2	CDRH3
V0052	GFSLSTSAM (SEQ ID NO: 325)	YWDDD (SEQ ID NO: 362)	RRRGYGMDY (SEQ ID NO: 435)
V0054	GFSLNTSGM (SEQ ID NO: 326)	YWDDD (SEQ ID NO: 362)	RVRGYGMDY (SEQ ID NO: 437)
V0055	GFSLSTSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RVRYYAMDY (SEQ ID NO: 438)
V0057	GFSLSTSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RVRYYAMDY (SEQ ID NO: 438)
V0058	GFSLSTFGM (SEQ ID NO: 327)	YWDDD (SEQ ID NO: 362)	RKRSYGMDY (SEQ ID NO: 440)

ID#	CDRL1	CDRL2	CDRL3
V0052	KASQSVSNDVA (SEQ ID NO: 495)	YASNRCT (SEQ ID NO: 540)	QQDYRSPLT (SEQ ID NO: 587)
V0054	KSSQSLLNSGNQKNYLA (SEQ ID NO: 496)	GTSTRES (SEQ ID NO: 542)	QNDHSHPYT (SEQ ID NO: 588)
V0055	KSSQSLLNSGNQKNYLA (SEQ ID NO: 496)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)
V0057	KSSQSLLNSGNQKNYLA (SEQ ID NO: 496)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)
V0058	KSSQSLLSSGNQKNYLA (SEQ ID NO: 497)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)

[0744] VH CDR sequence alignment yielded a CDRH1 consensus sequence of GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964), or more generally GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), where X1-X3 may be any amino acid, *e.g.*, X1 is S/T/N/Q and/or X2 is S/T/F/Y and/or X3 is

A/V/I/L/G; a CDRH2 consensus sequence of YWDDD (SEQ ID NO: 362), which was conserved among antibodies of this group; and a CDRH3 consensus sequence of R [R/V/K] R [G/Y/S] Y [G/A] MDY (SEQ ID NO: 966), or more generally R-X1-R-X2-Y-X3-MDY (SEQ ID NO: 967), where X1-X3 may be any amino acid, *e.g.*, X1 is R/K/H/A/V/I/L and/or X2 is G/A/V/I/L/S/T/Y/F and/or X3 is A/V/I/L/G.

[0745] VL CDR sequence alignment yielded a CDRL1 consensus sequence of K [A/S] SQS [V/L] [S/L] [N/S] [absent/S] [absent/G] [absent/N] [absent/Q] [absent/K] [absent/N] [D/Y] [V/L] A (SEQ ID NO: 968), or more generally K-X1-SQS-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-A (SEQ ID NO: 969), where X1-X12 may be any amino acid and/or where one or more of X5-X10 may be absent, *e.g.*, X1 is S/T/A/V/I/L and/or X2 is A/V/I/L and/or X3 is S/T/A/V/I/L and/or X4 is N/Q/S/T and/or X5 is S/T/absent and/or X6 is G/A/V/I/L/absent and/or X7 is N/Q/absent and/or X8 is N/Q/absent and/or X9 is K/R/H/absent and/or X10 is N/Q/absent and/or X11 is E/D/Y/F and/or X12 is A/V/I/L; a CDRL2 consensus sequence of [Y/G] [A/T] S [N/T] R [C/E] [T/S], or more generally X1-X2-S-X3-R-X4-X5, where X1-X5 may be any amino acid, *e.g.*, X1 is Y/F/G/A/V/I/L and/or X2 is A/V/I/L/T/S and/or X3 is N/Q/T/S and/or X4 is C/S/E/D and/or X5 is T/S; and a CDRL3 consensus sequence of Q [Q/N] D [Y/H] [R/S] [S/H] P [L/Y] T (SEQ ID NO: 972), or more generally Q-X1-D-X3-X4-X5-P-X6-T (SEQ ID NO: 973), where X1-X6 may be any amino acid, *e.g.*, X1 is Q/N and/or X2 is Y/F/H/R/K and/or X3 is R/K/H/S/T and/or X4 is S/T/H/K/R and/or A/V/I/L/Y/F.

Alignment between antibodies V0052, V0054, V0055, V0057, V0058, V0036, and V0049

[0746] As described in the Pepscan epitope analysis presented above, V0052 demonstrated affinity for peptides corresponding with residues 55-76, 159-194, 219-247, and 381-426 of human tau (SEQ ID NO: 920). Of these regions, V0052 affinity was greater for residues 57-72, 175-191, 223-238, and 383-400 of human tau (SEQ ID NO: 920). Binding of antibodies V0036, V0049, V0054, V0055, V0057, and V0058 to ePHF was shown by ELISA analysis to be blocked when ePHF was bound to plates coated with C10.2 capture antibody. C10.2 antibody is known to bind Peptide 12 (SEQ ID NO: 923) corresponding to amino acid residues 379-415 of human tau (SEQ ID NO: 920), which overlaps with residues involved in V0052 tau binding. In view of this overlap, CDR sequence alignment between antibodies V0036, V0049, V0052, V0054, V0055, V0057, and V0058 was carried out and used to identify consensus sequences.

[0747] Alignment between antibodies V0052, V0054, V0055, V0057, V0058, V0036, and V0049 is shown below.

ID#	CDRH1	CDRH2	CDRH3
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V0052	GFSLS TSAM (SEQ ID NO: 325)	YWDDD (SEQ ID NO: 362)	RRRGYGMDY (SEQ ID NO: 435)
V0054	GFSLNTSGM (SEQ ID NO: 326)	YWDDD (SEQ ID NO: 362)	RVRGYGMDY (SEQ ID NO: 437)
V0055	GFSLS TSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RVRYYAMDY (SEQ ID NO: 438)
V0057	GFSLS TSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RVRYYAMDY (SEQ ID NO: 438)
V0058	GFSLS TFGM (SEQ ID NO: 327)	YWDDD (SEQ ID NO: 362)	RKRSYGMDY (SEQ ID NO: 440)
V0036	GFSLS TSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RSRRGNYDY (SEQ ID NO: 421)
V0049	GFSLS TSGM (SEQ ID NO: 321)	YWDDD (SEQ ID NO: 362)	RGYY SNGNYFDY (SEQ ID NO: 432)

ID#	CDRL1	CDRL2	CDRL3
V0052	KASQSVSNDVA (SEQ ID NO: 495)	YASNRCT (SEQ ID NO: 540)	QQDYRSPLT (SEQ ID NO: 587)
V0054	KSSQSLN SGNQKNYLA (SEQ ID NO: 496)	GTSTRES (SEQ ID NO: 542)	QNDHSHPYT (SEQ ID NO: 588)
V0055	KSSQSLN SGNQKNYLA (SEQ ID NO: 496)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)
V0057	KSSQSLN SGNQKNYLA (SEQ ID NO: 496)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)
V0058	KSSQSL SSGNQKNYLA (SEQ ID NO: 497)	GASTRES (SEQ ID NO: 543)	QNDHSHPYT (SEQ ID NO: 588)
V0036	KSSQSL LDSGKTYLN (SEQ ID NO: 484)	LVSKLDS (SEQ ID NO: 532)	WQGTHFPQT (SEQ ID NO: 576)
V0049	SASSSISSTYLH (SEQ ID NO: 493)	RTSNLAS (SEQ ID NO: 538)	QQGSSIPRYT (SEQ ID NO: 585)

[0748] VH CDR sequence alignment yielded a CDRH1 consensus sequence of GFSL [S/N] T [S/F] [A/G] M (SEQ ID NO: 964), or more generally GFSL-X1-T-X2-X3-M (SEQ ID NO: 965), where X1-X3 may be any amino acid, *e.g.*, X1 is S/T/N/Q and/or X2 is S/T/F/Y and/or X3 is

G/A/I/L/V; a CDRH2 consensus sequence of YWDDD (SEQ ID NO: 362), which was conserved among antibodies of this group; and a CDRH3 consensus sequence of R [R/V/K/S/G] [Y/R] [Y/absent] [S/absent] [absent/N] [G/S/Y/R] [Y/N/G] [G/A/Y/N] [M/F/Y] DY, or more generally R-X1-X2-X3-X4-X5-X6-X7-X8-X9-DY, where each of X1-X9 may be any amino acid and/or where one or more of X3-X5 may be absent, *e.g.*, X1 is R/K/H/A/V/I/L/G/S/T and/or X2 is Y/F/R/K/H and/or X3 is Y/F/absent and/or X4 is S/T/absent and/or X5 is N/Q/absent and/or X6 is G/A/V/I/L/S/T/Y/F/R/K/H and/or X7 is Y/F/N/Q/G/A/V/I/L and/or X8 is G/A/V/I/L/Y/F/N/Q and/or X9 is M/F/Y.

[0749] VL CDR sequence alignment yielded a CDRL1 consensus sequence of [K/S] [S/A] S [Q/S] S [L/I/V] [L/S] [N/S/D] [D/S/T] [V/G/D/Y] [N/G/absent] [Q/absent] [K/absent] [N/T/absent] [Y/absent] [L/absent] [A/H/N], or more generally X1-X2-S-X3-S-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15, where each of X1-X15 may be any amino acid and/or where one or more of X9-X14 may be absent, *e.g.*, X1 is K/R/H/S/T and/or X2 is S/T/A/V/I/L and/or X3 is Q/N/S/T and/or X4 is L/I/V/A and/or X5 is A/V/I/L/S/T and/or X6 is N/Q/S/T/D/E and/or X7 is D/E/S/T and/or X8 is G/A/V/I/L/D/E/Y/F and/or X9 is N/Q/G/A/absent and/or X10 is Q/N/absent and/or X11 is K/R/H/absent and/or X12 is N/Q/T/S/absent and/or X13 is Y/F/absent and/or X14 is A/V/I/L/absent and/or X15 is A/V/I/L/H/K/R/N/Q; a CDRL2 consensus sequence of [Y/G/L/R] [A/T/V] S [N/T/K] [R/L] [C/E/D/A] [T/S], or more generally X1-X2-S-X3-X4-X5-X6, where X1-X6 may be any amino acid, *e.g.*, X1 is Y/F/G/A/V/I/L/R/K/H and/or X2 is A/V/I/L/T/S and/or X3 is N/Q/T/S/K/R/H and/or X4 is R/K/H/A/V/I/L and/or X5 is C/S/E/D/A/V/I/L and/or X6 is T/S; and a CDRL3 consensus sequence of [W/Q] [Q/N] [G/D] [T/S/Y/H] [H/S/R] [F/I/S/H] P [Q/R/L/Y] [absent/Y] T, or more generally X1-X2-X3-X4-X5-X6-P-X7-X8-T, where each of X1-X8 may be any amino acid and/or where X8 may be absent, *e.g.*, X1 is Q/N/W/F/Y and/or X2 is Q/N and/or X3 is G/A/V/I/L/D/E and/or X4 is T/S/Y/F/H/K/R and/or X5 is H/K/R/S/T and/or X6 is F/Y/A/V/I/L/S/T/H/K/R and/or X7 is Q/N/R/K/H/A/V/I/L/Y/F and/or X8 is Y/F/absent.

Example 11. Passive immunotherapy seeding model analysis

[0750] A passive immunotherapy seeding model was used to assess different anti-tau antibodies. For assessments, recombinant mouse IgG antibodies were prepared with clone-specific variable domain pairs selected from those presented in Table 3 and mouse IgG1 constant domains. In the model, FTD mutant tau transgenic mice carrying P301S tau mutations were used. Seeding was carried out by weekly intraparenchymal infusion of 75 ng ePHF to CA1 hippocampal regions of study mice, beginning at 8 weeks of age and continuing for 6 weeks. Antibodies were administered to mice at a dose of 40 mg/kg by intraperitoneal injection.

Administration was carried out 7 and 3 days prior to seeding and on days 4, 11, 18, 25, and 32 after initiation of seeding. Effect of antibody treatment on pathogenic tau level was determined in each case by ELISA analysis of ipsilateral hippocampal sample immunoreactivity with AT8 antibody, which is specific for pathogenic tau. Percent decrease in AT8 reactivity between samples from vehicle (control) treated mice and mice treated with various antibodies are presented in Table 26.

Table 26. AT8 reactivity

Treatment	% AT8 immunoreactivity relative to control
V0009	75%
V0023	49%
V0052	83%
PHF1	59%

[0751] Each of the antibodies tested yielded samples with reduced AT8 reactivity, with V0023 and PHF1 yielding the greatest reductions over samples from control mice and V0023 demonstrating the greatest efficacy.

Example 12. Engineering viral genomes for the expression of anti-tau antibodies

[0752] Viral genomes are designed for AAV delivery of anti-tau antibodies or variants thereof. Payload regions comprising or encoding antibody sequences provided in any of Tables 1-7 are cloned into viral genomes. The viral genomes may include, besides the antibody coding regions, any one or more of each of the following, a 5' ITR, a promoter (may have several components), one or more intron or exon sequences, one or more signal sequences, one or more linker sequences, a tag sequence, a polyadenylation sequence, a filler sequence and a 3' ITR. Sequence components may be selected from sequences provided in Tables 10-18.

[0753] A series of viral genomes are generated, wherein the order of heavy and light chains is alternated with respect to 5' to 3' direction. When read 5' to 3', viral genomes encoding a heavy chain antibody sequence, a linker region, and a light chain antibody sequence (heavy-linker-light) are prepared. Viral genomes encoding a light chain antibody sequence, a linker region, and a heavy chain antibody sequence (light-linker-heavy) are also prepared.

[0754] The viral genomes for expression of anti-tau antibodies are incorporated into AAV particles (*e.g.*, using an AAV1, AAV2, AAV2 variant, AAV2/3 variant, or VOY101 capsid).

Example 13. Production and Purification of AAV particles

[0755] Any of the viral genomes contemplated herein may be encapsulated in an AAV capsid to generate an AAV particle. AAV particles may be produced using methods known in the art, such as, for example, triple transfection or baculovirus mediated virus production. Any suitable permissive or packaging cell known in the art may be employed to produce the particles. Mammalian cells are often preferred. Also preferred are trans-complementing packaging cell lines that provide functions deleted from a replication-defective helper virus, *e.g.*, 293 cells or other E1a trans-complementing cells.

[0756] The gene cassette may contain some or all of the parvovirus (*e.g.*, AAV) cap and rep genes. Preferably, however, some or all of the cap and rep functions are provided in trans by introducing a packaging vector(s) encoding the capsid and/or Rep proteins into the cell. Most preferably, the gene cassette does not encode the capsid or Rep proteins. Alternatively, a packaging cell line is used that is stably transformed to express the cap and/or rep genes.

[0757] Recombinant AAV virus particles are, in some cases, produced and purified from culture supernatants according to the procedure as described in US20160032254, the contents of which are incorporated by reference. Production may also involve methods known in the art including those using 293T cells, sf9 insect cells, triple transfection or any suitable production method.

[0758] In some cases, 293T cells (adhesion/suspension) are transfected with polyethyleneimine (PEI) with plasmids required for production of AAV, *i.e.*, AAV2 rep, an adenoviral helper construct and an ITR flanked transgene cassette. The AAV2 rep plasmid also contains the cap sequence of the particular virus being studied. Twenty-four hours after transfection (no medium changes for suspension), which occurs in DMEM/F17 with/without serum, the medium is replaced with fresh medium with or without serum. Three (3) days after transfection, a sample is taken from the culture medium of the 293 adherent cells. Subsequently cells are scraped, or suspension cells are pelleted, and transferred into a receptacle. For adhesion cells, after centrifugation to remove cellular pellet, a second sample is taken from the supernatant after scraping. Next, cell lysis is achieved by three consecutive freeze-thaw cycles (-80C to 37C) or adding detergent triton. Cellular debris is removed by centrifugation or depth filtration and sample 3 is taken from the medium. The samples are quantified for AAV particles by DNase resistant genome titration by DNA qPCR. The total

production yield from such a transfection is equal to the particle concentration from sample 3 described above.

[0759] AAV particle titers are measured according to genome copy number (genome particles per milliliter). Genome particle concentrations are based on DNA qPCR of the vector DNA as previously reported (Clark *et al.* (1999) Hum. Gene Ther., 10:1031-1039; Veldwijk *et al.* (2002) Mol. Ther., 6:272-278).

CLAIMS

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

(i) the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 1144, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 1145, and the HC CDR3 comprises the amino acid sequence of SEQ ID NO: 410; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 1146, the LC CDR2 comprises the amino acid sequence of SEQ ID NO: 529, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO: 571;

(ii) the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 1165, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 1166, and the HC CDR3 comprises the amino acid sequence of SEQ ID NO: 1167; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 473, the LC CDR2 comprises the amino acid sequence of RVS, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO: 571; or

(iii) the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 314, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 341, and the HC CDR3 comprises the amino acid sequence of SEQ ID NO: 410; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 1154, the LC CDR2 comprises the amino acid sequence of SEQ ID NO: 529, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO: 571.

2. The antibody of claim 1, wherein the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 1144, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 1145, and the HC CDR3 comprises the amino acid sequence of SEQ ID NO: 410; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 1146, the LC CDR2 comprises the amino acid sequence of SEQ ID NO: 529, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO: 571.

3. The antibody of claim 1 or 2, 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.

4. The antibody of any one of claims 1-3, wherein 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: 21.

5. The antibody of any one of claims 1-4, wherein the VL comprises the amino acid sequence of any one of SEQ ID NO: 93, or an amino acid 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 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 NO: 93.

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

(i) the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 1147, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 1148, and the HC CDR3 comprises

the amino acid sequence of SEQ ID NO: 410; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 474, the LC CDR2 comprises the amino acid sequence of SEQ ID NO: 529, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO 571;

(ii) the HC CDR1 comprises the amino acid sequence of SEQ ID NO: 1149, the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 1150, and the HC CDR3 comprises the amino acid sequence of SEQ ID NO: 410; and the LC CDR1 comprises the amino acid sequence of SEQ ID NO: 475, the LC CDR2 comprises the amino acid sequence of SEQ ID NO: 530, and the LC CDR3 comprises the amino acid sequence of SEQ ID NO: 571.

9. The antibody of claim 8, wherein:

(i) 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/or 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

(ii) 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/or 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.

10. The antibody of any one of claims 1-9, which is a full length antibody, a bispecific antibody, an Fab, an F(ab')₂, an Fv, or a single chain Fv fragment (scFv).

11. The antibody of any one of claims 1-10, which is a humanized antibody.

12. 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.

13. The antibody of any one of claims 1-12, comprising a light chain constant region chosen from the light chain constant region of kappa or lambda.

14. The antibody of any one of claims 1-13, comprising a human IgG4 heavy chain constant region and a human kappa light chain constant region.

15. The antibody of any one of claims 1-14, which binds the C-terminus of a tau protein.

16. The antibody of any one of claims 1-15, which binds a tau protein which comprises at least one, two, three or more phosphorylated residues.

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

- (i) binds a microtubule binding domain of a tau protein;
 - (ii) binds a proline rich domain of a tau protein;
 - (iii) binds enriched paired helical filament tau protein (ePHF);
 - (iv) binds an epitope comprising a region formed by a complex of at least two tau proteins;
 - (v) binds to a tau protein with a dissociation constant (K_D) of less than about 120 nM;
- and/or
- (vi) reduces or inhibits aggregation of tau.

18. A nucleic acid encoding the antibody of any one of claims 1-17.

19. The nucleic acid of claim 18, wherein:

- (i) the nucleotide sequence encoding the VH comprises SEQ ID NO: 167, 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 SEQ ID NO: 241, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the nucleotide sequence encoding the VH comprises SEQ ID NO: 168, 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 SEQ ID NO: 242, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or

(iii) the nucleotide sequence encoding the VH comprises SEQ ID NO: 169, 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 SEQ ID NO: 243, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

20. A viral genome comprising a promoter operably linked to a nucleic acid encoding the antibody of any one of claims 1-17.

21. The viral genome of claim 20, 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.

22. The viral genome of claim 20 or 21, which further comprises:

- (i) an enhancer;
- (ii) a polyadenylation (polyA) signal region;

(iii) an ITR sequence positioned 5' relative to the nucleic acid encoding the antibody and/or an ITR sequence positioned 3' relative to the nucleic acid encoding the antibody;
(iv) an intron region;
(v) an exon region; and/or
(vi) a nucleotide sequence encoding a miR binding site.

23. A vector comprising the nucleic acid of claim 18 or 19, the viral genome of any one claims 20-22, or a nucleotide sequence encoding the antibody of any one of claims 1-17.

24. An AAV particle comprising:

- (i) a capsid protein; and
- (ii) the viral genome of any one of claims 20-22.

25. The AAV particle of claim 24, wherein the capsid protein comprises an AAV5 capsid protein or variant thereof; or an AAV9 capsid protein or variant thereof.

26. A host cell comprising the antibody of any one of claims 1-17, the nucleic acid of claim 18 or 19, the viral genome of any one of claims 20-22, the vector of claim 23, or the AAV particle of claim 24 or 25.

27. The host cell of claim 26, which 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 26 or 27 under conditions suitable for gene expression.

29. A pharmaceutical composition comprising the antibody of any one of claims 1-17, an AAV particle comprising the viral genome of any one of claims 20-22, or the AAV particle of claim 24 or 25; and a pharmaceutically acceptable excipient.

30. Use of the antibody of any one of claims 1-17, an AAV particle comprising the viral genome of any one of claims 20-22, the AAV particle of claim 24 or 25, 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, wherein the subject has, has been diagnosed with having, or is at risk of having a tauopathy.

31. Use of the antibody of any one of claims 1-17, an AAV particle comprising the viral genome of any one of claims 20-22, the AAV particle of claim 24 or 25, or the pharmaceutical composition of claim 29, in the manufacture of a medicament for treating a tauopathy in a subject.

32. The Use of claim 30 or 31, wherein the tauopathy is 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), or progressive supranuclear palsy (PSP).

33. The use of any one of claims 30-32, 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.

34. 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 tauopathy, wherein the additional therapeutic agent and/or therapy comprises a cholinesterase inhibitor, an N-methyl D-aspartate (NMDA) antagonist, an antipsychotic drug, an anti-anxiety drug, an anticonvulsant, a dopamine agonist, a monoamine oxidase B (MAO B) inhibitor, a catechol O-methyltransferase (COMT) inhibitor, an anticholinergic, amantadine, carbidopa-levodopa, deep brain stimulation (DBS), or a combination thereof.