complex phospho-epitopes on protein tau, particularly on aggregated tau protein that are believed to be responsible for synapto- and neuro-toxicity in tauopathies, including AD.

In one aspect, there is provided a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, which antibody recognizes and specifically binds to a phospho-epitope on a human Tau protein as shown in SEQ ID NO: 19 or on a fragment thereof, but does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said epitope comprises Tau aa 404-411 with the requirement of a phosphorylated Ser at position 409 (pS409).

In one embodiment, the disclosure ~~invention~~ relates to an antibody, particularly a monoclonal antibody, particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof, which recognizes and binds to at least one distinct binding site on the Tau protein.

The antibody, particularly the monoclonal antibody, particularly the chimeric or humanized antibodies according to the disclosure~~invention~~ as described in the various embodiments, recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a phospho-epitope on aggregated Tau protein, particularly to a pathological protein tau conformer, but does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said antibody has a high binding affinity to soluble and insoluble Tau protein, and modulates soluble and insoluble Tau levels, particularly in the brain, particularly with a

(a) dissociation constant of at least 100 nM, particularly at least 80 nM, particularly at least 70 nM, particularly at least 50 nM, particularly at least 10 nM, particularly of at least 8 nM, particularly of at least 5 nM, particularly of at least 2 nM, particularly of at least 1 nM, particularly of at least 500 pM, particularly of at least 400 pM, particularly of at least 300 pM, particularly of at least 200 pM, particularly of at least 100 pM, particularly of at least 50 pM and/or

(b) an association rate constant of 10^4 $M^{-1}s^{-1}$ or greater, particularly of between 3 - 5 x 10^4 $M^{-1}s^{-1}$ or greater, particularly of 10^5 $M^{-1}s^{-1}$ or greater; particularly of 0.5 – 9 x 10^5 $M^{-1}s^{-1}$ or greater; particularly of 10^6 $M^{-1}s^{-1}$ or greater, particularly of 1 – 4 x 10^6 $M^{-1}s^{-1}$ or greater, particularly of 10^7 $M^{-1}s^{-1}$ or greater.

In certain embodiments, the present disclosure~~invention~~ relates to an antibody, particularly a monoclonal antibody, particularly a chimeric or humanized antibody according to the disclosure~~invention~~ as described in the various embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to

non-related epitopes, wherein said antibody has a high binding affinity with a dissociation constant of at least 100 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 80 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 70 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 10 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at

least 200 pM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 100 pM and an association rate constant of 10^6 $M^{-1}s^{-1}$ or greater.

In various embodiments of the disclosure~~invention~~, the antibody, particularly the monoclonal antibody, particularly the chimeric or humanized antibody according to the disclosure~~invention~~ as described in the various embodiments specifically recognizes and binds to a phospho-epitope on a mammalian, particularly on the human Tau protein, particularly a microtubule-associated protein tau, particularly an aggregated microtubule-associated and hyperphosphorylated protein tau such as that present in paired helical filaments (PHF), which are the predominant structures in neurofibrillary tangles, neuropil threads and dystrophic neurites, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes.

In a specific embodiment of the disclosure~~invention~~, the human tau protein is the human Tau protein as shown in SEQ ID NO: 19.

In one embodiment, the present disclosure~~invention~~ provides an antibody, particularly a monoclonal antibody, particularly a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly an antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein as shown in SEQ ID NO: 19 or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said epitope comprises amino acid residues aa 404-411 of the human Tau protein as shown in SEQ ID NO: 19 with the requirement of phosphorylated Serine at position 409 (pS409).

In a specific embodiment, the present disclosure~~invention~~ provides an antibody, particularly a monoclonal antibody, particularly a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly an antibody of any of the preceding embodiments, which antibody preferentially recognizes and binds to some or all Tau amino acid residues selected from the group consisting of H407, pS409, N410, and V411, but particularly to pS409.

In another specific embodiment said antibody or fragment also recognizes and binds to the pS404 residue, even though to a lesser extent. In particular, the binding to the pS404 residue amounts to about 10%, particularly to about 20%, particularly to about 30% of the binding to the pS409 residue.

In one embodiment, the present ~~invention~~ disclosure provides an antibody, particularly a monoclonal antibody, particularly a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly an antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein as shown in SEQ ID NO: 19 or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said epitope comprises amino acid residues aa 405-411 of the human Tau protein as shown in SEQ ID NO: 19 comprising a phosphorylated Serine (Ser) at position 409 (pS409) and wherein said antibody or functional fragment thereof preferentially recognizes and binds to some or all Tau amino acid residues selected from the group consisting of H407, pS409, N410, and V411, but particularly to pS409.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 50%, at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 50%, at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least

93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto.

One embodiment of the present disclosure~~invention~~ relates to a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, or an amino acid sequence at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6 or an amino acid sequence at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%,

at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence at least at least 81%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence at least at least 71%, at least 75%, at least 8%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3 at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, or an amino acid sequence at least 82%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 50%, at least 68%, at least 70%, at least 80%, particularly at least 85%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at

least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence at least at least 85% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence at least 75% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3 at least 20% identical thereto, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, or an amino acid sequence at least 85% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 70% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 90% identical thereto, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into

human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 90% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 95% identical thereto, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 95% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 98% identical thereto, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into

human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4 or SEQ ID NO: 10, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6, or an amino acid sequence at least 98% identical thereto.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 4, a CDR2 with the amino acid sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6.

In one embodiment, the present disclosure~~invention~~ provides a chimeric antibody or a functional fragment thereof, or a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises a first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 1, a CDR2 with the amino acid sequence shown in SEQ ID NO: 2, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 3, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains integrated into human- or primate-derived framework regions in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 10, a CDR2 with the amino acid

sequence shown in SEQ ID NO: 5, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 6. The disclosure~~invention~~ further relates to a chimeric antibody or a functional fragment thereof, or a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions at least two peptides, particularly at least three peptides, particularly at least four peptides, particularly at least five peptides, particularly six peptides, which peptides are different and exhibit an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR), wherein the same CDR cannot be present twice in the antibody.

The disclosure~~invention~~ further relates to a chimeric antibody or a functional fragment thereof, or a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions at least two peptides, particularly at least three peptides, particularly at least four peptides, particularly at least five peptides, particularly six peptides, which peptides are different and exhibit an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 10 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR), wherein the same CDR cannot be present twice in the antibody.

In a specific embodiment, the disclosure~~invention~~ relates to a chimeric antibody or a functional fragment thereof, or a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR).

In a specific embodiment, the disclosure~~invention~~ relates to a chimeric antibody or a functional fragment thereof, or a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 10 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR).In one embodiment, the present disclosure~~invention~~

provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said antibody or antibody fragment comprises a

a. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 84%, particularly at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 89%, particularly at least 90%, particularly at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identity to the sequence shown in SEQ ID NO: 8; or a

b. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 84%, particularly at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, particularly at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,particularly at least 95%, particularly at least 96%, particularly at least 97%, particularly at least 98%, particularly at least 99% or 100% identity to the sequence shown in SEQ ID NO: 9.

In one embodiment, the present disclosure~~invention~~ provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological

protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises

a. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 84% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 89% identity to the sequence shown in SEQ ID NO: 8; or a

b. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 84% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21 and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 90% identity to the sequence shown in SEQ ID NO: 9.

In one embodiment, the present disclosure~~invention~~ provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises

a. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 90% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 90% identity to the sequence shown in SEQ ID NO: 8; or a

b. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 90% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 90% identity to the sequence shown in SEQ ID NO: 9.

In one embodiment, the present disclosure~~invention~~ provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises

a. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 95% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 95% identity to the sequence shown in SEQ ID NO: 8; or a

b. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence having at least 95% identity to the sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence having at least 95% identity to the sequence shown in SEQ ID NO: 9.

In one embodiment, the present disclosure~~invention~~ provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding antibody comprises

a. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence shown in SEQ ID NO: 7, SEQ ID NO: 20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence shown in SEQ ID NO: 8; or a

b. first binding domain, particularly a binding domain of a Heavy Chain Variable Region (HCVR), which contains an amino acid sequence shown in SEQ ID NO: 7, SEQ ID NO:

20 or SEQ ID NO: 21, and/or a second binding domain, particularly a binding domain of a Light Chain Variable Region (LCVR), which contains an amino acid sequence shown in SEQ ID NO: 9.

In one embodiment, the present disclosure~~invention~~ provides a humanized antibody or a functional fragment thereof, particularly a humanized monoclonal antibody or a functional fragment thereof, particularly a humanized antibody of any of the preceding embodiments, which antibody recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, which antibody further comprises a heavy chain constant region and a light chain constant region, particularly the heavy chain constant region as shown in SEQ ID NOs: 14-17 and the light chain constant region as shown in SEQ ID NO: 18.

In one embodiment said humanized antibody or a functional fragment thereof according to any of the preceding embodiments comprises a heavy chain constant region with a mutation in the hinge region, particularly a mutation in the hinge region which prevents Fab arm exchange and thus generation of bi-specific antibodies. In a specific embodiment, the heavy chain hinge region comprises a Ser to Pro exchange at position 228 (S228P).

In one embodiment said humanized antibody or a functional fragment thereof according to any of the preceding embodiments comprises a heavy chain constant region with a modification (e.g., a deletion or a mutation) at the C-terminus. In a specific embodiment, the heavy chain comprises a deletion of the C-terminal lysine (des-K). This C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region of the constant region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody. This mutation prevents random enzymatic cleavage of the C-terminal lysine by antibody producing cells such as, for example, CHO cells.

In another embodiment, said humanized antibody or a functional fragment thereof according to any of the preceding embodiments comprises a heavy chain constant region without a modification (e.g., a deletion or a mutation) at the C-terminus. In a specific embodiment, the heavy chain constant region comprises the C-terminal lysine (a lysine at the C-terminal end of the heavy chain constant region). As such, an antibody according to the present disclosure~~invention~~ can comprise an antibody with K447, with all K447 removed, or a mixture of antibodies with and without the K447 residue.

In one embodiment of the disclosure~~invention~~, the binding peptide of any of the preceding embodiments is an antibody, particularly an antibody of the -IgG1, IgG2, IgG3 or the IgG4 isotype, particularly a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody or a fully human antibody. In one embodiment of the disclosure~~invention~~, the binding peptide of any of the preceding embodiments is an antibody, particularly an antibody of the IgG1 N297G isotype, having an asparagine to glycine substitution at position 297 (EU numbering system) in the Fc region of the antibody, particularly a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody or a fully human antibody.

One embodiment of the disclosure~~invention~~ relates to a polynucleotide encoding the binding peptide of any one of the preceding embodiments.

In one embodiment, said polynucleotide comprises a nucleic acid molecule comprising a nucleotide sequence encoding an antibody variable region comprising SEQ ID NO: 1 - 3 representing the Complementarity Determining Regions (CDRs) 1, 2 and 3 of the Heavy Chain Variable Region (HCVR).

In another embodiment, said polynucleotide comprises nucleic acid molecule comprising a nucleotide sequence encoding an antibody variable region comprising SEQ ID NO: 4-6 representing the Complementarity Determining Regions (CDRs) 1, 2 and 3 of the Light Chain Variable Region (LCVR).

In another embodiment, said polynucleotide comprises nucleic acid molecule comprising a nucleotide sequence encoding an antibody variable region comprising SEQ ID NO: 10, 5 and 6 representing the Complementarity Determining Regions (CDRs) 1, 2 and 3 of the Light Chain Variable Region (LCVR).

In one embodiment, the disclosure~~invention~~ relates to a polynucleotide comprising a nucleic acid molecule selected from the group consisting of

a. a nucleic acid molecule comprising a nucleotide sequence as depicted in SEQ ID NOs: 11 and/or a nucleotide sequence as depicted in SEQ ID NOs: 12; or

b. a nucleic acid molecule comprising a nucleotide sequence that has at least 85% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 85% sequence identity to the sequence shown in SEQ ID NO: 12; or

c. a nucleic acid molecule comprising a nucleotide sequence that has at least 90% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 90% sequence identity to the sequence shown in SEQ ID NO: 12; or

d. a nucleic acid molecule comprising a nucleotide sequence that has at least 95% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 95% sequence identity to the sequence shown in SEQ ID NO: 12; or

e. a nucleic acid molecule comprising a nucleotide sequence that has at least 98% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 98% sequence identity to the sequence shown in SEQ ID NO: 12; or;

f. a nucleic acid molecule comprising a nucleotide sequence the complementary strand of which hybridizes to the nucleic acid molecule of any of a) – e);

g. a nucleic acid molecule comprising a nucleotide sequence that deviates from the nucleotide sequence defined in any of a) – f) by the degeneracy of the genetic code.

In one embodiment, the disclosure~~invention~~ relates to a polynucleotide comprising a nucleic acid molecule selected from the group consisting of

a. a nucleic acid molecule comprising a nucleotide sequence as depicted in SEQ ID NOs: 11 and/or a nucleotide sequence as depicted in SEQ ID NOs: 13; or

b. a nucleic acid molecule comprising a nucleotide sequence that has at least 85% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 85% sequence identity to the sequence shown in SEQ ID NO: 13; or

c. a nucleic acid molecule comprising a nucleotide sequence that has at least 90% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 90% sequence identity to the sequence shown in SEQ ID NO: 13; or

d. a nucleic acid molecule comprising a nucleotide sequence that has at least 95% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 95% sequence identity to the sequence shown in SEQ ID NO: 13; or

e. a nucleic acid molecule comprising a nucleotide sequence that has at least 98% sequence identity to the sequence shown in SEQ ID NO: 11 and/or a nucleotide sequence that has at least 98% sequence identity to the sequence shown in SEQ ID NO: 13; or;

f. a nucleic acid molecule comprising a nucleotide sequence the complementary strand of which hybridizes to the nucleic acid molecule of any of a) – e);

g. a nucleic acid molecule comprising a nucleotide sequence that deviates from the nucleotide sequence defined in any of a) – f) by the degeneracy of the genetic code.

In one embodiment, the disclosure~~invention~~ relates to a polynucleotide comprising a nucleic acid molecule comprising a nucleotide sequence as shown in SEQ ID NO: 11 and/or a nucleotide sequence as shown in SEQ ID NO: 12.

In one embodiment, the disclosure~~invention~~ relates to a polynucleotide comprising a nucleic acid molecule comprising a nucleotide sequence as shown in SEQ ID NO: 11 and/or a nucleotide sequence as shown in SEQ ID NO: 13.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 7 and the heavy chain constant region of SEQ ID NOs: 14-17.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 20 or SEQ ID NO: 21.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 20 or SEQ ID NO: 21, and the heavy chain constant region of SEQ ID NOs: 14-17.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain of SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Light Chain Variable Region (LCVR) of SEQ ID NO: 8 and the light chain constant region of SEQ ID NO: 18.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Light Chain Variable Region (LCVR) of SEQ ID NO: 9 and the light chain constant region of SEQ ID NO:18.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Light Chain of SEQ ID NO: 22 or SEQ ID NO: 23.

The present disclosure~~invention~~ further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain of SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31, and the Light Chain of SEQ ID NO: 22 or SEQ ID NO: 23.

The present disclosureinvention further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 7 and the heavy chain constant region of SEQ ID NOs: 14-17 and the Light Chain Variable Region (LCVR) of SEQ ID NO: 8 and the light chain constant region of SEQ ID NO: 18.

The present disclosureinvention further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 7 and the heavy chain constant region of SEQ ID NOs: 14-17 and the Light Chain Variable Region (LCVR) of SEQ ID NO: 9 and the light chain constant region of SEQ ID NO: 18.

The present disclosureinvention further provides a humanized antibody or a fragment thereof, which comprises the Heavy Chain Variable Region (HCVR) of SEQ ID NO: 20 or SEQ ID NO: 21, and the heavy chain constant region of SEQ ID NOs: 14-17, and the Light Chain Variable Region (LCVR) of SEQ ID NO: 8 or SEQ ID NO: 9, and the light chain constant region of SEQ ID NO: 18.

In one aspect, there is provided a polynucleotide encoding a chimeric or humanized antibody as described herein, or a functional fragment thereof.

In one embodiment, the disclosureinvention relates to a polynucleotide encoding the humanized antibodies of any one of the preceding embodiments.

In one aspect, there is provided a vector comprising a polynucleotide as described herein, wherein said polynucleotide is operably linked.

The chimeric or humanized antibodies according to the disclosureinvention as described in the various embodiments, recognize and specifically bind to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly to a phospho-epitope on aggregated Tau protein, particularly to a pathological protein tau conformer, but does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said antibodies have a high binding affinity to soluble and insoluble Tau protein, and modulates soluble and insoluble Tau levels, particularly in the brain, particularly with a

(c) dissociation constant of at least 100 nM, particularly at least 80 nM, particularly at least 70 nM, particularly at least 50 nM, particularly at least 10 nM, particularly of at least 8 nM, particularly of at least 5 nM, particularly of at least 2 nM, particularly of at least 1 nM, particularly of at least 500 pM, particularly of at least 400 pM, particularly of at least 300 pM, particularly of at least 200 pM, particularly of at least 100 pM, particularly of at least 50 pM and/or

(d) an association rate constant of 10^4 $M^{-1}s^{-1}$ or greater, particularly of between 3 - 5 x 10^4 $M^{-1}s^{-1}$ or greater, particularly of 10^5 $M^{-1}s^{-1}$ or greater; particularly of 0.5 – 9 x 10^5 $M^{-1}s^{-1}$ or

greater; particularly of 10^6 $M^{-1}s^{-1}$ or greater, particularly of 1 – 4 x 10^6 $M^{-1}s^{-1}$ or greater, particularly of 10^7 $M^{-1}s^{-1}$ or greater.

In certain embodiments, the present disclosure~~invention~~ relates to chimeric or humanized antibodies according to the disclosure~~invention~~ as described in the various embodiments, which antibodies recognize and specifically bind to a phospho-epitope on a mammalian, particularly on the

human Tau protein or on a fragment thereof, particularly to a pathological protein tau conformer, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said antibodies have a high binding affinity with a dissociation constant of at least 100 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 80 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 70 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 10 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 200 pM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 100 pM and an association rate constant of 10^6 $M^{-1}s^{-1}$ or greater.

In various embodiments of the disclosure~~invention~~, the chimeric or humanized antibodies according to the disclosure~~invention~~ as described in the various embodiments specifically recognize and bind to a phospho-epitope on a mammalian, particularly on the human Tau protein, particularly a microtubule-associated protein tau, particularly an aggregated microtubule-associated and hyperphosphorylated protein tau such as that present in paired helical filaments (PHF), which are the predominant structures in neurofibrillary tangles, neuropil threads and dystrophic neurites, but, in one embodiment, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes.

In a specific embodiment of the disclosure~~invention~~, the human tau protein is the human Tau protein as shown in SEQ ID NO: 19.

The chimeric or humanized antibodies according to any one of the preceding embodiments can thus be used for reducing the levels of total soluble tau protein, particularly of soluble phosphorylated tau protein, in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human containing increased levels of soluble tau protein and/or soluble phosphorylated tau protein.

The chimeric or humanized antibodies according to any one of the preceding embodiments can also be used for reducing the levels of paired helical filaments containing hyperphosphorylated tau protein (pTau PHF) in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human containing increased levels of said pTau paired helical filaments (pTau PHF).

Reduction of the level of total soluble tau protein and/or soluble phosphorylated tau protein and/or pTau paired helical filaments (pTau PHF) in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human containing increased levels of said tau protein variants, which contribute to tau-protein-associated diseases, disorders or conditions in said

mammal or human, may lead to an improvement and/or alleviation of the symptoms associated with such tau-protein-associated diseases, disorders or conditions.

The chimeric or humanized antibodies according to any one of the preceding embodiments can therefore be used in therapy, particularly in human therapy, for slowing or halting the progression of a tau-protein-associated disease, disorder or condition.

The chimeric or humanized antibodies according to any one of the preceding embodiments can further be used in therapy, particularly in human therapy, for improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc.

In one embodiment, the disclosure~~invention~~ relates to the chimeric or humanized antibodies according to any one of the preceding embodiments for use in therapy, particularly for use in the prevention or treatment of tauopathies, a group of tau-protein-associated diseases and disorders, or for alleviating the symptoms associated with tauopathies.

In one embodiment, the disclosure~~invention~~ relates to the chimeric or humanized antibodies according to any one of the preceding embodiments for retaining or increasing cognitive memory capacity in a mammal suffering from a tauopathy.

Binding of the peptides or antibodies according to the preceding embodiments to tau tangles and pTau on brains may be determined by applying protein immuno-reactivity testing of selected brain sections and by Western blotting of brain homogenates, respectively, as described in the Examples.

In one aspect, there is provided a pharmaceutical composition comprising the chimeric or humanized antibody as described herein, or a functional fragment thereof, together with a pharmaceutically acceptable carrier or excipient.

In another embodiment, the present disclosure~~invention~~ provides a pharmaceutical composition comprising a chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, according to any one of the preceding embodiments, or a combination thereof, in a therapeutically effective amount, optionally together with a pharmaceutically acceptable carrier.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in reducing the levels of total soluble tau protein, particularly of soluble phosphorylated tau protein, in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a

human containing increased levels of soluble tau protein and/or soluble phosphorylated tau protein.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in reducing the levels of paired helical filaments containing hyperphosphorylated tau protein (pTau PHF) in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human containing increased levels of said pTau paired helical filaments (pTau PHF).

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in therapy.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in the prevention or treatment of tauopathies, a group of tau-protein-associated diseases and disorders, or for alleviating the symptoms associated with tauopathies.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in retaining or increasing cognitive memory capacity in a mammal suffering from a tauopathy.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in the prevention or treatment of diseases and disorders which are caused by or associated with the formation of neurofibrillary lesions.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in the prevention or treatment of neurodegenerative diseases or disorders.

In one aspect, there is provided the chimeric or humanized antibody as described herein, or a functional fragment thereof, or the composition as described herein, for use in the prevention or treatment of Alzheimer's Disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, and prion protein cerebral amyloid angiopathy, traumatic brain injury and further diseases or disorders which do not show a distinct amyloid pathology including, but not limited to, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease, type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, Myotonic dystrophy.

In one embodiment, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof, is used in therapy, particularly in human therapy for the treatment or alleviation of the symptoms of tau-protein-associated diseases or disorders including neurodegenerative disorders such as tauopathies.

The chimeric or humanized antibodies and/or pharmaceutical compositions according to any one of the preceding embodiments may thus be used for slowing or halting the progression of a tau-protein-associated disease, disorder or condition, upon administration of said

antibodies and/or pharmaceutical compositions to an animal, particularly a mammal, particularly a human, suffering from such a disease or condition.

The chimeric or humanized antibodies and/or pharmaceutical compositions according to any one of the preceding embodiments may further be used for improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc, upon administration of said antibodies and/or pharmaceutical compositions to an animal, particularly a mammal, particularly a human, suffering from such a disease or condition.

In one embodiment, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof, is used in the prevention or treatment of diseases and disorders which are caused by or associated with the formation of neurofibrillary lesions, the predominant brain pathology in tauopathy comprising a heterogeneous group of neurodegenerative diseases or disorders including diseases or disorders which show co-existence of tau and amyloid pathologies including, but not limited to, Alzheimer's Disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, and prion protein cerebral amyloid angiopathy, traumatic brain injury and further diseases or disorders which do not show a distinct amyloid pathology including, but not limited to, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease, type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, Myotonic dystrophy.

In one embodiment, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof, is used in the treatment of Alzheimer's Disease.

In one aspect, there is provided the use of the chimeric or humanized antibody as described herein, or a functional fragment thereof, or a polynucleotide as described herein, or a pharmaceutical composition as described herein, or a combination thereof, in the manufacture of a medicament for modulating soluble and/or insoluble Tau levels, particularly in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human.

In one embodiment of the disclosure~~invention~~, a method is provided for modulating soluble and/or insoluble Tau levels, particularly in the brain, particularly in the brain cortex and/or hippocampus, of an animal, particularly a mammal or a human, comprising administering to said animal, particularly to said mammal or human, the chimeric or humanized antibody or a

functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one ~~aspect~~embodiment, modulation relates to reducing the levels of soluble tau protein, particularly of soluble phosphorylated tau protein, in the brain, particularly in the brain cortex and/or hippocampus, of an animal, particularly a mammal or a human containing increased levels of soluble tau protein and/or soluble phosphorylated tau protein.

In one embodiment of the ~~invention~~disclosure, a method is provided for reducing the levels of insoluble tau protein, particularly of paired helical filaments containing hyperphosphorylated tau protein (pTau PHF) in the brain, particularly in the brain cortex and/or hippocampus, of an animal, particularly a mammal or a human, containing increased levels of insoluble tau protein, particularly of pTau paired helical filaments (pTau PHF) comprising administering to said animal, particularly to said mammal or human, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one aspect, there is provided the use of the chimeric or humanized antibody as described herein, or a functional fragment thereof, or a polynucleotide as described herein, or a pharmaceutical composition as described herein, or a combination thereof in the manufacture of a medicament for slowing or halting the progression of a tau-protein-associated disease, disorder or condition in a mammal or human.

In one embodiment, the present ~~invention~~ disclosure relates to a method for slowing or halting the progression of a tau-protein-associated disease, disorder or condition in an animal, particularly a mammal or human comprising administering to said animal, particularly said mammal or human, suffering from such a disease or condition, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one aspect, there is provided the use of the chimeric or humanized antibody as described herein, or a functional fragment thereof, or a polynucleotide as described herein, or a pharmaceutical composition as described herein, or a combination thereof, in the manufacture of a medicament for improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc., in a mammal or a human.

In one embodiment, the present ~~invention~~ disclosure relates to a method for improving or alleviating the

symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc., in an animal, particularly a mammal or a human, comprising administering to said animal, particularly to said mammal or human, suffering from such a disease or condition, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one embodiment, the present disclosure~~invention~~ relates to a method for retaining or increasing cognitive memory capacity in a mammal suffering from a tauopathy.

In still another embodiment of the disclosure~~invention~~, a method is provided for the treatment of a tau-protein-associated disease or disorder including a neurodegenerative disease or disorder such as a tauopathy comprising administering to an animal, particularly to a mammal, but especially to human, suffering from such a disease or disorder, the chimeric or humanized

antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one embodiment of the disclosure~~invention~~, a method is provided for the treatment of diseases and disorders which are caused by or associated with the formation of neurofibrillary lesions, the predominant brain pathology in tauopathy comprising a heterogeneous group of neurodegenerative diseases or disorders including diseases or disorders which show co-existence of tau and amyloid pathologies including, but not limited to, Alzheimer's Disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, and prion protein cerebral amyloid angiopathy, traumatic brain injury and further diseases or disorders which do not show a distinct amyloid pathology including, but not limited to, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease, type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis Tangle only dementia, Postencephalitic Parkinsonism, Myotonic dystrophy, which method comprises administering to an animal, particularly to a mammal, but especially to human, suffering from such a disease or disorder, the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, a pharmaceutical composition according to any one of the preceding embodiments, or a combination thereof.

In another embodiment of the disclosure~~invention~~, a method is provided for inducing a passive immune response in an animal, particularly a mammal or a human, suffering from a neurodegenerative disorder such as tauopathy by administering to said animal or human the chimeric or humanized antibody or a functional fragment thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding embodiments, or a combination thereof.

In one aspect, a method of diagnosing a tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of a chimeric or humanized antibody as described herein, or a functional fragment thereof, to an epitope of the tau protein in a sample from said patient which includes the steps of

a. bringing the sample suspected to contain the tau protein into contact with the chimeric or humanized antibody as described herein or with a functional fragment thereof, wherein said antibody or fragment thereof binds an epitope of the tau protein;

b. allowing said said antibody or a functional fragment thereof, to bind to the tau protein to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau protein in the sample.

In still another embodiment of the disclosure ~~invention~~, a method of diagnosing a tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, to an epitope of the tau protein in a sample or *in situ* which includes the steps of

a. bringing the sample or a specific body part or body area suspected to contain the tau protein into contact with the chimeric or humanized antibody or a functional fragment

thereof to any one of the preceding embodiments, wherein said antibody or fragment thereof binds an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau protein to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau protein in the sample or specific body part or area.

In one aspect, a method for diagnosing a predisposition to tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of a chimeric or humanized antibody as described herein, or a functional fragment thereof, to an epitope of the tau protein in a sample from said patient, which includes the steps of

a. bringing the sample suspected to contain the tau antigen into contact with the chimeric or humanized antibody as described herein, or a functional fragment thereof, which antibody or fragment thereof binds an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample;

e. comparing the amount of said immunological complex to a normal control value;

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient is suffering from or is at risk of developing an tau- protein-associated disease or condition.

In still another embodiment of the disclosure~~invention~~, a method for diagnosing a predisposition to tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, to an epitope of the tau protein in a sample or *in situ,* which includes the steps of

a. bringing the sample or a specific body part or body area suspected to contain the tau antigen into contact with the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, which antibody or fragment thereof binds an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample or specific body part or area;

e. comparing the amount of said immunological complex to a normal control value;

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient is suffering from or is at risk of developing an tau- protein-associated disease or condition.

In one aspect, there is provided a method for monitoring minimal residual disease in a patient following treatment with the chimeric or humanized antibody as described herein, or a functional fragment thereof, wherein said method comprises:

a. bringing a sample from said patient suspected to contain the tau antigen into contact with the chimeric or humanized antibody as described herein, or a functional fragment thereof, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample,

e. comparing the amount of said immunological complex to a normal control value,

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient still suffers from a minimal residual disease.

In one embodiment of the disclosure~~invention~~, a method is provided for monitoring minimal residual disease in a patient following treatment with the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, wherein said method comprises:

a. bringing the sample or a specific body part or body area suspected to contain the tau antigen into contact with the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample or specific body part or area,

e. comparing the amount of said immunological complex to a normal control value,

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient still suffers from a minimal residual disease.

In one aspect, there is provided a method for predicting responsiveness of a patient being treated with the chimeric or humanized antibody as described herein, or a functional fragment thereof, comprising

a. bringing a sample from said patient suspected to contain the tau antigen into contact with the chimeric or humanized antibody as described herein, or a functional fragment thereof, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample,

e. comparing the amount of said immunological complex before and after onset of the treatment,

wherein a decrease in the amount of said aggregate indicates that said patient has a high potential of being responsive to the treatment.

In one embodiment, a method is provided for predicting responsiveness of a patient being treated with the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, comprising

a. bringing the sample or a specific body part or body area suspected to contain the tau antigen into contact with the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample or specific body part or area,

e. comparing the amount of said immunological complex before and after onset of the treatment,

wherein a decrease in the amount of said aggregate indicates that said patient has a high potential of being responsive to the treatment.

In one aspect, there is provided a test kit for detection and diagnosis of tau-protein-associated diseases, disorders or conditions comprising the chimeric or humanized antibody as described herein, or a functional fragment thereof.

In another embodiment, the disclosure~~invention~~ relates to a test kit for detection and diagnosis of tau-protein-associated diseases, disorders or conditions comprising the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments.

In one embodiment said test kit comprises a container holding one or more the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments, and instructions for using the antibodies for the purpose of binding to tau antigen to form an immunological complex and detecting the formation of the immunological

complex such that presence or absence of the immunological complex correlates with presence or absence of tau antigen.

In one aspect, there is provided a host cell comprising a vector as described herein.

In another embodiment, the disclosure~~invention~~ relates to a cell line, particularly a bacterial cell line, particularly an *E. coli* cell line, producing the chimeric or humanized antibody or a functional fragment thereof according to any one of the preceding embodiments,.

In one embodiment, the disclosure~~invention~~ relates to a cell line, which is *Escherichia coli* 2B6A10C11-H deposited on March 6, 2012 as DSM 25743.

In one embodiment, the disclosure~~invention~~ relates to a cell line, which is *Escherichia coli* 2B6A10C11-L deposited on March 6, 2012 as DSM 25744.

In one embodiment, the disclosure~~invention~~ relates to a cell line, which is *Escherichia coli* 3A8A12G7-H deposited on March 6, 2012 as DSM 25745.

In one embodiment, the disclosure ~~invention~~ relates to a cell line, which is *Escherichia coli* 3A8A12G7-L deposited on March 6, 2012 as DSM 25746.

In one aspect, there is provided a process for producing the humanized antibody as described herein, or a functional fragment thereof comprising culturing the host cell as described herein under conditions suitable for expression of the antibody or fragment, and recovering the antibody or fragment.

Brief Description of Figures and Sequences

FIGURES

Figure 1 shows binding of humanized anti-pTau antibodies hACI-36-2B6-Ab1 and hACI-36-3A8-Ab1 to pTau vaccine peptide (T4.5), without binding to the non-phosphorylated version of the same peptide (T4.6).

Figure 2 shows Tau tangles in the brain of 20 month old Tau transgenic (biGT) mice stained with humanized anti-pTau antibody hACI-36-2B6-Ab1. Staining is shown for Tau tangles in cortex (A) and hippocampus (B), with staining of neuropil threads visible in the hippocampus (B).

Figure 3 shows Tau tangles in the brain of 20 month old Tau transgenic (biGT) mice stained with humanized anti-pTau antibody hACI-36-3A8-Ab1 stains. Staining is shown for Tau tangles in cortex (A) and hippocampus (B), with staining of neuropil threads visible in the hippocampus (B).

Figure 4 shows Light chain of hACI-36-2B6-Ab1

Figure 5 shows Light chain of hACI-36-3A8-Ab1

Figure 6 shows Heavy chain of hACI-36-2B6-Ab1 and hACI-36-3A8-Ab1

SEQUENCES

38. The chimeric or humanized antibody of any one of claims 1-19, or a functional fragment thereof, or the composition of claim 31, for use in the prevention or treatment of diseases and disorders which are caused by or associated with the formation of neurofibrillary lesions.

39. The chimeric or humanized antibody of any one of claims 1-19, or a functional fragment thereof, or the composition of claim 31, for use in the prevention or treatment of neurodegenerative diseases or disorders.

40. The chimeric or humanized antibody of any one of claims 1-19, or a functional fragment thereof, or the composition of claim 31, for use in the prevention or treatment of Alzheimer's Disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, and prion protein cerebral amyloid angiopathy, traumatic brain injury and further diseases or disorders which do not show a distinct amyloid pathology including, but not limited to, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease, type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, Myotonic dystrophy.

41. ~~A method for modulating soluble and/or insoluble Tau levels, particularly in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human, comprising administering to said mammal or human,~~ Use of the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, or a polynucleotide according to any one of claims 20-28, or a pharmaceutical composition of claim 31, or a combination thereof, in the manufacture of a medicament for modulating soluble and/or insoluble Tau levels, particularly in the brain, particularly in the brain cortex and/or hippocampus, of a mammal or a human.

42. ~~A method for slowing or halting the progression of a tau-protein-associated disease, disorder or condition in a mammal or human comprising administering to said mammal or human, suffering from such a disease or condition,~~ Use of the chimeric or humanized antibody according to any one of claims 11-19, or a functional fragment thereof, or a polynucleotide according to any one of claims 20-28, or a

pharmaceutical composition of claim 31, or a combination thereof in the manufacture of a medicament for slowing or halting the progression of a tau-protein-associated disease, disorder or condition in a mammal or human.

43. ~~A method for improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss~~

~~of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc., in a mammal or a human, comprising administering to said mammal or human, suffering from such a disease or condition,~~ Use of the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, or a polynucleotide according to any one of claims 20-28, or a pharmaceutical composition of claim 31, or a combination thereof, in the manufacture of a medicament for improving or alleviating the symptoms associated with tau-protein-associated diseases, disorders or conditions such as, for example, impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, special navigation, etc., in a mammal or a human.

44. A method of diagnosing a tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, to an epitope of the tau protein in a sample from said patient ~~or *in situ*~~ which includes the steps of

    a. bringing the sample ~~or a specific body part or body area~~ suspected to contain the tau protein into contact with the chimeric or humanized antibody according to any one of claims 1-19 or with a functional fragment thereof, wherein said antibody or fragment thereof binds an epitope of the tau protein;

    b. allowing said said antibody or a functional fragment thereof, to bind to the tau protein to form an immunological complex;

    c. detecting the formation of the immunological complex; and

    d. correlating the presence or absence of the immunological complex with the presence or absence of tau protein in the sample ~~or specific body part or area~~.

45. A method for diagnosing a predisposition to tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, to an epitope of the tau protein in a sample from said patient ~~or *in situ*~~, which includes the steps of

    a. bringing the sample ~~or a specific body part or body area~~ suspected to contain the tau antigen into contact with the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, which antibody or fragment thereof binds an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample ~~or specific body part or area~~;

e. comparing the amount of said immunological complex to a normal control value;

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient is suffering from or is at risk of developing an tau-protein-associated disease or condition.

46. A method for monitoring minimal residual disease in a patient following treatment with the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, wherein said method comprises:

a. bringing ~~the~~ a sample from said patient ~~or a specific body part or body area~~ suspected to contain the tau antigen into contact with the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample ~~or specific body part or area~~,

e. comparing the amount of said immunological complex to a normal control value,

wherein an increase in the amount of said aggregate compared to a normal control value indicates that said patient still suffers from a minimal residual disease.

47. A method for predicting responsiveness of a patient being treated with the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, comprising

a. bringing ~~the~~ a sample from said patient ~~or a specific body part or body area~~ suspected to contain the tau antigen into contact with the chimeric or humanized antibody according to any one of claims 1-19, or a functional fragment thereof, which antibody or fragment thereof binds to an epitope of the tau protein;

b. allowing said antibody, or a functional fragment thereof, to bind to the tau antigen to form an immunological complex;

c. detecting the formation of the immunological complex; and

d. correlating the presence or absence of the immunological complex with the presence or absence of tau antigen in the sample ~~or specific body part or area~~,