against GSK-3 beta, for inhibiting excessive phosphorylation of tau (Id). However, there is a concern about possible side effects, since kinases such as GSK-3 beta are implicated not only in pathological conditions, but also in function controls in normal physiological processes. In fact, some of the sites where tau is phosphorylated by GSK-3 beta coincide with sites of tau phosphorylation seen in fetal and normal human brains (Burnes, et. al., supra) suggesting the possibility that this strategy may affect normal tau function.

[0007] Although it was believed that extracellular tau originates from leakage from degenerated nerve cells as a consequence of cell death, recent studies have suggested that following excessive intracellular phosphorylation, tau is processed and then actively secreted out of the cell. Phosphorylated tau secreted from the cell is thought to be dephosphorylated at certain phosphorylation sites and subsequently to act on muscarine receptors M1 and M3 of surrounding cells, thus resulting in various effects such as promoting intracellular tau phosphorylation and contributing to cell death (Miguel Diaz-Hernandes et al., Journal of Biological Chemistry, 2010, Vol.285, No.42, pp.32539-32548 and Venessa Plouffe et al., PLoS ONE, 2012, Vol.7, p.36873). Experiments relating to immunotherapy for tauopathies using tau protein as the target have been reported, as attempts aimed at executing specific action against tau (see Noble, supra, Kishimoto, supra, Asada, supra and Burns, supra).

[0008] The major symptoms in human cognitive disorders are memory impairment and cognitive function impairmen, which is especially important given the role of cognitive function in memory-based judgment, communication and performance. Motor function, on the other hand, while being a symptom found in chromosome 17-linked frontotemporal dementia with Parkinsonism (FTDP-17) and terminal-stage Alzheimer's disease, is not necessarily a major symptom exhibited in cognitive disorders. Therefore, the main issue to be considered for treating cognitive disorders is improvement of cognitive functions. However, there is currently suitable animal models for testing tauopathy-associated cognitive function impairment that would allow identification of a therapeutic or prophylactic agent for treating cognitive disorders. In addition, no such agent exists that exhibits specific and superior effects against cognitive disorders.

[0009] In view of the therapeutic and prophylactic applications against cognitive disorders in human subjects, there is a demand for a humanized anti-phosphorylated tau antibody which not only has high binding affinity to phosphorylated tau, but also exhibits reduced antigenicity to the human body.

V. Summary

[0010] Against this background, among a large number of phosphorylated sites in the tau protein which can undergo abnormal phosphorylation in the conditions of Alzheimer's disease, the present inventors focused on the phosphorylated site of the serine residue at position 413 (Ser413), and succeeded in producing a polyclonal rabbit antibody and a monoclonal mouse antibody which are specific to the Ser413-phosphorylated tau. The present inventors also administered the monoclonal mouse antibodies to model mice of cognitive disorders which showed abnormal expression of phosphorylated tau proteins, and confirmed that improvement in cognitive functions was observed (WO2013/180238A).

[0011] In some examples, the present disclosure provides proteins, such as antibodies, that include an antigen binding portion that specifically binds to Tau protein that is phosphorylated at serine residue 413 (pS413-Tau). In some examples, the present disclosure provides nucleic acids encoding the proteins. In some examples, the present disclosure provides cells that include such nucleic acids encoding the proteins. In some examples, the present disclosure provides methods for treating a tauopathy (e.g., Alzheimer's disease) by administering the proteins, nucleic acids, or cells disclosed herein to a patient in need thereof.

[0012] Accordingly, in some examples the disclosure provides a humanized antibody or a fragment or derivative thereof, which causes an antigen-antibody reaction with a tau protein or a tau peptide phosphorylated at least on an amino acid residue corresponding to Ser413 of SEQ ID NO: 1. In some cases, the humanized antibody or fragment or derivative thereof has an equilibrium dissociation constant of 1.86×10^{-8} M or less for the tau protein or tau peptide.

[0013] In further examples, the humanized antibody or fragment or derivative thereof has an improved selective affinity with the phosphorylated tau protein (or tau peptide, e.g. SEQ ID NO:8) compared to a non-phosphorylated tau protein (or tau peptide, e.g. SEQ ID NO:69).

[0014] In an additional example, the humanized antibody or fragment or derivative thereof described herein has an improved ability to enter the brain when administered into the blood.

[0015] In a further example, the humanized antibody or fragment or derivative thereof comprises CDRs as follows: a CDR-H1 sequence, an amino acid sequence having 80% or more homology with sequence 1M; as a CDR-H2 sequence, an amino acid sequence having 84% or more homology with sequence 2M or 2H1; as a CDR-H3 sequence, an amino acid sequence having 80% or more homology with sequence 3M; as a CDR-L1 sequence, an amino acid sequence having 87% or more homology with sequence 4L1 or 4M; as a CDR-L2 sequence, an

amino acid sequence having 85% or more homology with sequence 5M; and as a CDR-L3 sequence, an amino acid sequence having 77% or more homology with sequence 6M.

[0016] In an additional example, the humanized antibody or fragment or derivative thereof comprises CDRs as follows: as a CDR-H1 sequence, the amino acid sequence of sequence 1M; as a CDR-H2 sequence, the amino acid sequence of sequence 2H1 or an amino acid sequence differs from sequence 2H1 in that Ala at position 15 is substituted with Asp; as a CDR-H3 sequence, the amino acid sequence of sequence 3M; as a CDR-L1 sequence, the amino acid sequence of sequence 4L1 or an amino acid sequence that differs from sequence 4L1 in that Ser at position 5 is substituted with Asn; as a CDR-L2 sequence, the amino acid sequence of sequence 5M; and as a CDR-L3 sequence, the amino acid sequence of sequence 6M.

[0017] In a further example, the humanized antibody or fragment or derivative thereof has CDRs as follows: (1) as a CDR-H1 sequence, the amino acid sequence of 1M; as a CDR-H2 sequence, the amino acid sequence of 2H1; as a CDR-H3 sequence, the amino acid sequence of 3M; as a CDR-L1 sequence, the amino acid sequence of 4L1; as a CDR-L2 sequence, the amino acid sequence of 5M; and as a CDR-L3 sequence, the amino acid sequence of 6M, or (2) as a CDR-H1 sequence, the amino acid sequence of 1M; as a CDR-H2 sequence, the amino acid sequence of 2H1; as a CDR-H3 sequence, the amino acid sequence of 3M; as a CDR-L1 sequence, the amino acid sequence of 4M; as a CDR-L2 sequence, the amino acid sequence of 5M; and as a CDR-L3 sequence, the amino acid sequence of 6M, or (3) as a CDR-H1 sequence, the amino acid sequence of 1M; as a CDR-H2 sequence, the amino acid sequence of 2M; as a CDR-H3 sequence, the amino acid sequence of 3M; as a CDR-L1 sequence, the amino acid sequence of 4M; as a CDR-L2 sequence, the amino acid sequence of 5M; and as a CDR-L3 sequence, the amino acid sequence of 6M.

[0018] In additional examples the humanized antibody or fragment or derivative thereof comprises: as a heavy chain variable region, an amino acid sequence having 90% or more homology with a sequence selected from sequences VH11, VH12, VH47, VH61, VH62, VH64, and VH65; and as a light chain variable region, an amino acid sequence having 90% or more homology with a sequence selected from sequences VL15, VL36, VL46, VL47, VL48, and VL50.

[0019] In a further example, the humanized antibody or fragment or derivative thereof comprises: as a heavy chain variable region, the amino acid sequence of sequence VH65 or an amino acid sequence which differs from sequence VH65 in comprising one or more

substitutions selected from the group consisting of a substitution of Ala with Thr at position 28 (Kabat numbering: H28), a substitution of Asn with Ser at position 30 (Kabat numbering: H30), a substitution of Val with Gly at position 49 (Kabat numbering: H49), a substitution of Ala with Asp at position 64 (Kabat numbering: H61), and a substitution of Gln with Lys at position 78 (Kabat numbering: H75); and as a light chain variable region, the amino acid sequence of sequence VL47 or an amino acid sequence which differs from sequence VL47 in comprising one or more substitutions selected from the group consisting of a substitution of Asp with Glu at position 17 (Kabat numbering: L17), a substitution of Ser with Asn at position 28 (Kabat numbering: L27A), a substitution of Gln with Leu at position 42 (Kabat numbering: L37),a substitution of Gln with Arg at position 50 (Kabat numbering: L45), and a substitution of Arg with Leu at position 51 (Kabat numbering: L46).

[0020] In a further example, the humanized antibody or fragment or derivative thereof comprises any of the following sequence combinations: (a) sequence VH11 as a heavy chain variable region and sequence VL15 as a light chain variable region; (b) sequence VH11 as a heavy chain variable region and sequence VL36 as a light chain variable region; (c) sequence VH11 as a heavy chain variable region and sequence VL46 as a light chain variable region; (d) sequence VH11 as a heavy chain variable region and sequence VL47 as a light chain variable region; (e) sequence VH11 as a heavy chain variable region and sequence VL48 as a light chain variable region; (f) sequence VH11 as a heavy chain variable region and sequence VL50 as a light chain variable region; (g) sequence VH12 as a heavy chain variable region and sequence VL48 as a light chain variable region; (h) sequence VH47 as a heavy chain variable region and sequence VL48 as a light chain variable region; (i) sequence VH61 as a heavy chain variable region and sequence VL48 as a light chain variable region; (j) sequence VH62 as a heavy chain variable region and sequence VL48 as a light chain variable region; (k) sequence VH64 as a heavy chain variable region and sequence VL47 as a light chain variable region; (l) sequence VH64 as a heavy chain variable region and sequence VL48, and (m) sequence VH65 as a heavy chain variable region and sequence VL47.

[0021] In an additional example, the disclosure provides an agent for treating or preventing dementia, comprising the humanized antibody or fragment or derivative thereof as described herein.

[0022] In a further example, the disclosure provides methods and agents for treating or preventing dementia or a tauopathy, including Alzheimer's disease, corticobasal degeneration,

progressive supranuclear palsy, Pick's disease, argyrophilic grain dementia (argyrophilic grain disease), multiple system tauopathy with presenile dementia (MSTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia with neurofibrillary tangles, diffuse neurofibrillary tangle with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI) or frontotemporal lobar degeneration with tau pathology (FTLD-tau).

[0023] In an additional example, the disclosure provides pharmaceutical compositions comprising the humanized antibody or fragment or derivative thereof as described herein and a pharmaceutically acceptable carrier.

[0024] In a further example, the disclosure provides anti-pSer413 tau antibodies comprising: a) a heavy variable domain comprising a vhCDR1 comprising SEQ ID NO:86, a vhCDR2 comprising SEQ ID NO:115 and a vhCDR3 comprising SEQ ID NO:88; and b) a light variable domain comprising a set of vlCDRs selected from the group consisting of: i) a vlCDR1 comprising SEQ ID NO:102, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; ii) a vlCDR1 comprising SEQ ID NO:91, a vlCDR2 comprising SEQ ID NO82: and a vlCDR3 comprising SEQ ID NO:83; iii) a vlCDR1 comprising SEQ ID NO:92, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; iv) a vlCDR1 comprising SEQ ID NO:93, a vlCDR2 comprising SEQ ID NO82: and a vlCDR3 comprising SEQ ID NO:83; v) a vlCDR1 comprising SEQ ID NO:94, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; vi) a vlCDR1 comprising SEQ ID NO:95, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; vii) a vlCDR1 comprising SEQ ID NO:96, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; viii) a vlCDR1 comprising SEQ ID NO:97, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; ix) a vlCDR1 comprising SEQ ID NO:98, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; x) a vlCDR1 comprising SEQ ID NO:99, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; xi) a vlCDR1 comprising SEQ ID NO:100, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83; and xii) a vlCDR1 comprising SEQ ID NO:101, a vlCDR2 comprising SEQ ID NO:82 and a vlCDR3 comprising SEQ ID NO:83. In some cases, the antibody has a ratio of antibody binding to the phosphorylated peptide of SEQ ID NO:8 to antibody binding to the non-phosphorylated peptide of SEQ ID NO:69 of at least about 40.

[0025] In additional examples, the disclosure provides anti-pSer413 tau antibodies comprising: a) a heavy variable domain selected from SEQ ID NO:116 and SEQ ID NO:117; and b) a light variable domain selected from SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113 and SEQ ID NO:114. In some cases, the antibody has a ratio of antibody binding to the phosphorylated peptide of SEQ ID NO:8 to antibody binding to the non-phosphorylated peptide of SEQ ID NO:69 of at least about 40.

[0026] In an additional example, the antibodies of the disclosure comprises a heavy constant domain selected from SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142 and SEQ ID NO:144.

[0027] In a further example, the antibodies of the disclosure comprise a light constant domain selected from SEQ ID NO:79 and SEQ ID NO:80.

[0028] In an additional example, the antibodies of the disclosure comprise a variable heavy domain selected from SEQ ID NO:116 and SEQ ID NO:117.

[0029] In a further example, the antibodies of the disclosure comprise a variable light domain selected from SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113 and SEQ ID NO:114.

[0030] In an additional example, the antibodies comprise heavy and light chains selected from the pairs LC SEQ ID NO:184 and HC SEQ ID NO:144; LC SEQ ID NO:184 and HC SEQ ID NO:145; LC SEQ ID NO:184 and HC SEQ ID NO:146; LC SEQ ID NO:184 and HC SEQ ID NO:147; LC SEQ ID NO:184 and HC SEQ ID NO:148; LC SEQ ID NO:184 and HC SEQ ID NO:149; LC SEQ ID NO:184 and HC SEQ ID NO:150; LC SEQ ID NO:184 and HC SEQ ID NO:151; LC SEQ ID NO:184 and HC SEQ ID NO:152; LC SEQ ID NO:184 and HC SEQ ID NO:153; LC SEQ ID NO:184 and HC SEQ ID NO:154; LC SEQ ID NO:184 and HC SEQ ID NO:155; LC SEQ ID NO:184 and HC SEQ ID NO:156; LC SEQ ID NO:184 and HC SEQ ID NO:157; LC SEQ ID NO:184 and HC SEQ ID NO:158; LC SEQ ID NO:184 and HC SEQ ID NO:159; LC SEQ ID NO:184 and HC SEQ ID NO:160; LC SEQ ID NO:184 and HC SEQ ID NO:161; LC SEQ ID NO:185 and HC SEQ ID NO:144; LC SEQ ID NO:185 and HC SEQ ID NO:145; LC SEQ ID NO:185 and HC SEQ ID NO:146; LC SEQ ID NO:185 and HC SEQ ID NO:147; LC SEQ ID NO:185 and HC SEQ ID NO:148; LC SEQ ID NO:185 and HC SEQ

ID NO:149; LC SEQ ID NO:185 and HC SEQ ID NO:150; LC SEQ ID NO:185 and HC SEQ ID NO:151; LC SEQ ID NO:185 and HC SEQ ID NO:152; LC SEQ ID NO:185 and HC SEQ ID NO:153; LC SEQ ID NO:185 and HC SEQ ID NO:154; LC SEQ ID NO:185 and HC SEQ ID NO:155; LC SEQ ID NO:185 and HC SEQ ID NO:156; LC SEQ ID NO:185 and HC SEQ ID NO:157; LC SEQ ID NO:185 and HC SEQ ID NO:158; LC SEQ ID NO:185 and HC SEQ ID NO:159; LC SEQ ID NO:185 and HC SEQ ID NO:160 and LC SEQ ID NO:185 and HC SEQ ID NO:161.

[0031] In a further example, the antibody of the disclosure has a light chain comprising or consisting of SEQ ID NO:184 and a heavy chain comprising or consisting of SEQ ID NO:144.

[0032] In an additional example, the antibody of the disclosure has a light chain comprising or consisting of SEQ ID NO:184 and a heavy chain comprising or consisting of SEQ ID NO:152.

[0033] In a further example, the disclosure provides nucleic acid compositions comprising: a) a first nucleic acid encoding a light chain selected from SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184 and SEQ ID NO:185; and b) a second nucleic acid encoding a heavy chain selected from SEQ ID NO:144; SEQ ID NO:145; SEQ ID NO:146; SEQ ID NO:147; SEQ ID NO:148; SEQ ID NO:149; SEQ ID NO:150; SEQ ID NO:151; SEQ ID NO:152; SEQ ID NO:153; SEQ ID NO:154; SEQ ID NO:155; SEQ ID NO:156; SEQ ID NO:157; SEQ ID NO:158; SEQ ID NO:159; SEQ ID NO:160 and SEQ ID NO:161.

[0034] In an additional example, the disclosure provides expression vector compositions comprising a first and a second nucleic acid, wherein the first nucleic acid is contained in a first expression vector and the second nucleic acid is contained in a second expression vector.

[0035] In a further example, the disclosure provides an expression vector composition wherein the first nucleic acid and the second nucleic acid is contained in a single expression vector.

[0036] In an additional example, the disclosure provides host cells comprising the expression vector composition, and methods of making an anti-pSer413 tau antibody comprising

culturing the host cell under conditions wherein said antibody is expressed and recovering said antibody.

[0037] In a further example, the disclosure provides methods of treating a tauopathy in a subject comprising administering the antibodies of the disclosure.

[0037a] In one aspect, the disclosure provides an anti-pSer413 tau antibody or antigen binding fragment thereof comprising: (A) a heavy chain variable domain comprising: a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; and a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and (B) a light chain variable domain comprising a set of vlCDRs selected from the group consisting of: i) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:91; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; ii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:92; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; iii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:93; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; iv) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:94; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; v) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:95; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; vi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:96; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; vii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:97; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; viii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:98; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; ix) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:99; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; x) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:100; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:101; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82;

and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; and xii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83. In an additional aspect, the disclosure provides a use of the anti-pSer413 tau antibody or antigen binding fragment thereof as described in this disclosure in the manufacture of a medicament for treating a tauopathy in a subject.

[0037b] In another aspect, the disclosure provides an anti-pSer413 tau antibody or antigen binding fragment thereof comprising: (A) a heavy chain variable domain comprising a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and (B) a light chain variable domain comprising a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83. In an additional aspect, the disclosure provides a use of the anti-pSer413 tau antibody or antigen binding fragment thereof as described in the disclosure in the manufacture of a medicament for treating a tauopathy in a subject.

[0037c] In yet another aspect, the disclosure provides a humanized antibody, or antigen binding fragment thereof, which causes an antigen-antibody reaction with a tau protein or a tau peptide phosphorylated at least on an amino acid residue corresponding to Ser413 of SEQ ID NO: 1, comprising: (A) a heavy chain variable domain comprising: a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; and a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and (B) a light chain variable domain comprising a set of vlCDRs selected from the group consisting of: (i) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:91; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (ii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:92; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (iii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:93; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (iv) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:94; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (v) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:95; a vlCDR2 comprising an amino acid sequence of

SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (vi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:96; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (vii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:97; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (viii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:98; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:99; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (x) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:100; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; (xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:101; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; and (xii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83. In an additional aspect, the disclosure provides a use of the humanized antibody or antigen binding fragment thereof described in this disclosure in the manufacture of a medicament for treating a tauopathy in a subject.

[0037d] In yet another aspect, the disclosure provides a humanized antibody or antigen binding fragment thereof, which causes an antigen-antibody reaction with a tau protein or a tau peptide phosphorylated at least on an amino acid residue corresponding to Ser413 of SEQ ID NO: 1, comprising: (A) a heavy chain variable domain comprising a vhCDR1 comprising an amino acid sequence of 1M (SEQ ID NO: 10); a vhCDR2 comprising an amino acid sequence of 2H1 (SEQ ID NO: 12) or an amino acid sequence differs from sequence 2H1 (SEQ ID NO: 12) in that Ala at position 15 is substituted with Asp; a vhCDR3 comprising an amino acid sequence of 3M (SEQ ID NO: 13); and (B) a light chain variable domain comprising a vlCDR1 comprising an amino acid sequence of 4L1 (SEQ ID NO: 14) or an amino acid sequence differs from sequence 4L1 (SEQ ID NO: 14) in that Ser at position 5 is substituted with Asn; a vlCDR2 comprising an amino acid sequence of 5M (SEQ ID NO: 16); and a vlCDR3 comprising an amino acid sequence of 6M (SEQ ID NO: 17). In an additional aspect, the disclosure provides a use of the humanized antibody or antigen binding fragment thereof described in this disclosure in the manufacture of a medicament for treating a tauopathy in a subject.

VI. BRIEF DESCRIPTION OF THE DRAWINGS

[0038] The invention may be best understood from the following detailed description when read in conjunction with the accompanying drawings. Included in the drawings are the following figures:

[0039] **FIG. 1A and FIG. 1B** collectively show an alignment of various human isoforms of Tau protein, prepared using ClustalW.

[0040] **FIG. 2A** shows an alignment of light chain variable region sequences, highlighting CDR-L1, CDR-L2, and CDR-L3 sequences, according to the Kabat numbering system, of several anti-pS413-Tau binding proteins, in accordance with some embodiments of the disclosure.

[0041] **FIG. 2B** shows an alignment of heavy chain variable region sequences, highlighting CDR-H1, CDR-H2, and CDR-H3 sequences, according to the Kabat numbering system, of several anti-pS413-Tau binding proteins, in accordance with some embodiments of the disclosure.

[0042] **FIG. 3** illustrates the selective binding affinity of several anti-pS413-Tau antibodies for phosphorylated peptide PD17P, relative to non-phosphorylated peptide PD17, in accordance with some embodiments of the disclosure.

[0043] **FIG. 4** illustrates the binding affinity of several anti-pS413-Tau antibodies for phosphorylated Tau in brain homogenate from an Alzheimer's patient, in accordance with some embodiments of the disclosure.

[0044] **FIG. 5A and FIG. 5B** show pharmacokinetics of humanized antibody variants in mouse plasma over time. **FIG. 5A** demonstrates that five initial humanized antibody variants 2, 5, 6, 9, and 10 exhibited rapid elimination from the mouse plasma. **FIG. 5B** demonstrates that three later developed humanized antibody variants L15H11, L46H11, and L47H65 exhibited pharmacokinetics profiles comparable to the chimeric antibody.

What Is Claimed Is:

1. An anti-pSer413 tau antibody or antigen binding fragment thereof comprising:

(A) a heavy chain variable domain comprising: a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; and a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and

(B) a light chain variable domain comprising a set of vlCDRs selected from the group consisting of:

i) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:91; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

ii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:92; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

iii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:93; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

iv) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:94; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

v) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:95; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

vi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:96; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

vii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:97; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

viii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:98; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

ix) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:99; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

x) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:100; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:101; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; and

xii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83.

2. The anti-pSer413 tau antibody or antigen binding fragment thereof of claim 1, wherein the ratio of said antibody's binding affinity to a phosphorylated peptide of SEQ ID NO:8 to said antibody's binding affinity to a non-phosphorylated peptide of SEQ ID NO:69 is at least about 40 to 1.

3. Use of the anti-pSer413 tau antibody or antigen binding fragment thereof of claim 1 in the manufacture of a medicament for treating a tauopathy in a subject.

4. The use of claim 3, wherein the tauopathy is selected from a group consisting of Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, Pick's disease, argyrophilic grain dementia (argyrophilic grain disease), multiple system tauopathy with presenile dementia (MSTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia with neurofibrillary tangles, diffuse neurofibrillary tangle with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), frontotemporal lobar degeneration with tau pathology (FTLD-tau), Economo's encephalitis sequela, subacute sclerosing panencephalitis, and boxer's encephalopathy.

5. An anti-pSer413 tau antibody or antigen binding fragment thereof comprising: (A) a heavy chain variable domain comprising a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and (B) a light chain variable domain comprising a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83.

6. The anti-pSer413 tau antibody or antigen binding fragment thereof of claim 5, wherein the ratio of said antibody's binding affinity to a phosphorylated peptide of SEQ ID NO:8 to said antibody's binding affinity to a non-phosphorylated peptide of SEQ ID NO:69 is at least about 40 to 1.

7. Use of the anti-pSer413 tau antibody or antigen binding fragment thereof of claim 5 in the manufacture of a medicament for treating a tauopathy in a subject.

8. The use of claim 7, wherein the tauopathy is selected from a group consisting of Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, Pick's disease, argyrophilic grain dementia (argyrophilic grain disease), multiple system tauopathy with presenile dementia (MSTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia with neurofibrillary tangles, diffuse neurofibrillary tangle with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), frontotemporal lobar degeneration with tau pathology (FTLD-tau), Economo's encephalitis sequela, subacute sclerosing panencephalitis, and boxer's encephalopathy.

9. A humanized antibody, or antigen binding fragment thereof, which causes an antigen-antibody reaction with a tau protein or a tau peptide phosphorylated at least on an amino acid residue corresponding to Ser413 of SEQ ID NO: 1, comprising:

(A) a heavy chain variable domain comprising: a vhCDR1 comprising an amino acid sequence of SEQ ID NO:86; a vhCDR2 comprising an amino acid sequence of SEQ ID NO:115; and a vhCDR3 comprising an amino acid sequence of SEQ ID NO:88; and

(B) a light chain variable domain comprising a set of vlCDRs selected from the group consisting of:

(i) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:91; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

(ii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:92; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

(iii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:93; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

(iv) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:94; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

(v) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:95; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;

(vi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:96; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;
(vii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:97; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;
(viii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:98; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;
(xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:99; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;
(x) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:100; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83;
(xi) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:101; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83; and
(xii) a vlCDR1 comprising an amino acid sequence of SEQ ID NO:102; a vlCDR2 comprising an amino acid sequence of SEQ ID NO:82; and a vlCDR3 comprising an amino acid sequence of SEQ ID NO:83.

10. The humanized antibody or antigen binding fragment thereof of claim 9, wherein the ratio of said antibody's binding affinity to a phosphorylated peptide of SEQ ID NO:8 to said antibody's binding affinity to a non-phosphorylated peptide of SEQ ID NO:69 is at least about 40 to 1.

11. Use of the humanized antibody or antigen binding fragment thereof of claim 9 in the manufacture of a medicament for treating a tauopathy in a subject.

12. The use of claim 11, wherein the tauopathy is selected from a group consisting of Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, Pick's disease, argyrophilic grain dementia (argyrophilic grain disease), multiple system tauopathy with presenile dementia (MSTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia with neurofibrillary tangles, diffuse neurofibrillary tangle with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), frontotemporal lobar degeneration with tau pathology (FTLD-tau), Economo's encephalitis sequela, subacute sclerosing panencephalitis, and boxer's encephalopathy.

13. A humanized antibody or antigen binding fragment thereof, which causes an antigen-antibody reaction with a tau protein or a tau peptide phosphorylated at least on an amino acid residue corresponding to Ser413 of SEQ ID NO: 1, comprising:
(A) a heavy chain variable domain comprising a vhCDR1 comprising an amino acid sequence of 1M (SEQ ID NO: 10); a vhCDR2 comprising an amino acid sequence of 2H1 (SEQ ID NO: 12) or an amino acid sequence differs from sequence 2H1 (SEQ ID NO: 12) in that Ala at position 15 is substituted with Asp; a vhCDR3 comprising an amino acid sequence of 3M (SEQ ID NO: 13); and
(B) a light chain variable domain comprising a vlCDR1 comprising an amino acid sequence of 4L1 (SEQ ID NO: 14) or an amino acid sequence differs from sequence 4L1 (SEQ ID NO: 14) in that Ser at position 5 is substituted with Asn; a vlCDR2 comprising an amino acid sequence of 5M (SEQ ID NO: 16); and a vlCDR3 comprising an amino acid sequence of 6M (SEQ ID NO: 17).

14. The humanized antibody or antigen binding fragment thereof of claim 13, comprising:
(A) a vhCDR1 comprising an amino acid sequence of 1M (SEQ ID NO: 10); a vhCDR2 comprising an amino acid sequence of 2H1 (SEQ ID NO: 12); a vhCDR3 comprising an amino acid sequence of 3M (SEQ ID NO: 13); a vlCDR1 comprising an amino acid sequence of 4L1 (SEQ ID NO: 14); a vlCDR2 comprising an amino acid sequence of 5M (SEQ ID NO: 16); and a vlCDR3 comprising an amino acid sequence of 6M (SEQ ID NO: 17), or
(B) a vhCDR1 comprising an amino acid sequence of 1M (SEQ ID NO: 10); a vhCDR2 comprising an amino acid sequence of 2H1 (SEQ ID NO: 12); a vhCDR3 comprising an amino acid sequence of 3M (SEQ ID NO: 13); a vlCDR1 comprising an amino acid sequence of 4M (SEQ ID NO: 15); a vlCDR2 comprising an amino acid sequence of 5M (SEQ ID NO: 16); and a vlCDR3 comprising an amino acid sequence of 6M (SEQ ID NO: 17), or
(C) a vhCDR1 comprising an amino acid sequence of 1M (SEQ ID NO: 10); a vhCDR2 comprising an amino acid sequence of 2M (SEQ ID NO: 11); a vhCDR3 comprising an amino acid sequence of 3M (SEQ ID NO: 13); a vlCDR1 comprising an amino acid sequence of 4M (SEQ ID NO: 15); a vlCDR2 comprising an amino acid sequence of 5M (SEQ ID NO: 16); and a vlCDR3 comprising an amino acid sequence of 6M (SEQ ID NO: 17).

15. The humanized antibody or antigen binding fragment thereof of claim 13, wherein the ratio of said antibody's binding affinity to a phosphorylated peptide of SEQ ID NO:8 to said antibody's binding affinity to a non-phosphorylated peptide of SEQ ID NO:69 is at least about 40 to 1.

16. Use of the humanized antibody or antigen binding fragment thereof of claim 13 in the manufacture of a medicament for treating a tauopathy in a subject.

17. The use of claim 16, wherein the tauopathy is selected from a group consisting of Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, Pick's disease, argyrophilic grain dementia (argyrophilic grain disease), multiple system tauopathy with presenile dementia (MSTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia with neurofibrillary tangles, diffuse neurofibrillary tangle with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), frontotemporal lobar degeneration with tau pathology (FTLD-tau), Economo's encephalitis sequela, subacute sclerosing panencephalitis, and boxer's encephalopathy.