

CLAIMS

1. A method for measuring tau in a biological sample, the method comprising
 - (a) providing a biological sample selected from a blood sample or a CSF sample, wherein the biological sample (i) optionally comprises an isotope labeled internal standard of tau, and (ii) optionally is depleted of amyloid beta, N-terminal tau, mid-domain tau, or any combination thereof;
 - (b) removing proteins from the biological sample by protein precipitation and separation of the precipitated proteins to obtain a supernatant;
 - (c) purifying tau from the supernatant by solid phase extraction;
 - (d) cleaving the purified tau with a protease and then optionally desalting the resultant cleavage product by solid phase extraction to obtain a sample comprising proteolytic peptides of tau; and
 - (e) performing liquid chromatography - mass spectrometry with the sample comprising proteolytic peptides of tau to detect and measure the amount of at least one proteolytic peptide of tau.
2. The method of claim 1, wherein the biological sample is depleted of amyloid beta, N-terminal tau, mid-domain tau, or any combination thereof.
- ~~3. The method of claim 2, wherein (i) the biological sample is depleted of amyloid beta, N-terminal tau, and mid-domain tau, (ii) the biological sample is depleted of N-terminal tau and mid-domain tau, or (iii) the biological sample is depleted of mid-domain tau.~~
34. The method of claim 1, wherein the solid phase in step (c) comprises a reversed-phase sorbent that adsorbs tau.
45. The method of any one of the preceding claims, wherein:

step (b) comprises admixing an acid to precipitate proteins of the biological sample, optionally wherein the acid is perchloric acid; and/or

in step (e), the liquid chromatography - mass spectrometry is performed by a nano-LC/MS system.

56. A method for measuring tau in a biological sample, the method comprising

(a) decreasing in a biological sample by affinity depletion N-terminal tau, mid-domain tau, or N-terminal tau and mid-domain tau, and optionally decreasing by affinity depletion amyloid beta, wherein the biological sample is a blood sample or a CSF sample and the biological sample optionally comprises an isotope-labeled, tau internal standard;

(b) enriching MTBR tau by a method that comprises (i) removing additional proteins from the biological sample by protein precipitation and separation of the precipitated proteins to obtain a supernatant, and then purifying tau from the supernatant by solid phase extraction, or (ii) affinity purifying MTBR tau, thereby producing by either (i) or (ii) enriched MTBR tau;

(c) cleaving the enriched MTBR tau with a protease and then optionally desalting the resultant cleavage product by solid phase extraction to obtain a sample comprising proteolytic peptides of tau; and

(d) performing liquid chromatography-mass spectrometry (LC/MS) of the sample comprising proteolytic peptides of tau to detect and measure the amount of at least one proteolytic peptide of tau.

~~7. The method of claim 6, wherein step (a) comprises decreasing (i) N terminal tau, mid-domain tau, or N-terminal tau and mid-domain tau, and (ii) amyloid beta.~~

68. The method of claim 56, wherein the biological sample comprises human tau and wherein step (a) further comprises

contacting the biological sample with at least one epitope-binding agent that specifically binds to an epitope within amino acids 1 to 243 of tau-441, inclusive; or

contacting the biological sample with a first epitope-binding agent that specifically binds to an epitope within amino acids 1 to 103 of tau-441, inclusive, and a second epitope-binding agent that specifically binds to an epitope within amino acids 104 to 243 of tau-441, inclusive; or

contacting the biological sample with a first epitope-binding agent that specifically binds to an epitope within amino acids 1 to 103 of tau-441, inclusive, a second epitope-binding agent that specifically binds to an epitope within amino acids 104 to 243 of tau-441, inclusive; and a third epitope binding agent that specifically binds to an epitope of amyloid beta; or

contacting the biological sample with a first epitope-binding agent that specifically binds to an epitope within amino acids 1 to 103 of tau-441, inclusive, a second epitope-binding agent that specifically binds to an epitope of amyloid beta; or

contacting the biological sample with a first epitope-binding agent that specifically binds to an epitope within amino acids 104 to 243 of tau-441, inclusive; and a third epitope binding agent that specifically binds to an epitope of amyloid beta.

79. The method of claim 68, wherein the epitope-binding agent that specifically binds to amyloid beta is HJ5.1, the epitope-binding agent that specifically binds to an epitope within amino acids 1 to 103 of tau-441, inclusive, is HJ8.5, and the epitope-binding agent that specifically binds to an epitope within amino acids 104 to 243 of tau-441, inclusive, is Tau1.

~~10. The method of claim 8, wherein the epitope-binding agent that specifically binds to an epitope within amino acids 1 to 103 of tau-441, inclusive, is HJ8.5.~~

~~11. The method of claim 8, wherein the epitope-binding agent that specifically binds to an epitope within amino acids 104 to 243 of tau-441, inclusive, is Tau1.~~

~~12. The method of any one of claims 6 to 11, wherein solid phase extraction comprises a reversed-phase sorbent that adsorbs tau.~~

~~13. The method of any one of claims 6 to 11, wherein~~

~~the method for enriching MTBR tau comprises step (b)(i) and wherein the protein precipitation comprises admixing an acid to precipitate proteins of the biological sample, optionally wherein the acid is perchloric acid; and/or~~

~~in step (e), the liquid chromatography-mass spectrometry is performed by a nano-LC/MS system.~~

~~14. The method of claim 13, wherein the solid phase extraction performed in steps (b) and (c) comprises a reversed-phase sorbent that adsorbs tau.~~

~~15. The method of any one of claims 8 to 11, wherein~~

~~the method for enriching MTBR tau comprises step (b)(ii) and wherein affinity purifying MTBR tau comprises contacting the product of step (a) with an epitope-binding agent that specifically binds to an epitope that is C-terminal to the epitope of step (a); and/or~~

~~in step (e), the liquid chromatography-mass spectrometry is performed by a nano-LC/MS system.~~

846. The method of claim 45, wherein the epitope binding agent of step (b) specifically binds to an epitope

within amino acids 221 to 441 (inclusive) of tau-441, or

within amino acids 235 to 441 (inclusive) of tau-441, or

within amino acids 235 to 368 (inclusive) of tau-441, or

within amino acids 244 to 368 (inclusive) of tau-441, or

within amino acids 244 to 299 (inclusive) of tau-441.

947. The method of claim 846, wherein the epitope-binding agent is an antibody selected from the group consisting of 77G7, RD3, RD4, UCB0107, PT76, E2814 and 7G6.

~~18. The method of claim 15, 16 or 17, wherein the solid phase extraction performed in step (c) comprises a reversed-phase sorbent that adsorbs tau.~~

~~19. The method of any one of claims 1 to 5, wherein the protease is trypsin.~~

~~20. The method of claim 19, wherein step (d) comprises detecting and measuring the amount of at least one proteolytic peptide of tau, wherein the proteolytic peptide of tau has an amino acid sequence chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 9.~~

~~21. The method of claim 19, wherein step (d) comprises detecting and measuring the concentration of at least two proteolytic peptides of tau, wherein the two proteolytic peptides of tau have amino acid sequences chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.~~

~~22. The method of claim 21, wherein the at least two proteolytic peptides of tau have the amino acid sequence of SEQ ID NO: 6 and SEQ ID NO: 7, SEQ ID NO: 6 and SEQ ID NO: 8, SEQ ID NO: 3 and SEQ ID NO: 6, SEQ ID NO: 3 and SEQ ID NO: 7, SEQ ID NO: 3 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 7, SEQ ID NO: 2 and SEQ ID NO: 8, SEQ ID NO: 4 and SEQ ID NO: 7, SEQ ID NO: 4 and SEQ ID NO: 8, SEQ ID NO: 5 and SEQ ID NO: 7, SEQ ID NO: 5 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 6, SEQ ID NO: 4 and SEQ ID NO: 6, SEQ ID NO: 5 and SEQ ID NO: 6, or SEQ ID NO: 9 and SEQ ID NO: 5.~~

~~23. The method of any one of claims 6 to 11, wherein the protease is trypsin.~~

~~24. The method of claim 23, wherein step (d) comprises detecting and measuring the concentration at least one proteolytic peptide of MTBR tau, wherein the proteolytic peptide of tau has an amino acid sequence chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.~~

~~25. The method of claim 23, wherein step (d) comprises detecting and measuring the concentration of at least two proteolytic peptides of MTBR tau, wherein the two proteolytic peptides of tau have amino acid sequences chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.~~

~~26. The method of claim 25, wherein the at least two proteolytic peptides of MTBR tau have the amino acid sequence of SEQ ID NO: 6 and SEQ ID NO: 7, SEQ ID NO: 6 and SEQ ID NO: 8, SEQ ID NO: 3 and SEQ ID NO: 6, SEQ ID NO: 3 and SEQ ID NO: 7, SEQ ID NO: 3 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 7, SEQ ID NO: 2 and SEQ ID NO: 8, SEQ ID NO: 4 and SEQ ID NO: 7, SEQ ID NO: 4 and SEQ ID NO: 8, SEQ ID NO: 5 and SEQ ID NO: 7, SEQ ID NO: 5 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 6, SEQ ID NO: 4 and SEQ ID NO: 6, SEQ ID NO: 5 and SEQ ID NO: 6, and SEQ ID NO: 9 and SEQ ID NO: 5.~~

~~27. The method of claim 12, wherein the protease is trypsin.~~

~~28. The method of claim 13, wherein the protease is trypsin.~~

~~29. The method of claim 15, wherein the protease is trypsin.~~

~~1030. The method of any one of claims 27, 28, or 29, wherein step (d) comprises detecting and measuring the concentration at least one proteolytic peptide of MTBR tau, wherein the proteolytic peptide of tau has an amino acid sequence chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.~~

~~31. The method of any one of claims 27, 28, or 29, wherein step (d) comprises detecting and measuring the concentration of at least two proteolytic peptides of MTBR tau, wherein the proteolytic peptides of tau have amino acid sequences chosen from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.~~

~~32. The method of claim 31, wherein the at least two proteolytic peptides of MTBR tau have the amino acid sequence of SEQ ID NO: 6 and SEQ ID NO: 7, SEQ ID NO: 6 and SEQ ID NO: 8, SEQ ID NO: 3 and SEQ ID NO: 7, SEQ ID NO: 3 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 7, SEQ ID NO: 2 and SEQ ID NO: 8, SEQ ID NO: 4 and SEQ ID NO: 7, SEQ ID NO: 4 and SEQ ID NO: 8, SEQ ID NO: 5 and SEQ ID NO: 7, SEQ ID NO: 5 and SEQ ID NO: 8, SEQ ID NO: 2 and SEQ ID NO: 6, SEQ ID NO: 4 and SEQ ID NO: 6, SEQ ID NO: 5 and SEQ ID NO: 6, and SEQ ID NO: 9 and SEQ ID NO: 5.~~

~~33. The method of any one claims 6 to 32, wherein the method further comprises detecting and measuring the concentration of N-terminal tau, mid-domain tau, or amyloid beta removed from the biological sample in step (a).~~

~~34. A method for measuring Alzheimer disease (AD)-related pathology in a subject, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof, wherein the amount of the quantified MTBR tau species or their ratios is a representation of AD-related pathology in a brain of a subject.~~

1135. A method for measuring Alzheimer disease (AD)-related pathology in a subject, the method comprising measuring tau in a CSF or blood sample according to a method of any one of claims 16 to 948,

wherein the tau measured are MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof, wherein the

amount of the measured MTRB-tau species or their ratios is a representation of AD-related pathology in a brain of a subject.

~~36. The method of claim 34 or 35, wherein the AD-related pathology is tau deposition in the subject's brain.~~

~~37. The method of claim 34 or 35, wherein the AD-related pathology is amyloid beta deposition in the subject's brain or brain arteries.~~

~~38. A method for measuring Alzheimer disease (AD) related tau deposition in a brain of a subject, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the processed CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino sequence of SEQ ID NO: 3 (LQTAPVPMPDLK) in the processed CSF or blood sample, wherein the amount of the quantified MTRB-tau species is a representation of AD-related tau deposition in a brain of a subject.~~

~~39. A method for measuring Alzheimer disease (AD) related tau deposition in a brain of a subject, the method comprising measuring tau in a CSF or blood sample according to a method of any one of claims 6 to 18,~~

~~wherein the tau measured are MTBR tau species comprising the amino sequence of SEQ ID NO: 3 (LQTAPVPMPDLK), and wherein the amount of the measured MTRB-tau species is a representation of AD-related pathology in a brain of a subject.~~

~~40. A method for measuring Alzheimer disease (AD) related tau deposition in a brain of a subject, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8), or a combination thereof, wherein the amount of the quantified MTRB tau species or their ratios is a representation of AD-related tau deposition in a brain of a subject.~~

~~41. A method for measuring Alzheimer disease (AD)-related tau deposition in a brain of a subject, the method comprising measuring tau in a CSF or blood sample according to a method of any one of claims 6 to 18,~~

~~wherein the tau measured are MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence OF SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof, and wherein the amount of the measured MTRB tau species or their ratios is a representation of AD-related pathology in a brain of a subject.~~

~~42. A method for diagnosing Alzheimer's disease, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof; and~~

~~diagnosing Alzheimer's disease when the quantified MTBR tau species differs by about 1.5σ or more, where σ is the standard deviation defined by the normal distribution measured in a control population that is amyloid negative as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

1243. A method for diagnosing Alzheimer's disease, the method comprising

measuring tau in a CSF or blood sample according to a method of any one of claims 16 to 948, wherein the tau measured are MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof; and

diagnosing Alzheimer's disease when the quantified MTBR tau species differs by about 1.5σ or more, where σ is the standard deviation defined by the normal distribution measured in a control population that is amyloid negative as measured by PET imaging and/or A β 42/40 measurement in CSF.

~~44. A method for measuring Alzheimer disease (AD) progression in a subject, the method comprising~~

~~providing a first processed CSF or blood sample and a second processed CSF or blood sample, wherein each processed sample is obtained from a single subject, and each processed sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~for each processed sample, quantifying MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof; and~~

~~calculating the difference between the quantified MTBR tau species in the second sample and the first sample, wherein a statistically significant increase in the quantified MTBR tau species in the second sample indicates progression of the subject's Alzheimer's disease.~~

1345. A method for measuring Alzheimer disease (AD) progression in a subject, the method comprising

measuring tau in a first and a second CSF or blood sample according to a method of any one of claims ~~6-1 to 189~~, wherein the tau measured are MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or a combination thereof; and

calculating the difference between the quantified MTBR tau species in the second sample and the first sample, wherein a statistically significant increase in the quantified MTBR tau species in the second sample indicates progression of the subject's Alzheimer's disease.

1446. The method of ~~any one of claims 38-11 or claim 13~~ to 45~~13~~, wherein the subject is amyloid negative.

1547. The method of claim ~~46~~14, wherein the subject has no dementia.

1648. The method of claim ~~46~~14, wherein the subject has dementia.

1749. The method of ~~any one of claims 38-11 or claim 13~~ to 45~~to 45~~, wherein the subject is amyloid positive.

1850. The method of claim ~~49~~17, wherein the subject has no dementia.

1951. The method of claim ~~49~~17, wherein the subject has dementia.

~~52. The method of claim 46 or claim 49, wherein the subject has a CDR score of 0.5 to 1.0.~~

~~53. The method of claim 46 or claim 49, wherein the subject has a CDR score of > 1.0 to 2.0 (moderate AD).~~

~~54. The method of claim 46 or claim 49, wherein the subject has a CDR score of > 2.0.~~

2055. The method of any one of claims ~~1138~~ to 1954, the method further comprising quantifying amyloid beta, quantifying N-terminal tau, quantifying mid-domain tau,

quantifying post-translational modifications of tau, or identifying an ApoE isoform in the biological or CSF sample.

2156. The method of claim 20, wherein quantifying amyloid beta includes quantifying an Ab40/42 value, and quantifying post-translational modifications of tau include quantifying one or more of phospho-tau217, phospho-tau205, phospho-tau181, phospho-tau153, phospho-tau111, and phospho-tau208—A method for measuring tau pathology in a brain of a subject, the method comprising

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, MTBR tau species comprising the amino sequence of SEQ ID NO: 9, or combinations thereof, wherein the amount of the quantified MTBR tau species or their ratios is a representation of tau pathology in a brain of a subject.~~

2257. A method for measuring tau pathology in a brain of a subject, the method comprising measuring tau in a CSF or blood sample according to a method of any one of claims 16 to 948, wherein the tau measured are MTBR tau species comprising the amino acid sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, MTBR tau species comprising the amino sequence of SEQ ID NO: 9, or combinations thereof, wherein the amount of the quantified MTBR-tau species or their ratios is a representation of tau pathology in a brain of a subject.

~~58. A method for discriminating a 4R-tauopathy, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is depleted of mid-domain tau and enriched for MTBR tau; and~~

~~quantifying, in the processed sample, (a) MTBR tau species comprising the amino sequence of SEQ ID NO: 9, and (b) MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, or MTBR tau species comprising the amino sequence of SEQ ID NO: 8;~~

~~wherein the ratio of a quantified MTBR species from (a) to a quantified MTBR species from (b) discriminates a 4R-tauopathy.~~

~~59. A method for discriminating a 4R-tauopathy, the method comprising measuring tau in a biological sample according to a method of any one of claims 6 to 17, wherein the tau measured are (a) MTBR tau species comprising the amino sequence of SEQ ID NO: 9, and (b) MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, or MTBR tau species comprising the amino sequence of SEQ ID NO: 8;~~

~~wherein the ratio of a quantified MTBR species from (a) to a quantified MTBR species from (b) discriminates a 4R-tauopathy.~~

~~60. A method for discriminating a 3R-tauopathy or a 4R-tauopathy from Alzheimer's disease, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is (a) depleted of mid-domain tau, and (b) enriched for MTBR tau; and~~

~~quantifying, in the processed sample, (a) MTBR tau species comprising the amino sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, or combinations thereof, and (b) MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or combinations thereof,~~

~~wherein the ratio of a quantified MTBR species from (a) to a quantified MTBR species from (b) discriminates a 3R-tauopathy or a 4R-tauopathy from Alzheimer's disease.~~

~~61. A method for discriminating a 3R-tauopathy or a 4R-tauopathy from Alzheimer's disease, the method comprising measuring tau in a biological sample according to a method of any one of claims 6 to 18, wherein the tau measured are (a) MTBR tau species comprising the amino sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, or combinations thereof, and (b) MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6, MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or combinations thereof,~~

~~wherein the ratio of a quantified MTBR species from (a) to a quantified MTBR species from (b) discriminates a 3R-tauopathy or a 4R-tauopathy from Alzheimer's disease.~~

~~62. A method for diagnosing a 4R-tauopathy, the method comprising~~

~~measuring tau in a CSF or blood sample according to a method of any one of claims 6 to 18, wherein the tau measured are (a) MTBR tau species comprising the amino sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, or combinations thereof, and (b) MTBR tau species comprising the amino acid sequence of~~

~~SEQ ID NO: 6), MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence of SEQ ID NO: 8, or combinations thereof; and~~

~~diagnosing a 4R-tauopathy when the quantified MTBR tau species differs by about 1.5σ or more, where σ is the standard deviation defined by the normal distribution measured in a control population that does not have clinical signs or symptoms of a tauopathy and is amyloid negative as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

~~63. The method of any one of the claims 56 to 62, wherein the subject has no dementia.~~

~~64. The method of claim 63, wherein the 4R-tauopathy is corticobasal degeneration, Frontotemporal lobar degeneration, frontotemporal dementia, or progressive supranuclear palsy.~~

~~65. The method of any one of the claims 56 to 62, wherein the subject has dementia.~~

~~66. The method of claim 65, wherein the 4R-tauopathy is corticobasal degeneration, Frontotemporal lobar degeneration, frontotemporal dementia, or progressive supranuclear palsy.~~

~~67. A method for treating a subject in need thereof, the method comprising~~

~~providing a processed CSF or blood sample obtained from a subject, wherein the CSF or blood sample is (a) depleted of mid-domain tau, and (b) enriched for MTBR tau;~~

~~quantifying, in the processed sample, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 2, MTBR tau species comprising the amino sequence of SEQ ID NO: 3, MTBR tau species comprising the amino sequence of SEQ ID NO: 4, MTBR tau species comprising the amino sequence of SEQ ID NO: 5, MTBR tau species comprising the amino acid sequence of SEQ ID NO: 6), MTBR tau species comprising the amino sequence of SEQ ID NO: 7, MTBR tau species comprising the amino sequence~~

of SEQ ID NO: 8, MTBR tau species comprising the amino sequence of SEQ ID NO: 9, or combinations thereof; and

administering a treatment to the subject to alter tau pathology, wherein the subject's processed CSF or blood sample has quantified MTBR tau species, or ratios of the quantified MTBR tau species, that differ by about 1.5σ or more, where σ is the standard deviation defined by the normal distribution measured in a control population that does not have clinical signs or symptoms of a tauopathy and is amyloid negative as measured by PET imaging and/or A β 42/40 measurement in CSF, and wherein the amount of the quantified MTRB tau species or their ratios is a representation of tau pathology in a brain of a subject.

68. The method of claim 67, wherein the treatment alters or stabilizes the amount of the quantified MTBR species.

69. The method of claim 67 or 68, wherein the treatment is selected from the group consisting of cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists, antidepressants, gamma-secretase inhibitors, beta-secretase inhibitors, anti-A β antibodies, anti-tau antibodies, anti-TREM2 antibodies, TREM2 agonists, stem cells, dietary supplements, antagonists of the serotonin receptor 6, p38alpha MAPK inhibitors, recombinant granulocyte macrophage colony-stimulating factor, passive immunotherapies, active vaccines, tau protein aggregation inhibitors, therapies to improve blood sugar control, anti-inflammatory agents, phosphodiesterase 9A inhibitors, sigma-1 receptor agonists, kinase inhibitors, phosphatase activators, phosphatase inhibitors, angiotensin receptor blockers, CB1 and/or CB2 endocannabinoid receptor partial agonists, β -2 adrenergic receptor agonists, nicotinic acetylcholine receptor agonists, 5-HT_{2A} inverse agonists, alpha-2c adrenergic receptor antagonists, 5-HT_{1A} and 1D receptor agonists, Glutamyl-peptide cyclotransferase inhibitors, selective inhibitors of APP production, monoamine oxidase B inhibitors, glutamate receptor antagonists, AMPA receptor agonists, nerve growth factor stimulants, HMG-CoA reductase inhibitors, neurotrophic agents, muscarinic M1 receptor agonists, GABA

receptor modulators, PPAR-gamma agonists, microtubule protein modulators, calcium channel blockers, antihypertensive agents, and statins.

70. The method of claim 69, wherein the treatment is selected from the group consisting of anti-A β antibodies, anti-tau antibodies, anti-TREM2 antibodies, TREM2 agonists, gamma-secretase inhibitors, beta-secretase inhibitors, a kinase inhibitor, a phosphatase activator, a vaccine, and a tau protein aggregation inhibitor.

71. The method of claim 70, wherein the kinase inhibitor is an inhibitor of a thousand-and-one amino acid kinase (TAOK), CDK, GSK-3 β , MARK, CDK5, or Fyn.

72. The method of claim 70, wherein the phosphatase activator increases the activity of protein phosphatase 2A.

73. The method of claim 70, wherein the vaccine is CAD106 or AF20513.

74. The method of claim 70, wherein the tau protein aggregation inhibitor is TRx0237 or methylthioninium chloride.

75. The method of claim 70, wherein the anti-A β antibody is aducanumab.