and/or reactivity to a normal tau protein and being administered under conditions and in an amount(s) effective to prevent or treat Alzheimer's disease or other tauopathy is reported in WO 2012/106363.

In WO 2012/149365 an antibody which shows reactivity with aggregated tau and substantially no reactivity with non-aggregated Tau, wherein the aggregated tau comprises at least two tau proteins cross-linked to each other, either directly or through a linker, at one or more cysteine residues is reported.

A composition useful in treating Tauopathy e.g. Alzheimer disease comprises antibody binding to Tau, phosphorylated serine modified compound at specific position specifically binding to specific phosphorylated Tau and its fragment and carrier is reported in WO 2010/142423.

In EP 1 876 185 A an antibody which recognizes phosphorylated polypeptides is reported. In WO 2013/151762 a humanized tau antibody is reported. In WO 2014/016737 novel chicken monoclonal antibodies against human phosphorylated tau and uses thereof are reported. In WO 2014/016737are reported novel chicken monoclonal antibodies against human phosphorylated tau and uses thereof. Antibodies selective for pathological tau dimers and prefibrillar pathological tau oligomers and their uses in treatment, diagnosis and monitoring of tauopathies are reported in WO 2012/149365.

SUMMARY

The ~~invention~~ disclosure provides anti-human Tau(pS422) antibodies, especially humanized anti-human Tau(pS422) antibodies, and methods of using the same.

The humanized antibodies as reported herein were not available by standard humanization methods. It was required to introduce non-standard mutations in the amino acid sequence in order to obtain a humanized antibody with comparable binding characteristics as the parent rabbit antibody comprising variable domains with the amino acid sequence of SEQ ID NO: 07 and SEQ ID NO: 11. This is especially important as the antibodies as reported herein are intended to cross the human blood-brain-barrier and to be effective within the human brain. Thus, the generally applied criteria for the selection of humanized antibodies are not sufficiently stringent in order to be applied directly in the current case.

~~One aspect~~ There is ~~as~~ reported herein ~~is~~ a (humanized) antibody that specifically binds to human Tau(pS422), wherein the antibody

i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or

ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or

iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

v) specifically binds to human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A.

The antibodies as reported herein show a selectivity with respect to human Tau phosphorylated at the serine at position 422, with respect to not-phosphorylated wild-type human Tau and the Tau mutant S422A. The not-phosphorylated wild-type human Tau and the Tau mutant S422A are not bound at all or with a lower affinity, respectively.

~~One aspect as~~ There is reported herein ~~is~~ a (humanized) antibody that specifically binds to human Tau(pS422), characterized in that the antibody comprises

a) in the heavy chain variable domain the HVRs of SEQ ID NO: 08, 18 and 10, or

b) in the heavy chain variable domain the HVRs of SEQ ID NO: 08, 09 and 10.

In one embodiment the antibody comprises

a) in the light chain variable domain the HVRs of SEQ ID NO: 13, 14 and 15, or

b) in the light chain variable domain the HVRs of SEQ ID NO: 12, 05 and 15.

In one ~~embodiment~~ aspect, there is provided a humanized ~~the~~ antibody that specifically binds to human Tau(pS422), wherein the antibody comprises

a) in the heavy chain variable domain the HVRs of SEQ ID NO: 08, 18 and 10, and in the light chain variable domain the HVRs of SEQ ID NO: 13, 14 and 15, or

c) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G,

d) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G,

e) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain, or

f) a full length antibody of the human subclass IgG4 with the mutations S228P and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain.

~~One aspect as~~ There is reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 18 and SEQ ID NO: 10,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody

i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or

ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or

iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or

vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or

vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or

viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or

ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

~~One aspect as~~There is reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 09 and SEQ ID NO: 10,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 12, SEQ ID NO: 05 and SEQ ID NO: 15,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody

i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or

ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or

iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or

vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or

vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or

viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or

ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

There is~~One aspect as~~ reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 09 and SEQ ID NO: 10,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody
   i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or
   ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or
   iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or
   iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or
   v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or
   vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or
   vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or
   viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or
   ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

~~One aspect as~~ There is reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

~~One aspect as~~ There is reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain has the amino acid sequence of SEQ ID NO: 19,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain has the amino acid sequence of SEQ ID NO: 16,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody
   i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or
   ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or
   iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or
   iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or
   v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or
   vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or
   vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or

viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or

ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

There is ~~One aspect as~~ reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain has the amino acid sequence of SEQ ID NO: 19,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain has the amino acid sequence of SEQ ID NO: 17,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody

i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or

ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or

iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or

vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or

vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or

viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or

ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

There is ~~One aspect as~~ reported herein ~~is~~ a (humanized) anti-human Tau(pS422) antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain has the amino acid sequence of SEQ ID NO: 21,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain has the amino acid sequence of SEQ ID NO: 17,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) the antibody

i) specifically binds to a polypeptide that has the amino acid sequence of SEQ ID NO: 03, and/or

ii) does not bind to full length human Tau (SEQ ID NO: 01) at 1 µg/mL, and/or

iii) specifically binds to full length human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

iv) specifically binds to aggregates of human Tau phosphorylated at the serine at position 422 (SEQ ID NO: 02), and/or

v) specifically binds to full length human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A, and/or

vi) has an EC_{50} value for the human Tau(pS422) fragment that has the amino acid sequence of SEQ ID NO: 03 of 6 ng/mL or less, and/or

vii) has an EC_{50} value for the full length human Tau(pS422) that has the amino acid sequence of SEQ ID NO: 02 of 4.5 ng/mL or less, and/or

viii) has an EC_{50} value for aggregates of human Tau (pS422) that has the amino acid sequence of SEQ ID NO: 02 of 30 ng/mL or less, and/or

ix) has an EC_{50} value for the human Tau that has the amino acid sequence of SEQ ID NO: 01 and that has the amino acid mutation S422A of 125 ng/mL or less.

In ~~one preferred embodiment of all aspects~~the disclosure, the anti-human Tau(pS422) antibody is characterized in that the antibody has in the heavy chain variable domain at positions 4, 24 and 78 a valine residue.

In the disclosure,~~one preferred embodiment of all aspects~~ the anti-human Tau(pS422) antibody is characterized in that the antibody has in the heavy chain variable domain at position 71 an arginine residue.

There is ~~One aspect as~~ reported herein ~~is~~ an isolated nucleic acid encoding a (humanized) antibody as reported herein.

There is ~~One aspect as~~ reported herein ~~is~~ a host cell comprising the nucleic acid as reported herein.

There is ~~One aspect as~~ reported herein ~~is~~ a method of producing a (humanized) antibody comprising the steps of culturing the host cell as reported herein so that the antibody is produced.

In one embodiment the method further comprises the step of recovering the antibody from the cell or the cultivation medium.

One aspect as reported herein is a pharmaceutical formulation comprising the (humanized) antibody as reported herein and a pharmaceutically acceptable carrier.

In one embodiment the pharmaceutical formulation further comprises an additional therapeutic agent.

In one embodiment the additional therapeutic agent is an anti-amyloid therapeutic agent. In one embodiment the anti-amyloid therapeutic agent is an anti-human alpha-synuclein antibody or an anti-Abeta antibody.

~~One aspect as~~There is reported herein ~~is~~ the (humanized) antibody as reported herein for use as a medicament.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in treating Alzheimer's disease.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in treating prodromal Alzheimer's disease.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in treating mild Alzheimer's disease.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in reducing Tau(pS422)-induced neurodegeneration.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in maintaining cognition and function.

~~One aspect as~~ There is reported herein ~~is~~ the (humanized) antibody as reported herein for use in slowing the rate of cognitive and functional decline.

There is ~~One aspect as~~ reported herein ~~is~~ the (humanized) antibody as reported herein for use in slowing down the rate of neurofibrillary tangle accumulation.

In the disclosure, ~~one embodiment of the previous aspects~~ the use is by reducing neurofibrillary tangle burden by clearing Tau(pS422).

In the disclosure, ~~one embodiment of the previous aspects~~ the use is by preventing neurofibrillary tangle build up.

In the disclosure, ~~one embodiment of the previous aspects~~ the use is by removing/clearing neurofibrillary tangles.

In one embodiment the preventing and/or removing is by promoting the intracellular clearance of Tau aggregates.

In the disclosure, ~~one embodiment of the previous aspects~~ the use is by inhibiting neurofibrillary tangle spreading. In one embodiment the inhibiting is by preventing interneuronal transfer of pathological Tau forms/seeds.

~~Aspects of t~~The current ~~invention~~ disclosure also relates to ~~are also~~ methods of treatment comprising administering the (humanized) antibody as reported herein for treating Alzheimer's disease, for treating prodromal Alzheimer's disease, for treating mild Alzheimer's disease, for reducing Tau(pS422)-induced neurodegeneration, for maintaining cognition and function, for slowing the rate of cognitive and functional decline, and/or for slowing down the rate of neurofibrillary tangle accumulation.

One aspect as reported herein is the use of the (humanized) antibody as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for treatment of Alzheimer's disease.

In one embodiment the medicament is for treatment of prodromal Alzheimer's disease.

In one embodiment the medicament is for treatment of mild Alzheimer's disease.

In one embodiment the medicament is for reducing Tau(pS422) induced neurodegeneration.

In one embodiment the medicament is for maintaining cognition and function.

In one embodiment the medicament is for slowing the rate of cognitive and functional decline.

There is ~~One aspect as~~ reported herein ~~is~~ a method of treating an individual having Alzheimer's disease comprising administering to the individual an effective amount of a (humanized) anti-human Tau(pS422) antibody as reported herein.

There is ~~One aspect as~~ reported herein ~~is~~ a method of reducing Tau(pS422) induced neurodegeneration in an individual comprising administering to the individual an effective amount of a (humanized) anti-human Tau(pS422) antibody as reported herein to reduce Tau(pS422) induced neurodegeneration.

There is ~~One aspect as~~ reported herein ~~is~~ a method of maintaining cognition and function in an individual comprising administering to the individual an effective amount of a (humanized) anti-human Tau(pS422) antibody as reported herein to maintain cognition and function.

There is ~~One aspect as~~ reported herein ~~is~~ a method of slowing the rate of cognitive and functional decline in an individual comprising administering to the individual an effective amount of a (humanized) anti-human Tau(pS422) antibody as reported herein to slow the rate of cognitive and functional decline.

There is ~~One aspect as~~ reported herein ~~is~~ the use of a (humanized) anti-human Tau(pS422) antibody as reported herein in the reduction of Tau(pS422) induced neurodegeneration.

There is ~~One aspect as~~ reported herein ~~is~~ the use of a (humanized) anti-human Tau(pS422) antibody as reported herein in maintaining cognition and function.

There is ~~One aspect as~~ reported herein ~~is~~ the use of a (humanized) anti-human Tau(pS422) antibody as reported herein in slowing the rate of cognitive and functional decline.

The antibodies as reported herein can be used in the treatment of Alzheimer's disease.

With the (humanized) antibodies as reported herein inhibition/reduction of progression of Alzheimer's disease and neuropathology can be effected.

The (humanized) antibodies as reported herein can be used to protect from development of Alzheimer's disease or even used to stop the progression of Alzheimer's disease.

In one embodiment the (humanized) antibody as reported herein i) binds to Tau(pS422) on brain sections of Tau(pS422) transgenic mice and Alzheimer's disease patients; and/or labels Tau(pS422) in Tau(pS422) transgenic cells.

The (humanized) antibodies as reported herein can be used for the treatment of Alzheimer's disease.

There is ~~One aspect as~~ reported herein ~~is~~ a (humanized) antibody that specifically binds to the amino acid sequence of SEQ ID NO: 03 in human Tau(pS422).

The (humanized) antibodies as reported herein specifically bind to/recognize early and late stage disease-relevant forms of human Tau(pS422).

There is ~~One aspect as~~ reported herein ~~is~~ the use of the (humanized) antibody as reported herein for the prevention of human Tau (pS422)-related Alzheimer's disease spread.

There is ~~One aspect as~~ reported herein ~~is~~ the use of the (humanized) antibody as reported herein for the reduction of lysosomal membrane disintegration.

There is ~~One aspect as~~ reported herein ~~is~~ the use of the (humanized) antibody as reported herein for the stabilization of lysosome membrane against human Tau(pS422) induced destabilization and/or disintegration.

There is ~~One aspect as~~ reported herein ~~is~~ the use of the (humanized) antibody as reported herein for the prevention of Alzheimer's disease progression.

The (humanized) antibodies as reported herein function by antibody mediated inhibition of human Tau(pS422) seeding and spreading between cells.

The (humanized) antibodies as reported herein protect lysosomes from fibrillar damage by binding to human Tau(pS422).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Sequence alignment of rabbit and humanized light chain variable domains; CDRs are enboxed.

Figure 2: Sequence alignment of rabbit and humanized heavy chain variable domains; CDRs are enboxed.

Figure 3: Biochemical binding of different combinations of humanized VH and VL to (A) phosphorylated tau peptide, (B) phosphorylated full-length human tau, (C) not-phosphorylated tau peptide, (D) not-phosphorylated full-length human tau; (1) = VH00/VL00, (2)