- inhibitors of the kinases that are thought to increase the phosphorylation of tau to pathological levels
- compounds that block the cytoplasmic aggregation of hyper-phosphorylated protein tau.

These approaches suffer various draw-backs of specificity and efficacy, a problem they share with attempts to modify the metabolism of APP and amyloid, all emphasizing the importance of a continuous search for additional treatment options, including immunotherapy against tau.

Practically no efforts have been devoted to define - let alone target - the pathological tau conformers *in vivo*. In the Aβ42 phase II clinical trial, the tangle pathology did not appear to be well considered nor analyzed in much depth (Nicoll et al., 2003; Masliah et al., 2005). On the other hand, experimental immunotherapy targeting amyloid in a preclinical mouse model with combined AD-like pathology demonstrated also an effect on tau pathology although tau aggregates persisted (Oddo et al., 2004).

Some doubts have been cast on the feasibility of approaching intra-cellular protein tau by immunotherapy. These have been countered by the most recent experimental study in a tauopathy mouse model (Asuni et al., 2007). They showed reduction in tangle pathology and functional improvements by vaccination with a protein tau derived phospho-peptide. These data corroborate previous reports of immunotherapy targeting α-synuclein in Parkinson's Disease (PD) and Lewy body disease models (Masliah et al., 2005, 2011) and of superoxide dismutase in an amyotrophic lateral sclerosis (ALS) model (Urushitiani et al., 2007). These diseases are examples whereinintra-cellular proteins lead to synaptic defects and neurodegeneration by as yet not fully understood mechanisms. On the other hand, full-length recombinant protein tau produced in and isolated from bacteria appears not suitable as vaccine, although the adjuvants used, i.e. complete Freunds and pertussis toxin, could have contributed to the negative outcome of that study (Rosenmann et al., 2006).

There is an unmet need for passive and/or active immunotherapies that work to counteract the pathological protein conformers that are known - or presumed - to cause neurodegenerative disorders, such as amyloid pathology in AD caused, for example, by intra-neuronal aggregates of hyper-phosphorylated protein tau that are as typical for AD as amyloid.

SUMMARY

In one aspect, the present invention refers to an antibody or functional part thereof that specifically binds to a phospho-epitope on a mammalian Tau protein, therein said antibody or functional part thereof has a high binding affinity to soluble and insoluble Tau protein, and

modulates soluble and insoluble Tau levels, wherein the phospho-epitope is amino acids 405-411 or 405-412 having a phosphorylated Ser at position 409 (pS409), and wherein the antibody or functional part thereof binds the mammalian Tau protein with a dissociation constant of less than 10 nM as measured by surface plasmon resonance, wherein the antibody or functional part thereof does not bind to the corresponding unphosphorylated epitope.

In another aspect, the present invention refers to a pharmaceutical composition comprising the antibody or functional part thereof as disclosed herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present invention refers to a cell line that produces the antibody or functional part thereof as disclosed herein.

In a further aspect, the present invention refers to a polynucleotide encoding the antibody or functional part thereof as disclosed herein.

In another aspect, the present invention refers to a method of diagnosing a tau-protein-associated disease, disorder or condition, or of diagnosing a predisposition to a tau-protein-associated disease, disorder or condition, in a patient comprising detecting the immunospecific binding of an antibody or functional part thereof to an epitope of the tau protein in a sample which includes the steps of

a) bringing the sample suspected to contain the tau protein into contact with an antibody or functional part thereof as disclosed herein;

b) allowing the antibody or functional part 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;

wherein diagnosing a predisposition to a tau-protein-associated disease, disorder or condition further includes the step of:

e) comparing the amount of said immunological complex to a normal control value, wherein an increase in the amount of said immunological complex 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.

This unmet need could be met within the scope of the present invention by providing binding proteins recognizing and binding to major pathological phospho-epitopes of the tau protein. In particular, the present invention provides specific antibodies against linear and

conformational, simple and 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.

Accordingly, the present ~~invention~~disclosure relates in one ~~embodiment~~example to a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, which binding peptide or protein or 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 phospho-epitope on aggregated Tau protein, particularly to a pathological protein tau conformer, but, in one ~~embodiment~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or 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 dissociation constant of 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.

In a second ~~embodiment~~example, the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or antibody has 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 2 – 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 a third ~~embodiment~~example, the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or antibody has a high binding affinity with a dissociation

constant of at least 4 nM and an association rate constant of 10^5 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 3 nM and an association rate constant of 10^6 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 2 nM and an association rate constant of 10^4 $M^{-1}s^{-1}$ or greater, particularly a dissociation constant of at least 1 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.

One ~~embodiment~~example (4) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody binds to an epitope on a mammalian, particularly on the human Tau protein as shown in SEQ ID NO: 67, selected from the group consisting of Tau aa 15-20 comprising a phosphorylated Tyr at position 18 (Y18), Tau aa 405-412 comprising a phosphorylated Ser at position 409 (pS409), Tau aa 405-411 comprising a phosphorylated Ser at position 409 (pS409); and Tau aa 208-218 comprising a phosphorylated Thr at position 212 (pT212) and a phosphorylated Ser at position 214 (pS214).

One ~~embodiment~~example (5) relates to the binding peptide or antibody of any of the preceding ~~embodiments~~examples, wherein said peptide binds to an epitope on a mammalian, particularly on the human Tau protein, but especially the human Tau protein as shown in SEQ ID NO: 67, comprising Tau aa 15-20 with a phosphorylated Tyr at position 18 (Y18).

One ~~embodiment~~example (6) relates to the binding peptide or antibody of any o the preceding ~~embodiments~~examples, wherein said peptide binds to an epitope on a mammalian, particularly on the human Tau protein, but especially the human Tau protein as shown in SEQ ID NO: 67, comprising Tau aa 405-412 with a phosphorylated Ser at position 409 (pS409).

One ~~embodiment~~example (7) relates to the binding peptide or antibody of any of the preceding ~~embodiments~~examples, wherein said peptide binds to an epitope on a mammalian, particularly on the human Tau protein, but especially the human Tau protein as shown in SEQ ID NO: 67, comprising Tau aa 405-411 with a phosphorylated Ser at position 409 (pS409).

One ~~embodiment~~example (8) relates to the binding peptide or antibody of any of the preceding ~~embodiments~~examples, wherein said peptide binds to an epitope on a mammalian, particularly on the human Tau protein, but especially the human Tau protein as shown in SEQ ID NO: 67, comprising Tau aa 208-218 with a phosphorylated Thr at position 212 (pT212) and a phosphorylated Ser at position 214 (pS214).

In another ~~embodiment~~example (9), the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains, particularly in sequence, a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29, 32, 73, 81, 93, 101, 106, or an amino acid sequence at least 70%, particularly 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: 22, 25, 30, 33, 74, 82, 94, 102, 107, or an amino acid sequence 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: 23, 26, 31, 34, 75, 83, 95, 103, 108, or an amino acid sequence at least 60%, particularly at least 70%, particularly 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 which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, 70, 78, 89, 98, or an amino acid sequence 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: 13, 16, 19, 71, 79, 90, 99, 115, or an amino acid sequence 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: 14, 17, 20, 72, 80, 91, 100, 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.

One ~~embodiment~~example (10) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: SEQ ID NO: 21, 24, 27, 28, 29, 32, 73, 81, or an amino acid sequence at least 85% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, 74, 82, or an amino acid sequence at least 95% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, 75, 83, or an amino acid sequence at least 80% identical thereto; and/or an antibody domain which contains a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, 70, 78, or an amino acid sequence at least 95% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, 71, 79, or an amino acid sequence at least 85% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, 72, 80, or an amino acid sequence at least 85% identical thereto.

One ~~embodiment~~example (11) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29, 32, 73, 81, or an amino acid sequence at least 90% identical thereto; a CDR2 with the

amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, 74, 82, or an amino acid sequence at least 95% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, 75, 83, or an amino acid sequence at least 90% identical thereto; and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, 70, 78, or an amino acid sequence at least 95% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, 71, 79, or an amino acid sequence at least 95% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, 72, 80, or an amino acid sequence at least 90% identical thereto

One ~~embodiment~~example (12) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain (antibody domain) which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29, 32, 73, 81, or an amino acid sequence at least 90% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, 74, 82, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, 75, 83, or an amino acid sequence at least 90% identical thereto; and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, 70, 78, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, 71, 79, or an amino acid sequence at least 95% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, 72, 80, or an amino acid sequence at least 90% identical thereto.

One ~~embodiment~~example (13) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in

sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29, 32, or an amino acid sequence at least 98% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, or an amino acid sequence at least 95% identical thereto; and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, or an amino acid sequence at least 95% identical thereto and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, or an amino acid sequence at least 90% identical thereto.

One ~~embodiment~~example (14) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29, 32, or an amino acid sequence at least 98% identical thereto; a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, or an amino acid sequence at least 98% identical thereto; and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, or an amino acid sequence at least 98% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, or an amino acid sequence at least 90% identical thereto.

One ~~embodiment~~example (15) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, 24, 27, 28, 29,

32, 73, 81, 93, 101, or 106, a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, 25, 30, 33, 74, 82, 94, 102, or 107, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, 26, 31, 34, 75, 83, 95, 103, or 108, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, 15, 18, 70, 78, 89, or 98, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, 16, 19, 71, 79, 90, 99, or 115, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, 17, 20, 72, 80, 91, or 100.

One ~~embodiment~~example (16) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 21, or an amino acid sequence at least 76%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 22, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 23, or an amino acid sequence at least 66%, particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, or an amino acid sequence at least 88%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, or an amino acid sequence at least 66%, particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto.

One ~~embodiment~~example (17) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a

functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, *which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain *which contains in sequence* a CDR1 with the amino acid sequence shown in SEQ ID NO: 24, or SEQ ID NO: 27, or SEQ ID NO: 28, or an amino acid sequence at least 88%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 25, or an amino acid sequence at least 95%, particularly 98%, particularly 99% and a CDR3 with the amino acid sequence shown in SEQ ID NO: 26, or an amino acid sequence at least 66%, particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 12, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 13, or an amino acid sequence at least 88%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 14, or an amino acid sequence at least 66% , particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto.

One ~~embodiment~~example (18) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (15) comprising a first binding domain, wherein the CDR1 has the amino acid sequence shown in SEQ ID NO: 27, or an amino acid sequence at least 88% identical thereto.

One ~~embodiment~~example (19) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (15), comprising a first binding domain wherein the CDR1 has the amino acid sequence shown in SEQ ID NO: 28, or an amino acid sequence at least 88% identical thereto.

One ~~embodiment~~example (20) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 29, a CDR2 with the amino acid sequence shown in SEQ ID NO: 30, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 31, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 15, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 16, or an amino acid sequence at least 94%, 95%, 96%, 97%, 98%, or 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 17, or an amino acid sequence at least 36%, particularly at least 40%, particularly at least 50%, particularly at least 60%, particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto.

One ~~embodiment~~example (21) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 32, a CDR2 with the amino acid sequence shown in SEQ ID NO: 33, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 34, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 18, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, a CDR2

with the amino acid sequence shown in SEQ ID NO: 19, or an amino acid sequence at least 95%, 96%, 97%, 98% or 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 20, or an amino acid sequence at least 63%, particularly at least 70%, particularly at least 75%, particularly at least 80%, particularly at least 85%, particularly at least 90%, particularly at least 95%, particularly at least 98%, particularly at least 99% identical thereto.

One ~~embodiment~~example (22) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 73, a CDR2 with the amino acid sequence shown in SEQ ID NO: 74, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 75, or an amino acid sequence at least 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 which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 70, or an amino acid sequence at least 95%, particularly 98%, particularly 99% identical thereto, a CDR2 with the amino acid sequence shown in SEQ ID NO: 71, or an amino acid sequence at least 94%, 95%, 96%, 97%, 98%, or 99% identical thereto, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 72, or an amino acid sequence at least 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~~example (23) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does

not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 81, a CDR2 with the amino acid sequence shown in SEQ ID NO: 82, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 83, 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/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 78, a CDR2 with the amino acid sequence shown in SEQ ID NO: 79, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 80, or an amino acid sequence at least 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~~example (24) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 93, a CDR2 with the amino acid sequence shown in SEQ ID NO: 94, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 95, 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 to any one of the above CDRs and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 89, a CDR2 with the amino acid sequence shown in SEQ ID NO: 90, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 91, or an amino acid sequence at least 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 to any one of the above CDRs.

One ~~embodiment~~example (25) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 101, a CDR2 with the amino acid sequence shown in SEQ ID NO: 102, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 103, 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 to any one of the above CDRs and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 98, a CDR2 with the amino acid sequence shown in SEQ ID NO: 99, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 100, or an amino acid sequence at least 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 to any one of the above CDRs.

One ~~embodiment~~example (26) of the present ~~invention relates~~disclosure describes ~~to~~ a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 106, a CDR2 with the amino acid sequence shown in SEQ ID NO: 107, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 108, 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 to any one of the above CDRs and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence shown in SEQ ID NO: 89, a CDR2 with the amino acid sequence shown in SEQ ID NO: 115, and a CDR3 with the amino acid sequence shown in SEQ ID NO: 91, 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 to any one of the above CDRs.

In another ~~embodiment~~example (27), the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 6, 7, 8, 9, 10, 11, or an amino acid sequence at least 90% identical thereto, and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 1, 2, 3, 4, 5, or an amino acid sequence at least 85% identical thereto.

In one ~~embodiment~~example (28), the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 6, 7, 8, 9, 10, 11, or an amino acid sequence at least 90% identical thereto, and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 1, 2, 3, 4, 5, or an amino acid sequence at least 91% identical thereto.

One ~~embodiment~~example (29) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain (antibody domain) which contains the amino acid sequence shown in SEQ ID NO: 6, 7, 8, 9, 10, 11, or an amino acid sequence at least 95% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 1, 2, 3, 4, 5, or an amino acid sequence at least 91% identical thereto.

In another ~~embodiment~~example (30), the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes, wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 69, 77, 116/92, 97, 105, or an amino acid sequence 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 which contains the amino acid sequence shown in SEQ ID NO: 68, 76, 88, 96, 104, or an amino acid sequence at least 80%, particularly at least 85%, particularly at least 86%, particularly at least 87%, particularly at least 88%, particularly 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% identical thereto.

One ~~embodiment~~example (31) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes *wherein said binding peptide or antibody comprises a first binding domain which contains the* amino acid sequence shown in SEQ ID NO: 6 or SEQ ID NO: 7, or an amino acid sequence at least 90% and 94%, respectively, identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 1, or an amino acid sequence at least 91% identical thereto.

One ~~embodiment~~example (32) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly *a* monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, *does not bind to the corresponding unphosphorylated epitope and/or to* non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 8, or an amino acid sequence at least 95% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 2, or an amino acid sequence at least 90% identical thereto.

One ~~embodiment~~example (33) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, *does not bind to the corresponding unphosphorylated epitope and/or to* non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 9, or an amino acid sequence at least 95% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 3, or an amino acid sequence at least 90% identical thereto.

One ~~embodiment~~example (34) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does

not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 10, or an amino acid sequence at least 99% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 4, or an amino acid sequence at least 89% identical thereto.

One ~~embodiment~~example (35) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 11, or an amino acid sequence at least 98% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 5, or an amino acid sequence at least 87% identical thereto.

One ~~embodiment~~example (36) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 69, or an amino acid sequence at least 98% or 99% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 68, or an amino acid sequence at least 90%, 91%, 92% or 93% identical thereto.

One ~~embodiment~~example (37) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 77, or an amino acid sequence at least 93%, 94% or 95% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 76, or an amino acid sequence at least 88%, 89%, or 90% identical thereto.

One ~~embodiment~~example (38) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~example, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 116, 92, or 118, or an amino acid sequence at least 93%, 94% or 95% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 88, or an amino acid sequence at least 90%, 91%, 92% or 93% identical thereto.

One ~~embodiment~~example (39) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 97, or an amino acid sequence at least 99% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 96, or an amino acid sequence at least 86%, 87%, 88% or 90% identical thereto.

One ~~embodiment~~example (40) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a first binding domain which contains the amino acid sequence shown in SEQ ID NO: 105, or an amino acid sequence at least 98%, or 99% identical thereto; and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 104, or an amino acid sequence at least 88%, 89%, or 90% identical thereto.

In another ~~embodiment~~example (41), the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to embodiments (22) – (24), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 21-34 and said second binding domain contains the CDRs as shown in SEQ ID NOs: 12-20.

One ~~embodiment~~example (42) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to embodiment (31), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 21-23 and SEQ ID NOs: 24-26, respectively, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 12-14.

One ~~embodiment~~example (43) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (32), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 27, 25, 26 and said second binding domain contains the CDRs as shown in SEQ ID NOs: 12-14.

One ~~embodiment~~example (44) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (33), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 28, 25 and 26, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 12-14.

One ~~embodiment~~example (45) of the ~~present invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (34), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 29-31, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 15-17.

One ~~embodiment~~example (46) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (35), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 32-34, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 18-20.

One ~~embodiment~~example (47) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (27), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 73-75, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 70-72.

One embodimentexample (48) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (27), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 81-83, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 78-80.

One embodimentexample (49) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (27), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 101-103, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 98-100.

One ~~embodiment~~example (50) of the present ~~invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, according to ~~embodiment~~example (27), wherein said first binding domain contains the CDRs as shown in SEQ ID NOs: 89, 115, and 91, and said second binding domain contains the CDRs as shown in SEQ ID NOs: 106-108.

In still another ~~embodiment~~example (51), the ~~present invention relates to~~disclosure describes a binding peptide or protein or a functional part thereof, particularly to an antibody, particularly a monoclonal antibody or a functional part thereof, particularly a binding peptide or antibody of any of the preceding ~~embodiments~~examples, which binding peptide or 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes wherein said binding peptide or antibody comprises a

1. first binding domain which contains the amino acid sequence shown in SEQ ID NO: 105 and/or a second binding domain which contains the amino acid sequence shown in SEQ ID NO: 104.

In one ~~embodiment~~example (52) of the ~~invention~~disclosure, the binding peptide of any of the preceding embodiments is an antibody, particularly an antibody of the IgG2a, IgG2b or the IgG3 isotype, particularly a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody or a fully human antibody.

One ~~embodiment~~example (48) of the ~~invention~~disclosure relates to a polynucleotide encoding the binding peptide of any one of the preceding ~~embodiments~~examples.

In on ~~embodiment~~example (53), said polynucleotide comprises a nucleic acid molecule selected from the group consisting of

a. a nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence as depicted in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

b. a nucleic acid molecule comprising a nucleotide sequence that has at least 85% sequence identity to the sequence shown in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

c. a nucleic acid molecule comprising a nucleotide sequence that has at least 90% sequence identity to the sequence shown in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

d. a nucleic acid molecule comprising a nucleotide sequence that has at least 95% sequence identity to the sequence shown in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

e. a nucleic acid molecule comprising a nucleotide sequence that has at least 98% sequence identity to the sequence shown in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

f. a nucleic acid molecule comprising a nucleotide sequence that has at least 99% sequence identity to the sequence shown in SEQ ID NOs: 35-45, SEQ ID NOs: 84-87, SEQ ID NO: 109-112 and 117;

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

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

wherein said nucleic acid molecule as defined in any of a) – h) recognizes and specifically binds to a phospho-epitope on a mammalian, particularly on the human Tau protein or on a fragment thereof, particularly on the human Tau protein as shown in SEQ ID NO: 67, selected from the group consisting of Tau aa 15-20 comprising a phosphorylated Tyr at position 18 (Y18), Tau aa 405-412 comprising a phosphorylated Ser at position 409 (pS409), Tau aa 405-411 comprising a phosphorylated Ser at position 409 (pS409); and Tau aa 208-218 comprising a phosphorylated Thr at position 212 (pT212) and a phosphorylated Ser at position 214 (pS214), Tau aa 393-401, comprising a phosphorylated Ser at position 396 (pS396), Tau aa 396-401 comprising a phosphorylated Ser at position 396 (pS396), Tau aa 394-400 comprising a phosphorylated Ser at position 396 (pS396), Tau aa 402-406 comprising a phosphorylated Ser at position 404 (pS404), and Tau aa 393-400 comprising a phosphorylated Ser at position 396 (pS396), wherein, in one ~~embodiment~~example, said binding peptide has a high binding affinity with a dissociation constant of 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 has 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 6 – 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, but, in one ~~embodiment~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes.

In various ~~embodiments~~examples (54) of the ~~invention~~disclosure, a binding peptide is provided or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, according to any one of the preceding ~~embodiments~~examples, or a combination thereof, which is capable of specifically recognizing and binding 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~~example, does not bind to the corresponding unphosphorylated epitope and/or to non-related epitopes.

In a specific ~~embodiment~~example (55) of the ~~invention~~disclosure, the human tau protein is the human Tau protein as shown in SEQ ID NO: 67.

The binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples can thus be used (56) 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 binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples can also be used (57) 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 (58).

The binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples can therefore be used (59) in therapy, particularly in human therapy, for slowing or halting the progression of a tau-protein-associated disease, disorder or condition.

The binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples can further be used (60) 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~~example (61), the ~~invention~~disclosure relates to the binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples for use in therapy, particularly for use in the treatment of tauopathies, a group of tau-protein-associated diseases and disorders, or for alleviating the symptoms associated with tauopathies.

In one ~~embodiment~~example (62), the ~~invention~~disclosure relates to the binding peptides and antibodies according to any one of the preceding ~~embodiment~~examples for retaining or increasing cognitive memory capacity in a mammal suffering from a tauopathy.

In a specific ~~embodiment~~example (63) of the ~~invention~~disclosure, binding peptides and antibodies comprising at least one or all of the light chain CDRs of antibodies ACI-36-2B6-Ab1, ACI-36-2B6-Ab2, ACI-36-3A8-Ab1, and ACI-36-3A8-Ab2 as given in SEQ ID NOs: 25, 26, 27, and SEQ ID NOs: 21, 22, 23, respectively, and/or at least one or all of the heavy chain CDRs of antibodies ACI-36-2B6-Ab1, ACI-36-2B6-Ab2, ACI-36-3A8-Ab1, and ACI-36-3A8-Ab2 as given in SEQ ID NOs: 12, 13, 14, are 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, learning, special navigation, etc.

In another specific ~~embodiment~~example (64) of the ~~invention~~disclosure, the antibodies comprising the light chain of antibodies ACI-36-2B6-Ab1, ACI-36-2B6-Ab2, ACI-36-3A8-Ab1, and ACI-36-3A8-Ab2 as given in SEQ ID NO: 8 and SEQ ID NOs: 6, 7, respectively, and/or the heavy chain of antibodies ACI-36-2B6-Ab1, ACI-36-2B6-Ab12, ACI-36-3A8-Ab1, and ACI-36-3A8-Ab2 as given in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, are 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, learning, special navigation, etc.

In another specific ~~embodiment~~example (65) of the ~~invention~~disclosure, binding peptides and antibodies comprising at least one or all of the light chain CDRs of antibodies ACI-33-6C10-Ab1 and ACI-33-6C10-Ab2 as given in SEQ ID NOs: 29, 30, 31, and/or at least one or all of the heavy chain CDRs of antibodies ACI-33-6C10-Ab1 and ACI-33-6C10-Ab2 as given in SEQ ID NOs: 15, 16, 17, are 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, learning, special navigation, etc.

In another specific ~~embodiment~~example (66) of the ~~invention~~disclosure, binding peptides and antibodies comprising at least one or all of the light chain CDRs of antibodies ACI-41-7C2-Ab1 and ACI-41-7C2-Ab2 as given in SEQ ID NOs: 32, 33, 34, and/or at least one or all of the heavy chain CDRs of antibodies ACI-41-7C2-Ab1 and ACI-41-7C2-Ab2 as given in SEQ ID NOs: 18, 19, 20, are 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, learning, special navigation, etc.

In another specific ~~embodiment~~example (67) of the ~~invention~~disclosure, binding peptides and antibodies comprising at least one or all of the light chain CDRs of antibodies ACI-35-2A1-Ab1; ACI-35-2A1-Ab2; ACI-35-4A6-Ab1; ACI-35-4A6-Ab2; ACI-35-1D2-Ab1; ACI-35-2G5-Ab1; as given in SEQ ID NOs: 73-75, 81-83, 93-95, 101-103, 106-108 and/or at least one or all of the heavy chain CDRs of antibodies ACI-35-2A1-Ab1; ACI-35-2A1-Ab2; ACI-35-4A6-Ab1; ACI-35-4A6-Ab2; ACI-35-1D2-Ab1; ACI-35-2G5-Ab1; as given in SEQ ID NOs: 70-72, 78-80, 89-91, 98-100, are 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, learning, special navigation, etc.*

In another specific ~~embodiment~~example (68) of the ~~invention~~disclosure, binding peptides and antibodies comprising at least one or all of the light chain CDRs of antibodies ACI-35-2G5-Ab2; ACI-35-2G5-Ab3 as given in SEQ ID NOs: 106-108 and/or at least one or all of the heavy chain CDRs of antibodies ACI-35-2G5-Ab2; ACI-35-2G5-Ab3; as given in SEQ ID NOs: 89, 115 and 91, are 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, learning, special navigation, etc.

Binding of the peptides or antibodies according to the preceding ~~embodiment~~examples 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 another ~~embodiment~~example (69), the present ~~invention~~disclosure ~~describes~~provides a pharmaceutical composition comprising a binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, according to any one of the preceding ~~embodiment~~examples, or a combination thereof, in a therapeutically effective amount together with a pharmaceutically acceptable carrier.

In one ~~embodiment~~example (70), the binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, 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 binding peptides, antibodies and/or pharmaceutical compositions according to any one of the preceding ~~embodiment~~examples may thus be used (71) for slowing or halting the progression of a tau-protein-associated disease, disorder or condition, upon administration of said binding peptides, antibodies and/or pharmaceutical compositions to an animal, particularly a mammal, particularly a human, suffering from such a disease or condition.

The binding peptides, antibodies and/or pharmaceutical compositions according to any one of the preceding ~~embodiment~~examples may further be used (72) 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 binding peptides, antibodies and/or pharmaceutical compositions to an animal, particularly a mammal, particularly a human, suffering from such a disease or condition.

In one ~~embodiment~~example (73), the binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof, is used in 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 heterogenous group of neurodegenerative diseases or disorders including diseases or disorders which show co-exsistance 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~~example (74), the binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof, is used in the treatment of Alzheimer's Disease.

In one ~~embodiment~~example (75) 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof.

In one example~~aspect~~, 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~~example (76) of the disclosure~~invention~~, 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof.

In one ~~embodiment~~example (77), the present disclosure describes~~invention 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof.

In one ~~embodiment~~example (78), the present disclosure describes~~invention 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 binding peptide or a functional part thereof, particularly an antibody, particularly a

monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding examplembodiments, or a combination thereof.

In one examplembodiment (79), the present disclosure describesinvention relates to a method for retaining or increasing cognitive memory capacity in a mammal suffering from a tauopathy.

In still another examplembodiment (80) of the disclosureinvention, 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition, according to any one of the preceding examplembodiments, or a combination thereof.

In one examplembodiment (81) of the disclosureinvention, 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 heterogenous group of neurodegenerative diseases or disorders including diseases or disorders which show co-exsistance 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide or a pharmaceutical composition according to any one of the preceding examplembodiments, or a combination thereof.

In another examplembodiment (82) of the disclosureinvention, 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, or a combination thereof.

In still another ~~embodiment~~example (83) of the ~~invention~~disclosure, a method of diagnosing a tau-protein-associated disease, disorder or condition in a patient is provided comprising detecting the immunospecific binding of a binding peptide or an active fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding ~~embodiment~~examples, 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 a binding peptide or a fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding example~~claims~~, wherein said binding peptide or antibody or fragment thereof binds an epitope of the tau protein;
b. allowing said binding peptide, particularly said antibody, particularly said monoclonal antibody or a functional part 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 still another ~~embodiment~~example (84) of the ~~invention~~disclosure, 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 binding peptide or an active fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding ~~embodiment~~examples, 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 a binding peptide or an active fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding ~~embodiment~~examples, which peptide or fragment thereof binds an epitope of the tau protein;

b. allowing said binding peptide, particularly said antibody, particularly said monoclonal antibody or a functional part 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 ~~embodiment~~example (85) of the disclosure~~invention~~, a method is provided for monitoring minimal residual disease in a patient following treatment with the binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, 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 binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding ~~embodiment~~examples, which peptide or fragment thereof binds to an epitope of the tau protein;

b. allowing said binding peptide, particularly said antibody, particularly said monoclonal antibody or a functional part 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 ~~embodiment~~example (86), a method is provided for predicting responsiveness of a patient being treated with the binding peptide or a functional part thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, or a polynucleotide, or a pharmaceutical composition, according to any one of the preceding ~~embodiment~~examples, comprising

a. bringing the sample or a specific body part or body area suspected to contain the tau antigen into contact with a binding peptide or an active fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof according to any one of the preceding examplembodiments, which peptide or fragment thereof binds to an epitope of the tau protein;
b. allowing said binding peptide, particularly said antibody, particularly said monoclonal antibody or a functional part 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 another exampleembodiment (87), the disclosure describesinvention relates to a test kit for detection and diagnosis of tau-protein-associated diseases, disorders or conditions comprising a binding peptide or an active fragment thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding examplembodiments.

In one examplembodiment (88) said test kit comprises a container holding one or more binding peptides or active fragments thereof, particularly an antibody, particularly a monoclonal antibody or a functional part thereof, according to any one of the preceding examplembodiments and instructions for using the binding peptides or 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 still another examplembodiment (89), the present disclosure describesinvention relates to an epitope selected from the group consisting of Tau aa 15-20 of human tau protein shown in SEQ ID NO: 67 comprising a phosphorylated Tyr at position 18 (Y18), Tau aa 405-412 comprising a phosphorylated Ser at position 409 (pS409), Tau aa 405-411 comprising a phosphorylated Ser at position 409 (pS409); and Tau aa 208-218 comprising a phosphorylated Thr at position 212 (pT212) and a phosphorylated Ser at position 214 (pS214).

In one examplembodiment (90), said epitope consists of Tau aa 15-20 with a phosphorylated Tyr at position 18 (Y18).

In one ~~embodiment~~example (91), said epitope consists of Tau aa 405-412 with a phosphorylated Ser at position 409 (pS409).

In one ~~embodiment~~example (92), said epitope consists of Tau aa 405-411 with a phosphorylated Ser at position 409 (pS409).

In another ~~embodiment~~example (93), the ~~invention relates to~~disclosure describes a cell line producing a binding peptide or an active fragment thereof, particularly an antibody, particularly *a monoclonal antibody or a functional part thereof according to any one of the* preceding ~~embodiment~~examples.

In one ~~embodiment~~example (94), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 6C10F9C12A11 deposited on August 25, 2010 as DSM ACC3079.

In one ~~embodiment~~example (95), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 6C10E5E9C12 deposited on August 25, 2010 as DSM ACC3081.

In one ~~embodiment~~example (96), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 6H1A11C11 deposited on August 25, 2010 as DSM ACC3080.

In one ~~embodiment~~example (97), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 6H1G6E6 deposited on August 25, 2010 as DSM ACC3088.

In one ~~embodiment~~example (98), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 2B6A10C11 deposited on August 25, 2010 as DSM ACC3084.

In one ~~embodiment~~example (99), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 2B6G7A12 deposited on March 10, 2010 as DSM ACC3087.

In one ~~embodiment~~example (100), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 3A8A12G7 deposited on August 25, 2010 as DSM ACC3086.

In one ~~embodiment~~example (101), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 3A8E12H8 deposited on August 25, 2010 as DSM ACC3085.

In one ~~embodiment~~example (102), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 7C2(1)F10C10D3 deposited on August 25, 2010 as DSM ACC3082.

In one ~~embodiment~~example (103), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line 7C2(2)B9F11D5 deposited on August 25, 2010 as DSM ACC3083.

In one ~~embodiment~~example (103a), the ~~invention relates to~~disclosure describes a cell line, *which is hybridoma cell line A4-4A6-48 deposited on August 30, 2011 as DSM ACC3136.*

In one ~~embodiment~~example (103b), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line A6-2G5-30 deposited on August 30, 2011 as DSM ACC3137.

In one ~~embodiment~~example (103c), the ~~invention relates to~~disclosure describes a cell line, *which is hybridoma cell line A6-2G5-41 deposited on August 30, 2011 as DSM ACC3138.*

In one ~~embodiment~~example (103d), the ~~invention relates to~~disclosure describes a cell line, which is hybridoma cell line A4-2A1-18 deposited on August 30, 2011 as DSM ACC3139.

In one examplembodiment (103e), the disclosure describesinvention relates to a cell line, which is hybridoma cell line A4-2A1-40 deposited on August 30, 2011 as DSM ACC3140.
In one examplembodiment (103e), the disclosure describesinvention relates to a cell line, which is hybridoma cell line A6-1D2-12 deposited on September 6, 2011 as DSM ACC3141.

In one exampleembodiment (104), the disclosure describesinvention relates to a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 6C10F9C12A11 deposited on August 25, 2010 as DSM ACC3079 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 54 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 53 and SEQ ID NO: 54 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one examplembodiment (105), the disclosure describesinvention relates to a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 6C10E5E9C12 deposited on August 25, 2010 as DSM ACC3081 using

a. a mix of primers comprising a 5'-primer of SEQ ID NO: 48 and SEQ ID NO: 49 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 53 and SEQ ID NO: 54 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one examplembodiment (106), the disclosure describesinvention relates to a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 6H1A11C11 deposited on August 25, 2010 as DSM ACC3080 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a primer pair comprising a 5'-primer of SEQ ID NO: 46 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one exampleembodiment (107), the disclosure describesinvention relates to a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded

by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 6H1G6E6 deposited on August 25, 2010 as DSM ACC3088 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a primer pair comprising a 5'-primer of SEQ ID NO: 46 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (108), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 2B6A10C11 deposited on August 25, 2010 as DSM ACC3084 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 46 and SEQ ID NO: 52 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (109), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 2B6G7A12 deposited on August 25, 2010 as DSM ACC3087 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 46 and SEQ ID NO: 52 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (110), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 3A8A12G7 deposited on August 25, 2010 as DSM ACC3086 using

a_1. a mix of primers comprising a 5'-primer of SEQ ID NO: 48 and SEQ ID NO: 49 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; or

a_2. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a primer pair comprising a 5'-primer of SEQ ID NO: 46 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (111), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 3A8E12H8 deposited on August 25, 2010 as DSM ACC3085 using

a_1. a mix of primers comprising a 5'-primer of SEQ ID NO: 48 and SEQ ID NO: 49 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; or

a_2. a primer pair comprising a 5'-primer of SEQ ID NO: 50 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a primer pair comprising a 5'-primer of SEQ ID NO: 46 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (112), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 7C2(1)F10C10D3 deposited on August 25, 2010 as DSM ACC3082 using

a. a mix of primers comprising a 5'-primer of SEQ ID NO: 49; SEQ ID NO: 56 and SEQ ID NO: 57 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain;

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 53 and SEQ ID NO: 55 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (113), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line 7C2(2)B9F11D5 deposited on August 25, 2010 as DSM ACC3083 using

a. a pair of primers comprising a 5'-primer of SEQ ID NO: 57 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain;

b. a mix of primers comprising a 5'-primer of SEQ ID NO: 53 and SEQ ID NO: 55 and a 3'-primer of SEQ ID NO: 47 for amplification of a second binding domain.

In one ~~embodiment~~example (114), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A4-2A1-18 deposited on August 30, 2011 as DSM ACC3139 using

a. a primer pair comprising a 5'-primer of SEQ ID NO: 149 and a 3'-primer of SEQ ID NO: 51 for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 120, 123, 124, 136, 137, 138, 139, and 140 and a 3'-primer selected from the group consisting of SEQ ID NOs: 131, 134, and 141-148, for amplification of a second binding domain.

In one ~~embodiment~~example (115), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A6-2G5-30 deposited on August 30, 2011 as DSM ACC3137 using

a. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 51 and 169-174 and a 3'-primer of SEQ ID NO: 51, for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 124, 127, and 150-158 and a 3'-primer selected from the group consisting of SEQ ID NOs: 130, and 159-168, for amplification of a second binding domain.

In one ~~embodiment~~example (116), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A4-2A1-40 deposited on August 30, 2011 as DSM ACC3140 using

a. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 178, 179 and 180 and a 3'-primer of SEQ ID NO: 51, for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 121, 127, 139, 154, 155, and 175 and a 3'-primer selected from the group consisting of SEQ ID NOs: 128, 129, 147, 176, and 177, for amplification of a second binding domain.

In one ~~embodiment~~example (117), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A6-2G5-41 deposited on August 30, 2011 as DSM ACC3138 using

a. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 51 and 188-192 and a 3'-primer of SEQ ID NO: 51, for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 120, 124, 126, 181, 182 and 183 and a 3'-primer selected from the group consisting of SEQ ID NOs: 144, 145 and 184-187, for amplification of a second binding domain.

In one ~~embodiment~~example (118), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A4-4A6-48 deposited on August 30, 2011 as DSM ACC3136 using

a. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 50 and 201-204 and a 3'-primer of SEQ ID NO: 51, for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 121, 137, 151 and 193-197 and a 3'-primer selected from the group consisting of SEQ ID NOs: 131, 141, 144, 166, 198, 199 and 200, for amplification of a second binding domain.

In one ~~embodiment~~example (119), the ~~invention relates to~~disclosure describes a monoclonal antibody or a functional part thereof comprising a light chain (VL) and/or a heavy chain (VH) domain, which is encoded by a polynucleotide located on a nucleotide fragment that can be obtained by PCR amplification of DNA of hybridoma cell line A6-1D2-12 deposited on September 6, 2011 as DSM ACC3141 using

a. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 209-214, and 219-221 a 3'-primer of SEQ ID NO: 215, for amplification of a first binding domain; and/or

b. a mix of primers comprising a 5'-primer selected from the group consisting of SEQ ID NOs: 216, 217 and 218 and a 3'-primer of SEQ ID NOs: 208, for amplification of a second binding domain.

In one ~~embodiment~~example (120), the antibody according to any one of the preceding ~~embodiments~~examples may be a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody, a human antibody, a camelid antibody, a diabody, or a modified or engineered antibody.

In one ~~embodiment~~example (121), the binding peptide or functional part thereof may be a fragment comprising a heavy chain and/or a light chain, particularly a heavy chain as show in SEQ ID NOs: 1-5 and/or a light chain as shown in SEQ ID NOs: 6-11, particularly a Fab or a $F(ab')_2$ fragment.

In a specific ~~embodiment~~example (122), the ~~invention relates to~~disclosure describes a heavy chain as show in SEQ ID NOs: 1-5.

In another specific ~~embodiment~~example (123), the ~~invention relates to~~disclosure describes a light chain as shown in SEQ ID NOs: 6-11.

In one ~~embodiment~~example (124), the ~~invention provides~~disclosure describes a method for producing the binding peptides or antibodies of any one of the preceding ~~embodiments~~example, comprising the step of culturing the cell line of any of the preceding embodiments in a suitable cultivation medium and, optionally, purifying the binding peptides or antibody from the cell line or cultivation medium.

Brief Description of Figures and Sequences

FIGURES

Figure 1 shows antibody binding to phospho-Tau in brain sections from biGT (Tau bigenic) mice using TAUPIR.

Figure 2 shows antibody binding to phospho-Tau in brain sections from AD and tauopathy patients using TAUPIR using ACI-36-3A8-Ab1 antibody.

Figure 3 shows the effect of anti-Tau antibody treatment following 1 week in vivo study on pTau epitope pT231 using MSD.

Claims:

1. An antibody or functional part thereof that specifically binds to a phospho-epitope on a mammalian Tau protein, wherein said antibody or functional part thereof has a high binding affinity to soluble and insoluble Tau protein, and modulates soluble and insoluble Tau levels, wherein the phospho-epitope is amino acids 405-411 or 405-412 having a phosphorylated Ser at position 409 (pS409), and wherein the antibody or functional part thereof binds the mammalian Tau protein with a dissociation constant of less than 10 nM, wherein the antibody or functional part thereof does not bind to the corresponding unphosphorylated epitope.

2. The antibody or functional part thereof of claim 1, wherein the antibody or functional part thereof binds the phospho-epitope on the mammalian Tau protein with a dissociation constant of less than 5 nM.

3. The antibody or functional part thereof of claim 1 or claim 2, wherein the antibody or functional part thereof binds the phospho-epitope on the mammalian Tau protein with an association rate constant of 10^4 $M^{-1}S^{-1}$ or greater.

4. The antibody or functional part thereof of claim 1 or claim 2, wherein the antibody or functional part thereof binds the phospho-epitope on the mammalian Tau protein with an association rate constant of 10^5 $M^{-1}S^{-1}$ or greater.

5. The antibody or functional part thereof of any one of claims 1 to 4, wherein the mammalian Tau is human Tau.

6. The antibody or functional part thereof of claim 1, wherein the antibody or functional part thereof comprises:

a) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 21, a CDR2 with the amino acid sequence of SEQ ID NO: 22, and a CDR3 with the amino acid sequence of SEQ ID NO: 23, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of

SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

b) a first binding domain which contains in sequence a CDR1 with an amino acid sequence that is at least 85% identical to SEQ ID NO: 27, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

c) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 24, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

d) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 27, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

e) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 28, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

f) a first binding domain which contains the amino acid sequence of SEQ ID NO: 6, 7, 8, or 9, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1, 2, or 3; or

g) a first binding domain which contains the amino acid sequence of SEQ ID NO: 6, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1; or

h) a first binding domain which contains the amino acid sequence of SEQ ID NO: 7, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1; or

i) a first binding domain which contains the amino acid sequence of SEQ ID NO: 8, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 2; or

j) a first binding domain which contains the amino acid sequence of SEQ ID NO: 9, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 3.

7. The antibody or functional part thereof of any one of the preceding claims, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, or a fully human antibody.

8. The antibody or functional part thereof of any one of the preceding claims, wherein the antibody is of the IgG2a, IgG2b, or the IgG3 isotype.

9. A pharmaceutical composition comprising the antibody or functional part thereof of any one of the preceding claims and a pharmaceutically acceptable carrier.

10. The antibody or functional part thereof or the pharmaceutical composition of any one of the preceding claims for use in treating or alleviating the symptoms of a neurodegenerative disease or disorder, wherein the neurodegenerative disease or disorder is optionally caused by or associated with the formation of neurofibrillary lesions or a tauopathy.

11. The antibody or functional part thereof for use according to claim 10, wherein administering the antibody or functional part thereof results in the alleviation of cognitive deficits.

12. The antibody or functional part thereof for use according to claim 10 or claim 11, wherein the alleviation of cognitive deficits comprises an arrest in the progression of the cognitive deficits and/or a restoration of cognitive memory capacity.

13. The antibody or functional part thereof for use according to any one of claims 10 to 12, wherein the neurodegenerative disease or disorder is selected from 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, and combinations thereof.

14. A cell line that produces the antibody or functional part thereof of any one of claims 1 to 8.

15. The cell line of claim 14 which is a hybridoma cell line selected from 3A8A12G7 deposited on August 25, 2010, as DSM ACC3086; 2B6A10C11 deposited on August 25, 2010, as DSM ACC3084; 3A8E12H8 deposited on August 25, 2010, as DSM ACC3085; 2B6G7A12 deposited on August 25, 2010, as DSM ACC3087; 6H1A11C11 deposited on August 25, 2010, as DSM ACC3080; and 6H1G6E6 deposited on August 25, 2010, as DSM ACC3088.

16. A polynucleotide encoding the antibody or functional part thereof of any one of claims 1 to 8.

17. The antibody or functional part thereof of any one of the preceding claims for use in diagnosing a tau-protein-associated disease, disorder or condition, or in diagnosing a predisposition to a tau-protein-associated disease, disorder or condition, in a patient comprising detecting the immunospecific binding of an antibody or functional part thereof 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 an antibody or functional part thereof according to any one of claims 1 to 8;
b) allowing the antibody or functional part 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;

wherein diagnosing a predisposition to a tau-protein-associated disease, disorder or condition further includes the step of:

e) comparing the amount of said immunological complex to a normal control value, wherein an increase in the amount of said immunological complex 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.

18. A method of diagnosing a tau-protein-associated disease, disorder or condition, or of diagnosing a predisposition to a tau-protein-associated disease, disorder or condition, in a patient comprising detecting the immunospecific binding of an antibody or functional part thereof to an epitope of the tau protein in a sample which includes the steps of

a) bringing the sample suspected to contain the tau protein into contact with an antibody or functional part thereof according to any one of claims 1 to 8;
b) allowing the antibody or functional part 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;

wherein diagnosing a predisposition to a tau-protein-associated disease, disorder or condition further includes the step of:

e) comparing the amount of said immunological complex to a normal control value, wherein an increase in the amount of said immunological complex 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.

Claims:

1. An antibody or functional part thereof that specifically binds to a phospho-epitope on a mammalian Tau protein, therein said antibody or functional part thereof has a high binding affinity to soluble and insoluble Tau protein, and modulates soluble and insoluble Tau levels, wherein the phospho-epitope is amino acids 405-411 or 405-412 having a phosphorylated Ser at position 409 (pS409), and wherein the antibody or functional part thereof binds the mammalian Tau protein with a dissociation constant of less than 10 nM as measured by surface plasmon resonance, wherein the antibody or functional part thereof does not bind to the corresponding unphosphorylated epitope.

2. The antibody or functional part thereof of claim 1, wherein the antibody or functional part thereof binds the phosphoepitope on the mammalian Tau protein with a dissociation constant of less than 5 nM.

3. The antibody or functional part thereof of claim 1 or claim 2, wherein the antibody or functional part thereof binds the phospho-epitope on the mammalian Tau protein with an association rate constant of 104 M-1S-1 or greater.

4. The antibody or functional part thereof of claim 1 or claim 2, wherein the antibody or functional part thereof binds the phospho-epitope on the mammalian Tau protein with an association rate constant of 105 M-1S-1 or greater.

5. The antibody or functional part thereof of any one of claims 1 to 4, wherein the mammalian Tau is human Tau.

6. The antibody or functional part thereof of claim 1, wherein the antibody or functional part thereof comprises:

a) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 21, a CDR2 with the amino acid sequence of SEQ ID NO: 22, and a CDR3 with the amino acid sequence of SEQ ID NO: 23, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

b) a first binding domain which contains in sequence a CDR1 with an amino acid sequence that is at least 85% identical to SEQ ID NO: 27, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

c) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of .SEQ, ID NO: 24, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

d) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 27, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

e) a first binding domain which contains in sequence a CDR1 with the amino acid sequence of':SEQ ID NO: 28, a CDR2 with the amino acid sequence of SEQ ID NO: 25, and a CDR3 with the amino acid sequence of SEQ ID NO: 26, and/or a second binding domain which contains in sequence a CDR1 with the amino acid sequence of SEQ ID NO: 12, a CDR2 with the amino acid sequence of SEQ ID NO: 13, and a CDR3 with the amino acid sequence of SEQ ID NO: 14; or

f) a first binding domain which contains the amino acid sequence of SEQ ID NO: 6, 7, 8, or 9, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1, 2, or 3; or

g) a first binding domain which contains the amino acid sequence of SEQ ID NO: 6, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1; or

h) a first binding domain which contains the amino acid sequence of SEQ ID NO: 7, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 1; or

i) a first binding domain which contains the amino acid sequence of SEQ ID NO: 8, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 2; or

j) a first binding domain which contains the amino acid sequence of SEQ ID NO: 9, and/or a second binding domain which contains the amino acid sequence of SEQ ID NO: 3.

7. The antibody or functional part thereof of any one of the preceding claims, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody; or a fully human antibody.

8. The antibody or functional part thereof of any one of the preceding claims, wherein the antibody is of the IgG2a, IgG2b, or the IgG3 isotype.

9. A pharmaceutical composition comprising the antibody or functional part thereof of any one of the preceding claims and a pharmaceutically acceptable carrier.

10. The antibody or functional part thereof or the pharmaceutical composition of any one of the preceding claims for use in treating or alleviating the symptoms of a neurodegenerative disease or disorder, wherein the neurodegenerative disease

or disorder is optionally caused by or associated with the formation of neurofibrillary lesions or a tauopathy.

11. The antibody or functional part thereof or the pharmaceutical composition for use according to claim 10, wherein administering the antibody or functional part thereof results in the alleviation of cognitive deficits.

12. The antibody or functional part thereof or the pharmaceutical composition for use according to claim 10 or claim 11, wherein the alleviation of cognitive deficits comprises an arrest in the progression of the cognitive deficits and/or a restoration of cognitive memory capacity.

13. The antibody or functional part thereof or the pharmaceutical composition for use according to any one of claims 10 to 12, wherein the neurodegenerative disease or disorder is selected from 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, and combinations thereof.

14. A cell line that produces the antibody or functional part thereof of any one of claims 1 to 8.

15. The cell line of claim 14 which is a hybridoma cell line selected from 3A8A12G7 deposited on August 25, 2010, as DSM ACC3086; 2B6A10C11 deposited on August 25, 2010, as DSM ACC3084; 3A8E12H8 deposited on August 25, 2010, as DSM ACC3085; 2B6G7A12 deposited on August 25, 2010, as DSM ACC3087; 6H1A11C11 deposited on August 25, 2010, as DSM ACC3080; and 6H1G6E6 deposited on August 25, 2010, as DSM ACC3088.

16. A polynucleotide encoding the antibody or functional part thereof of any one of claims 1 to 8.

17. The antibody or functional part thereof according to any one of claims 1 to 8 for use in diagnosing a tau-proteinassociated disease, disorder or condition, or in diagnosing a predisposition to a tau-protein-associated disease, disorder or condition, in a patient comprising detecting the immunospecific binding of an antibody or functional part thereof to an epitope of the tau protein *in situ* which includes the steps of

a) bringing the specific body part or body area suspected to contain the tau protein into contact with an antibody or functional part thereof according to any one of claims 1 to 8;

b) allowing the antibody or functional part 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 specific body part or area;

wherein diagnosing a predisposition to a tau-protein-associated disease, disorder or condition further includes the step of:

e) comparing the amount of said immunological complex to a normal control value, wherein an increase in the amount of said immunological complex 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.

18. A method of diagnosing a tau-protein-associated disease, disorder or condition, or of diagnosing a predisposition to a tau-protein-associated disease, disorder or condition, in a patient comprising detecting the immunospecific binding of an antibody or functional part thereof to an epitope of the tau protein in a sample which includes the steps of

a) bringing the sample suspected to contain the tau protein into contact with an antibody or functional part thereof according to any one of claims 1 to 8;

b) allowing the antibody or functional part 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;

wherein diagnosing a predisposition to a tau-protein-associated disease, disorder or condition further includes the step of:

e) comparing the amount of said immunological complex to a normal control value, wherein an increase in the amount of said immunological complex 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.