CLAIMS

~~We claim:~~

1. A method of measuring p217+ tau peptides in a sample, comprising:

   ~~(i)~~ a. contacting the sample with a capture antibody ~~directed against a p217+ tau epitope~~comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 32, 33, and 34, respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs:35, 36, and 37, respectively, to capture the p217+ tau peptides in the sample, and

   b. contacting the captured p217+ tau peptides from (a) with at least one of a ~~first~~ detection antibody ~~directed against an epitope comprising amino acid residues 119 to 126 of tau protein and a second detection~~selected from

      i. an antibody ~~directed against an epitope containing amino acid residues~~comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 12, 13, and 14, respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs: 15, 16, and 17, respectively, and

      ii. an antibody comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 2, 3, and 4, respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs: 5, 6, and 7 ~~to 20 of tau protein~~ , respectively,

   ~~(ii)~~ to thereby measure at least one of an amount of the p217+ tau peptides and an amount of long p217+ tau peptides, respectively~~,~~ .

   ~~wherein the numbering of the amino acid is with reference to the amino acid sequence set forth in SEQ ID NO: 1~~

2. The method of claim 1, comprising contacting the captured p217+ tau peptides with ~~the first~~both detection ~~antibody and the second detection antibody~~antibodies to thereby measure the amount of the p217+ tau peptides and the amount of long p217+ tau peptides,

respectively, and ~~optionally~~ determining a ratio of the amount of the long p217+ tau peptides to the amount of p217+ tau peptides.

3. The method of claim 2, further comprising

(i) determining an amount of short p217+ tau peptides via subtracting the amount of the long p217+ tau peptides from the amount of the p217+ tau peptides, and

(ii) ~~optionally~~ determining a ratio of the amount of the short p217+ tau peptides to the amount of p217+ tau peptides, or a ratio of the amount of the long p217+ tau peptides to the amount of short p217+ tau peptides.

~~4. A method of measuring p217+ tau peptides in a sample:~~

~~(i) contacting the sample with a capture antibody directed against a p217+ tau epitope to capture p217+ tau peptides in the sample, and contacting the sample with a phosphorylation-independent capture antibody directed against an epitope between amino acids 150 and 250 of tau protein, preferably an epitope comprising amino acids 159-163 of tau protein, to capture total tau peptides in the sample;~~

~~(ii) conducting at least one of:~~

~~a. contacting the captured p217+ tau peptides with a first detection antibody directed against an epitope comprising amino acid residues 119 to 126 of tau protein to thereby measure an amount of p217+ tau peptides, contacting the captured total tau peptides with the first detection antibody to thereby measure an amount of total tau peptides, and determining a ratio of the amount of p217+ tau peptides to the amount of total tau peptides; and~~

~~b. contacting the captured p217+ tau peptides with a second detection antibody directed against an epitope comprising amino acid residues 7 to 20 of tau protein to thereby measure an amount of long p217+ tau peptides, and contacting the captured total tau peptides with the second detection antibody to thereby measure an amount of total long tau peptides, and determining a ratio of the amount of long p217+ tau peptides to the amount of total long tau peptides,~~

~~wherein the numbering of the amino acid is with reference to the amino acid sequence set forth in SEQ ID NO: 1.~~

5. The method of claim 4, further comprising determining an amount of short p217+ tau peptides via subtracting the amount of the long p217+ tau peptides from the amount of the p217+ tau peptides, determining an amount of total short tau peptides via subtracting the amount of the total long tau peptides from the amount of the total tau peptides, and determining a ratio of the amount of short p217+ tau peptides to the amount of total short tau peptides.

6.4. The method of any one of claims 1 to 53, wherein the sample is a biological sample from a subject selected from the group consisting of blood, brain homogenate, or cerebral spinal fluid (CSF) from the subject.

7.5. The method of claim 64, wherein the biological sample is blood.

8.6. The method of claim 64, wherein the biological sample is CSF.

9.7. The method of claim 6 wherein 4, further comprising fractionating the biological sample has been fractionated using reverse phase high-performance liquid chromatography (rpHPLC).) prior to contacting the sample with the capture antibody.

10. The method of claim 64, further comprising:

a. determining ifof the subject suffers from a tauopathy or is at risk of developing a tauopathy;

b. determining if the subject is suitable for a treatment with an anti-p217+ tau antibody;

c. determining the effectiveness of a treatment of a tauopathy in the subject; or

d. monitoring a treatment with an anti-p217+ tau antibody in a subject,

8. wherein the determining or monitoring comprises comprising comparing at least one of the:

a. amount of the p217+ tau peptides, the

b. amount of the long p217+ tau peptides, the and

c. amount of the short p217+ tau peptides, and the ratios thereof

from the subject with a corresponding baseline value.,

wherein an increase in the amount as compared to the baseline value indicates the subject suffers from or is at risk from suffering from a tauopathy.

~~11.~~ The method of claim ~~10, comprising monitoring a treatment with an anti-p217+ tau antibody in a subject, the method comprising:~~

~~(i) obtaining a biological sample from the subject;~~

~~(ii) separating the biological sample into a first sample containing p217+ tau peptides free of the anti-p217+ tau antibody, and a second sample containing p217+ tau peptides bound to the anti-p217+ tau antibody;~~

~~(iii) separating the second sample, preferably via rpHPLC, to obtain a third sample containing p217+ tau peptides free of anti-p217+ tau antibody;~~

~~(iv) contacting each of the first sample and the third sample with a capture antibody directed against a p217+ tau epitope to capture p217+ tau peptides in each of the first and third samples,~~

~~(v)~~9. ~~conducting at least one of (a) contacting the captured p217+ tau peptides with a first detection antibody directed against an epitope~~4, further comprising ~~amino acid residues 119 to 126 of tau protein to thereby measure an amount of p217+ tau peptides in each of the first and third samples, and (b) contacting the captured p217+ tau peptides with a second detection antibody directed against an epitope~~determining the effectiveness of a treatment of a tauopathy in the subject comprising ~~amino acid residues 7 to 20 of tau protein to thereby measure an amount of long p217+ tau peptides in each of the first and third samples, optionally (c) determining an amount of short p217+ tau peptides via subtracting the amount of the long p217+ tau peptides from the amount of the p217+ tau peptides in each of the first and third samples;~~comparing at least one of:

~~monitoring the treatment with the anti-p217+ tau antibody based on at least one of the~~

a. amount of the p217+ tau peptides, ~~the~~

b. amount of the long p217+ tau peptides, ~~the~~ and

~~(vi)~~c. amount of the short p217+ tau peptides, ~~and ratios thereof, in each of the first and third samples.~~

~~12. The method of claim 10, comprising monitoring a treatment with an anti-p217+ tau antibody in a subject, the method comprising:~~

~~(i) obtaining a biological sample~~ from the subject with a corresponding baseline value,

~~(ii) obtaining a semi-denatured sample from the biological sample containing total p217+ tau peptides, wherein the semi-denatured sample is heated to denature the antibodies in the sample, and obtaining a non-denatured sample from the biological sample containing p217+ tau peptides free of the anti-p217+ tau antibody,~~

~~(iii) contacting each of the semi-denatured sample and the non-denatured sample with a capture antibody directed against a p217+ tau epitope to capture p217+ tau peptides in each of the samples,~~

~~(iv) conducting at least one of (a) contacting the captured p217+ tau peptides with a first detection antibody directed against an epitope comprising amino acid residues 119 to 126 of tau protein to thereby measure an amount of p217+ tau peptides in each of the samples, and (b) contacting the captured p217+ tau peptides with a second detection antibody directed against an epitope comprising amino acid residues 7 to 20 of tau protein to thereby measure an amount of long p217+ tau peptides in each of the samples, optionally (c) determining an amount of short p217+ tau peptides via subtracting the amount of the long p217+ tau peptides from the amount of the p217+ tau peptides in each of the first and third samples, and~~

~~(v) monitoring the treatment with the anti-p217+ tau antibody based on at least one of the amount of the p217+ tau peptides, the amount of the long p217+ tau peptides, the amount of the short p217+ tau peptides, and ratios thereof, in each of the samples.~~

wherein a decrease in the amount as compared to the baseline value indicates the treatment is effective.

~~13.~~10. The method of any one of claims 1 to ~~12~~9, wherein the capture antibody is conjugated to a bead, and wherein the detection antibody is biotinylated.

~~14.~~11. The method of any of claims 1~~-13~~ to 10, wherein the lower limit of quantification of the method is about 40 fg/ml of the p217+ tau peptides and the lower limit of detection of the method is about 2 fg/ml of the p217+ tau peptides.

~~15.~~12. The method of any one of claims ~~7-14~~8 to 11, wherein the tauopathy is selected from the group consisting of familial Alzheimer's disease, sporadic Alzheimer's disease, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy, corticobasal degeneration, Pick's disease, progressive subcortical gliosis, tangle only dementia, diffuse neurofibrillary tangles with calcification, argyrophilic grain dementia, amyotrophic lateral sclerosis parkinsonism-dementia complex, Down syndrome, Gerstmann-Sträussler-Scheinker disease, Hallervorden-Spatz disease, inclusion body myositis, Creutzfeld-Jakob disease, multiple system atrophy, Niemann-Pick disease type C, prion protein cerebral amyloid angiopathy, subacute sclerosing panencephalitis, myotonic dystrophy, non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, chronic traumatic encephalopathy, and dementia pugulistica (boxing disease~~), preferably the tauopathy is Alzheimer's disease.~~).

13. The method of claim 12, wherein the tauopathy is Alzheimer's disease.

14. The method of claim 12, wherein the tauopathy is progressive supranuclear palsy.

15. The method of any one of claims 1 to ~~15~~14, wherein the capture antibody comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: 32, 33, and 34, respectively, and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: 35, 36, and 37, respectively.

~~16.~~ The method of any one of claims 1 to ~~; preferably, the capture~~ 15, wherein the antibody ~~has a heavy chain variable region comprising polypeptide sequence of SEQ ID NO: 28 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 29.~~of (b)(i)

~~17.~~16. ~~The method of any one of claims 1 to~~ 16, ~~wherein the first detection antibody~~ comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: 2, 3, and 4, respectively; and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: 5, 6, and 7, respectively~~; preferably, the first detection antibody comprises a heavy chain variable region~~

~~having the polypeptide sequence of SEQ ID NO: 8 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 9~~.

~~18.~~17. The method of any one of claims 1 to ~~17~~16, wherein the ~~second detection~~ antibody of (b)(ii) comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: 12, 13, and 14, respectively; and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: 15, 16, and 17, respectively~~; preferably, the detection antibody comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 18 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 19~~.

~~19.~~18. A kit comprising:

~~a. a capture antibody directed against a p217+ tau epitope, optionally a phosphorylation-independent capture antibody directed against a tau epitope between amino acids 150 and 250 of tau protein; and~~

a. a capture antibody comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 32, 33, and 34, respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs: 35, 36, and 37, respectively; and

b. at least one detection antibody ~~directed against a tau protein epitope comprising amino acid residues 7 to 20~~comprising

~~b.~~ i. an antibody comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 12, 13, and 14, respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs: 15, 16, and 17, respectively, or ~~116 to 127 of tau protein.~~

ii. an antibody comprising an immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 comprising the polypeptide sequences of SEQ ID NOs: 2, 3, and 4,

respectively, and an immunoglobulin light chain LCDR1, LCDR2, and LCDR3 comprising the polypeptide sequences of SEQ ID NOs: 5, 6, and 7, respectively.

~~20.~~19. The kit of claim ~~19~~18, wherein the capture antibody comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: 32, 33, and 34, respectively, and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: 35, 36 ~~and 37, respectively; preferably, the capture antibody has a heavy chain variable region comprising polypeptide sequence of SEQ ID NO: 28 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 29, and the phosphorylation-independent capture antibody is directed against a tau epitope comprising amino acids 159-163 of tau protein~~, and 37, respectively.

~~21.~~20. The kit of claim ~~19~~18 or ~~20~~19, wherein

a. ~~the~~a first detection antibody comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: ~~2, 3~~12, 13, and ~~4~~14, respectively; and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: ~~5, 6~~15, 16, and ~~7~~17, respectively; ~~preferably, the first detection antibody comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 8~~ and

~~a.~~ a ~~light chain variable region having the polypeptide sequence of SEQ ID NO: 9; and~~

b. ~~the~~ second detection antibody comprises immunoglobulin heavy chain HCDR1, HCDR2, and HCDR3 having the polypeptide sequences of SEQ ID NOs: ~~12, 13~~2, 3, and ~~14~~4, respectively; and immunoglobulin light chain LCDR1, LCDR2, and LCDR3 having the polypeptide sequences of SEQ ID NOs: ~~15, 16~~5, 6, and ~~17~~7, respectively~~;~~ ~~preferably, the detection antibody comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 18 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 19~~.