class of neurodegenerative diseases associated with aggregation of the microtubule-associated protein Tau, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), and frontotemporal dementia (FTD).

[0006] The underlying mechanism of Tau-mediated neurotoxicity is poorly understood and the trigger for Tau aggregation in neurons is yet to be elucidated. Thus, while therapeutic approaches targeting Tau are being explored, there remains a need for specific and effective therapeutic agents that target Tau.

SUMMARY

[0007] Described herein are monoclonal antibodies, or antigen-binding fragments thereof, that specifically bind a human Tau isoform or fragment. In one aspect, the present disclosure refers to a monoclonal antibody comprising a heavy chain and a light chain, or an antigen-binding fragment thereof, that specifically binds a human Tau, wherein: the heavy chain comprises a heavy chain complementarity determining region 1 (HCDR1) comprising SEQ ID NO: 732, a heavy chain complementarity determining region 2 (HCDR2) comprising SEQ ID NO: 734, and a heavy chain complementarity determining region 3 (HCDR3) comprising SEQ ID NO: 736, and the light chain comprises a light chain complementarity determining region 1 (LCDR1) comprising SEQ ID NO: 846, a light chain complementarity determining region 2 (LCDR2) comprising SEQ ID NO: 848, and a light chain complementarity determining region 3 (LCDR3) comprising SEQ ID NO: 850 as defined according to the method of Kabat; or the heavy chain comprises a HCDR1 comprising SEQ ID NO: 1002, a HCDR2 comprising SEQ ID NO: 1004, and a HCDR3 comprising SEQ ID NO: 1006 and the light chain comprises a LCDR1 comprising SEQ ID NO: 1116, a LCDR2 comprising SEQ ID NO: 1118, and a LCDR3 comprising SEQ ID NO: 1120 as defined by IMGT. In some examples, the antibody is murine antibody, a chimeric antibody, or a humanized antibody. In some examples, the antibody isotype is IgG1. In some examples, the antibody comprises: a heavy chain complementarity determining region 1 (HCDR1), a heavy chain complementarity determining region 2 (HCDR2), and a heavy chain complementarity determining region 3 (HCDR3) as set forth in SEQ ID NO: 196 and a light chain complementarity determining region 1 (LCDR1), a light chain complementarity determining region 2 (LCDR2), and a light chain complementarity determining region 3 (LCDR3) as set forth in SEQ ID NO: 411; a HCDR1, a HCDR2, and a HCDR3 as set forth in

SEQ ID NO: 268 and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 465; or a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 402 and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 572. In some examples, the monoclonal antibody or antigen-binding fragment thereof comprises a HCDR1 comprising SEQ ID NO: 594, a HCDR2 comprising SEQ ID NO: 596, a HCDR3 comprising SEQ ID NO: 598, a LCDR1 comprising SEQ ID NO: 738, a LCDR2 comprising SEQ ID NO: 740, and a LCDR3 comprising SEQ ID NO: 742 as defined according to the method of Kabat; a HCDR1 comprising SEQ ID NO: 864, a HCDR2 comprising SEQ ID NO: 866, a HCDR3 comprising SEQ ID NO: 868, a LCDR1 comprising SEQ ID NO: 1008, a LCDR2 comprising SEQ ID NO: 1010, and a LCDR3 comprising SEQ ID NO: 1012 as defined by IMGT; a HCDR1 comprising SEQ ID NO: 642, a HCDR2 comprising SEQ ID NO: 644, a HCDR3 comprising SEQ ID NO: 646, a LCDR1 comprising SEQ ID NO: 774, a LCDR2 comprising SEQ ID NO: 776, and a LCDR3 comprising SEQ ID NO: 778 as defined according to the method of Kabat; a HCDR1 comprising SEQ ID NO: 912, a HCDR2 comprising SEQ ID NO: 914, a HCDR3 comprising SEQ ID NO: 916, a LCDR1 comprising SEQ ID NO: 1044, a LCDR2 comprising SEQ ID NO: 1046, and a LCDR3 comprising SEQ ID NO: 1048 as defined by IMGT; a HCDR1 comprising SEQ ID NO: 732, a HCDR2 comprising SEQ ID NO: 734, a HCDR3 comprising SEQ ID NO: 736, a LCDR1 comprising SEQ ID NO: 846, a LCDR2 comprising SEQ ID NO: 848, and a LCDR3 comprising SEQ ID NO: 850 as defined according to the method of Kabat; or a HCDR1 comprising SEQ ID NO: 1002, a HCDR2 comprising SEQ ID NO: 1004, a HCDR3 comprising SEQ ID NO: 1006, a LCDR1 comprising SEQ ID NO: 1116, a LCDR2 comprising SEQ ID NO: 1118, and a LCDR3 comprising SEQ ID NO: 1120 as defined by IMGT.

[0008] According to some examples, the aforementioned monoclonal antibodies or antigen-binding fragments thereof comprise sequence modifications. In some examples, modification(s) is position 49 of the light chain according to the method of Kabat is not cysteine, the residue at position 57 of the heavy chain according to the method of Kabat is not cysteine, the residue at position 34 of the light chain according to the method of Kabat is glutamate, the residue at position 36 of the light chain according to the method of Kabat is not phenylalanine, the residue at position 46 of the light chain according to the method of Kabat is not arginine, the residue at position 94 of the heavy chain according to the method of Kabat is not lysine, the residue at position 71 of the heavy chain according to the method of Kabat is not arginine, or any

combination thereof. In some embodiments in which the residue at position 49 of the light chain according to the method of Kabat is not cysteine, the residue is serine. In some examples in which the residue at position 57 of the heavy chain according to the method of Kabat is not cysteine, the residue is serine. In some examples in which the residue at position 36 of the light chain according to the method of Kabat is not phenylalanine, the residue is tyrosine. In some examples in which the residue at position 46 of the light chain according to the method of Kabat is not arginine, the residue is leucine. In some examples in which the residue at position 71 of the heavy chain according to the method of Kabat is not arginine, the residue is valine.

[0009] In some examples of the monoclonal antibody or antigen-binding fragment that specifically binds human Tau, the antibody comprises: a heavy chain variable domain (HCVD) comprising SEQ ID NO: 268 and a light chain variable domain (LCVD) comprising SEQ ID NO: 465; a HCVD comprising SEQ ID NO: 268 and a LCVD comprising SEQ ID NO: 581; a HCVD comprising SEQ ID NO: 384 and a LCVD comprising SEQ ID NO: 545 ; a HCVD comprising SEQ ID NO: 393 and a LCVD comprising SEQ ID NO: 545; a HCVD comprising SEQ ID NO: 402 and a LCVD comprising SEQ ID NO: 545; a HCVD comprising SEQ ID NO: 384 and a LCVD comprising SEQ ID NO: 572; a HCVD comprising SEQ ID NO: 393 and a LCVD comprising SEQ ID NO: 572; or a HCVD comprising SEQ ID NO: 402 and a LCVD comprising SEQ ID NO: 572.

[0010] In one aspect, the present disclosure refers to a monoclonal antibody, or an antigen-binding fragment thereof, that specifically binds a human Tau, wherein the antibody is produced by the cell line having ATCC deposit number PTA-124524. In some examples of the monoclonal antibody or antigen-binding fragment that specifically binds human Tau, the antibody is produced by the cell line having ATCC deposit number PTA-124523 or ATCC deposit number PTA-124524.

[0011] In some examples, the antibodies or antigen-binding fragments described herein bind monomeric wild-type human 2N4R Tau with a K_D of less than about 0.5 nM as measured by surface plasmon resonance. In some examples, the antibodies or antigen-binding fragments bind human Tau at an epitope comprising the amino acid sequence HVPG (SEQ ID NO: 1133). Also described are biepitopic antibodies or antigen-binding fragments that bind human Tau at an epitope comprising the amino acid sequence HVPG (SEQ ID NO: 1133) within repeat region 2 or repeat region 4. In certain examples, the antibodies or antigen-binding fragments bind human

Tau at an epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79). Also described are biepitopic antibodies or antigen-binding fragments that bind human Tau at an epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79) within repeat region 2 or repeat region 4. In some examples, the monoclonal antibody or antigen-binding fragment binds human Tau at the epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79) within repeat region 2 and/or repeat region 4 with a binding preference that is at least about 10-fold greater than binding at an epitope comprising the amino acid sequence HKPGG (SEQ ID NO: 182) within repeat region 3 or at an epitope comprising the amino acid sequence HQPGG (SEQ ID NO: 183) within repeat region 1, as determined by a peptide binding assay. In some examples, the antibodies or antigen-binding fragments described herein do not bind Tau at an epitope comprising the amino acid sequence HVSGG (SEQ ID NO: 184) within repeat region 2 or at an epitope comprising the amino acid sequence HVLGG (SEQ ID NO: 185) within repeat region 2.

[0012] In some examples, the monoclonal antibodies or antigen-binding fragments as described herein are labeled.

[0013] Further described are nucleic acid molecules encoding any of the described monoclonal antibodies or antigen-binding fragments, vectors comprising the nucleic acid molecules, cells that express the nucleic acid molecules, and methods of producing the anti-Tau antibodies or antigen-binding fragments by culturing such cells under conditions suitable for production thereof. The methods of producing may further involve recovery of the antibody or antigen-binding fragment.

[0014] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment as disclosed herein and a pharmaceutically acceptable carrier. Also disclosed herein are pharmaceutical compositions of any of the described monoclonal antibodies, or antigen-binding fragments thereof, that specifically bind a human Tau and a pharmaceutically acceptable carrier.

[0015] Methods of use of the described monoclonal antibodies, or antigen-binding fragments thereof, that specifically bind a human Tau also are described provided herein. In some embodiments examples, the antibodies or antigen-binding fragments that specifically bind a human Tau are for use as a medicament. In some aspectsexamples, the antibodies or antigen-binding fragments that specifically bind a human Tau are for use in the treatment of a Tauopathy or in the preparation of a medicament for the treatment of a Tauopathy. Methods of treating a Tauopathy in a subject also are provided. In some embodimentsexamples, the methods of treating a Tauopathy involve administering to the subject any of the described monoclonal antibodies, or antigen-binding fragments thereof, that specifically bind a human Tau under conditions effective to treat the Tauopathy in the subject. In some aspectsexamples, the Tauopathy is Alzheimer's disease, frontotemporal dementia, or progressive supranuclear palsy. The frontotemporal dementia may be Pick’s Disease, for example.

[0016] Further provided are methods for decreasing sarkosyl-insoluble Tau levels in a subject by administering to the subject any of the described monoclonal antibodies, or antigen-binding fragments thereof, that specifically bind a human Tau. Also provided are methods for inhibiting Tau aggregation in a subject by administering to the subject any of the described

What is Claimed:

1. A monoclonal antibody comprising a heavy chain and a light chain, or an antigen-binding fragment thereof, that specifically binds a human Tau, wherein:

   the heavy chain comprises a heavy chain complementarity determining region 1 (HCDR1) comprising SEQ ID NO: 732, a heavy chain complementarity determining region 2 (HCDR2) comprising SEQ ID NO: 734, and a heavy chain complementarity determining region 3 (HCDR3) comprising SEQ ID NO: 736, and the light chain comprises a light chain complementarity determining region 1 (LCDR1) comprising SEQ ID NO: 846, a light chain complementarity determining region 2 (LCDR2) comprising SEQ ID NO: 848, and a light chain complementarity determining region 3 (LCDR3) comprising SEQ ID NO: 850 as defined according to the method of Kabat; or

   the heavy chain comprises a HCDR1 comprising SEQ ID NO: 1002, a HCDR2 comprising SEQ ID NO: 1004, and a HCDR3 comprising SEQ ID NO: 1006 and the light chain comprises a LCDR1 comprising SEQ ID NO: 1116, a LCDR2 comprising SEQ ID NO: 1118, and a LCDR3 comprising SEQ ID NO: 1120 as defined by IMGT.

2. The monoclonal antibody or antigen-binding fragment according to claim 1, wherein the residue at position 49 of the light chain according to the method of Kabat is not cysteine.

3. The monoclonal antibody or antigen-binding fragment according to claim 2, wherein the residue at position 49 of the light chain according to the method of Kabat is serine.

4. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 57 of the heavy chain according to the method of Kabat is not cysteine.

5. The monoclonal antibody or antigen-binding fragment according to claim 4, wherein the residue at position 57 of the heavy chain according to the method of Kabat is serine.

6. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 34 of the light chain according to the method of Kabat is glutamate.

7. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 36 of the light chain according to the method of Kabat is not phenylalanine.

8. The monoclonal antibody or antigen-binding fragment according to claim 7 wherein the residue at position 36 of the light chain according to the method of Kabat is tyrosine.

9. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 46 of the light chain according to the method of Kabat is not arginine.

10. The monoclonal antibody or antigen-binding fragment according to claim 9 wherein the residue at position 46 of the light chain according to the method of Kabat is leucine.

11. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 94 of the heavy chain according to the method of Kabat is not lysine.

12. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the residue at position 71 of the heavy chain according to the method of Kabat is not arginine.

13. The monoclonal antibody or antigen-binding fragment according to claim 12 wherein position 71 of the heavy chain according to the Kabat method is valine.

14. The monoclonal antibody or antigen-binding fragment according to claim 1, the antibody comprising:

    a heavy chain variable domain (HCVD) comprising SEQ ID NO: 402 and a light chain variable domain (LCVD) comprising SEQ ID NO: 572.

15. The monoclonal antibody or antigen-binding fragment according to claim 1, wherein the antibody is a humanized antibody.

16. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the antibody is IgG1.

17. The monoclonal antibody or antigen-binding fragment according to claim 1 wherein the antibody binds monomeric wild-type human 2N4R Tau with a K_D of less than about 0.5 nM as measured by surface plasmon resonance.

18. The monoclonal antibody or antigen-binding fragment according to claim 1, wherein the antibody or antigen-binding fragment binds to human Tau at an epitope comprising the amino acid sequence HVPG (SEQ ID NO: 1133).

19. The monoclonal antibody or antigen-binding fragment according to claim 18, wherein the antibody or antigen-binding fragment is biepitopic and binds to human Tau at an epitope comprising the amino acid sequence HVPG (SEQ ID NO: 1133) within repeat region 2 or repeat region 4.

20. The monoclonal antibody or antigen-binding fragment according to claim 1, wherein the antibody or antigen-binding fragment binds to human Tau at an epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79).

21. The monoclonal antibody or antigen-binding fragment according to claim 20, wherein the antibody or antigen-binding fragment is biepitopic and binds to human Tau at an epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79) within repeat region 2 or repeat region 4.

22. The monoclonal antibody or antigen-binding fragment according to claim 1, wherein the antibody or antigen-binding fragment binds human Tau at the epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79) within repeat region 2 with a binding preference that is at least about 10-fold greater than binding at an epitope

comprising the amino acid sequence HKPGG (SEQ ID NO: 182) within repeat region 3 or than binding at an epitope comprising the amino acid sequence HQPGG (SEQ ID NO: 183) within repeat region 1, or

wherein the antibody or antigen-binding fragment binds human Tau at the epitope comprising the amino acid sequence HVPGG (SEQ ID NO: 79) within repeat region 4 with a binding preference that is at least about 10-fold greater than binding at an epitope comprising the amino acid sequence HKPGG (SEQ ID NO: 182) within repeat region 3 or than binding at an epitope comprising the amino acid sequence HQPGG (SEQ ID NO: 183) within repeat region 1,

as determined by a peptide binding assay.

23. A monoclonal antibody, or an antigen-binding fragment thereof, that specifically binds a human Tau, wherein the antibody is produced by the cell line having ATCC deposit number PTA-124524.

24. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 1 and a pharmaceutically acceptable carrier.