

ANTI-TAU ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 62/171,693, filed June 5, 2015, which is incorporated by reference herein in its entirety for any purpose.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-Tau antibodies and methods of using the same.

BACKGROUND

[0003] Neurofibrillary tangles and neuropil threads (NTs) are the major neuropathological hallmarks of Alzheimer's Disease (AD). NTs are composed of the microtubule-associated Tau protein that has undergone post-translational modifications including phosphorylation, and develop by aggregation of hyperphosphorylated Tau conformers. AD shares this pathology with many neurodegenerative tauopathies, in particular with certain types of frontotemporal dementia (FTD). Tau protein appears to be a major player in the cognitive demise in AD and related neurodegenerative tauopathies.

[0004] Therapeutic approaches that target Tau protein are scarce and comprise mainly inhibitors of the kinases that are thought to increase the phosphorylation of Tau to pathological levels, and compounds that block the cytoplasmic aggregation of hyper-phosphorylated Tau protein. These approaches suffer various draw-backs of specificity and efficacy. There is a need for additional therapeutic agents that target the pathological protein conformers that are known or presumed to cause neurodegenerative disorders.

SUMMARY

[0005] The disclosure provides anti-Tau antibodies and methods of using the same.

[0006] Disclosed is an isolated antibody that binds to human Tau is provided, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some embodiments, the antibody binds an epitope within amino acids 2 to 24 of mature human Tau. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric

L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307;

- c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47;
- d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67;
- e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217;
- f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37; or
- g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[0009a] In one aspect, there is provided an isolated monoclonal antibody that binds to human Tau, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau, wherein the antibody comprises: HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 342, 12, 22, 282, and 292; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 343, 13, 23, 283, and 293; HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 344, 14, 24, 284, and 294; HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 345, 15, 25, 285, 295, and 468 to 556; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 346, 16, 26, 286, and 296; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 347, 17, 27, 287, and 297.

[0010] In some embodiments, the antibody comprises:

degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some embodiments, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0031] In one aspect, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease. In one aspect, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

[0032] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for treating a Tau protein associated disease in an individual. In some embodiments, the Tau protein associated disease is a tauopathy. In some embodiments, the tauopathy is a neurodegenerative tauopathy. In some embodiments, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some embodiments, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0033] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

[0033a] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

[0034] In one aspect, a method of detecting neurofibrillary tangles, neuropil threads, or dystrophic neuritis is provided, comprising contacting a sample with an antibody

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that binds to human Tau, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau, wherein the antibody comprises:

HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 342, 12, 22, 282, and 292; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 343, 13, 23, 283, and 293; HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 344, 14, 24, 284, and 294; HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 345, 15, 25, 285, 295, and 468 to 556; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 346, 16, 26, 286, and 296; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 347, 17, 27, 287, and 297.

2. The antibody of claim 1, wherein the antibody comprises:

- a) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 340, 10, 20, 280, 290, 560, 570, and 580; or
- b) a light chain variable region (VL) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 341, 11, 21, 281, 291, 561, 571, and 581; or
- c) a VH as in (a) and a VL as in (b).

3. The antibody of claim 1, wherein the antibody comprises:

- a) a heavy chain variable region (VH) comprising a sequence selected from SEQ ID NOs: 340, 10, 20, 280, 290, 560, 570, and 580; or
- b) a light chain variable region (VL) comprising a sequence selected from SEQ ID NOs: 341, 11, 21, 281, 291, 561, 571, and 581; or
- c) a VH as in (a) and a VL as in (b).

4. The isolated antibody of any one of the preceding claims, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; HVR-H3 comprising the amino acid

sequence of SEQ ID NO: 344; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345;

HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

5. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 340 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 341.

6. The isolated antibody of any one of the preceding claims, wherein the antibody comprises:

a) a heavy chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 349; or

b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349.

7. An isolated antibody that binds to human Tau, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349.

8. An isolated antibody that binds to human Tau, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain consisting of the amino acid sequence of SEQ ID NO: 349.

9. The isolated antibody of any one of the preceding claims, wherein the antibody is a humanized antibody.

10. The isolated antibody of any one of the preceding claims, wherein the antibody is an IgG1 or an IgG4 antibody.

11. The isolated antibody of claim 10, wherein the antibody is an IgG4 antibody.

12. The isolated antibody of claim 11, wherein the antibody comprises M252Y, S254T, and T256E mutations.

13. The isolated antibody of claim 11 or claim 12, wherein the antibody comprises an S228P mutation.

14. The isolated antibody of any one of claims 1 to 9, which is an antibody fragment.

15. The isolated antibody of any one of the preceding claims, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, or less than 50 nM.

16. The isolated antibody of any one of the preceding claims, wherein the human Tau comprises the sequence of SEQ ID NO: 2.

17. The isolated antibody of any one of the preceding claims, which binds cynomolgus monkey Tau (SEQ ID NO: 4).

18. An isolated nucleic acid that encodes the antibody of any one of the preceding claims.

19. A host cell comprising the nucleic acid of claim 18.

20. A method of producing an antibody comprising culturing the host cell of claim 19 under conditions suitable for producing the antibody.

21. An immunoconjugate comprising the isolated antibody of any one of claims 1 to 17 and a second therapeutic agent.

22. A labeled antibody comprising the antibody of any one of claims 1 to 17 and a detectable label.

23. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

24. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for treating a Tau protein associated disease in an individual.

25. The use of claim 24, wherein the Tau protein associated disease is a tauopathy.

26. The use of claim 25, wherein the tauopathy is a neurodegenerative tauopathy.

27. The use of claim 25 or claim 26, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor

neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

28. The use of any one of claims 25 to 27, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

29. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

30. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

31. The use of any one of claims 24 to 30, wherein the medicament is to be administered with at least one additional therapy.

32. The use of claim 31, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, Tau inhibitors, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

33. The isolated antibody of any one of claims 1 to 17 for use as a medicament.

34. The isolated antibody of any one of claims 1 to 17 for use in treating a tauopathy in an individual.

35. The isolated antibody of claim 34, wherein the tauopathy is a neurodegenerative tauopathy.

36. The isolated antibody of claim 34 or claim 35, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down Syndrome, Gerstmann-Sträussler-Scheinker disease,

inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallervorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

37. The isolated antibody of any one of claims 34 to 36, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

38. An isolated antibody of any one of claims 1 to 17 for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

39. An isolated antibody of any one of claims 1 to 17 for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

40. The isolated antibody of any one of claims 34 to 39, wherein the antibody is for use with at least one additional therapy.

41. The isolated antibody of claim 40, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, anti-amyloid beta antibodies, anti-BACE1 antibodies, and BACE1 inhibitors.

42. A method of detecting neurofibrillary tangles, neurophil threads, or dystrophic neuritis comprising contacting a sample with the antibody of any one of claims 1 to 17.

43. The method of claim 42, wherein the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.