The present invention provides novel methods and compositions comprising highly specific and highly effective antibodies, particularly chimeric antibodies including fragments thereof, more particularly partially or fully humanized antibodies including fragments thereof, having the ability to specifically recognize and bind to specific epitopes from a range of β-amyloid antigens, which my be presented to the antibody in a monomeric, dimeric, trimeric, etc, a polymeric form, in form of an aggregate, fibers, filaments or in the condensed form of a plaque. The antibodies enabled by the teaching of the present invention are particularly useful for the treatment of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, and others, including macular degeneration, to name just a few.

SUMMARY OF THE INVENTION

In a first aspect, the present invention refers to a humanized antibody or an active fragment thereof, which binds to beta-amyloid, comprising (i) human- or primate-derived framework regions, (ii) a heavy chain variable region (HCVR) comprising HCVR complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, HCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 2, HCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 3, and amino acid Leu at Kabat position 47 and amino acid Ser at Kabat position 94 in the framework region of the HCVR and (iii) a light chain variable region (LCVR) comprising LCVR CDR1 comprising the amino acid sequence of SEQ ID NO: 4, LCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or the amino acid sequence RVSNRFS or KVSSRFS, and LCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

In a second aspect, the present invention refers to a humanized antibody or an active fragment thereof, which binds to beta-amyloid, comprising human- or primate-derived framework regions, wherein the humanized antibody or active fragment thereof comprises:

(i) a heavy chain variable region (HCVR) comprising an amino acid sequence that is at least 98% identical to the amino acid sequence that is SEQ ID NO: 15, and a light chain variable region (LCVR) comprising LCVR CDR1 comprising the amino acid sequence of SEQ ID NO: 4, LCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or the amino acid sequence RVSNRFS or KVSSRFS, and LCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 6; or

(ii) a heavy chain variable region (HCVR) comprising HCVR complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, HCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and HCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 3, and a light chain variable region (LCVR) comprising an amino acid sequence that is at least 98% identical to the amino acid sequence that is SEQ ID NO: 12.

In a third aspect, the present invention refers to a humanized antibody or an active fragment thereof, which binds to beta-amyloid, comprising human- or primate-derived framework regions, wherein the humanized antibody or active fragment thereof comprises:

(i) a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 15, and a light chain variable region (LCVR) comprising LCVR CDR1 comprising the amino acid sequence of SEQ ID NO: 4, LCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or the amino acid sequence RVSNRFS or KVSSRFS, and LCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 6; or

(ii) a heavy chain variable region (HCVR) comprising HCVR complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, HCVR CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and HCVR CDR3 comprising the amino acid sequence of SEQ ID NO: 3, and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 12.

In a fourth aspect, the present invention refers to a humanized antibody or active fragment thereof, which binds to beta-amyloid, comprising a light chain comprising the amino acid sequence of SEQ ID NO: 13 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 16 or SEQ ID NO: 16 in which the C-terminal Lys has been removed.

In a fifth aspect, the present invention refers to a humanized antibody or active fragment thereof, which binds to beta-amyloid, comprising an LCVR comprising the amino acid sequence of SEQ ID NO: 12 and an HCVR comprising the amino acid sequence of SEQ ID NO: 15.

In a sixth aspect, the present invention refers to a pharmaceutical composition comprising the humanized antibody or active fragment thereof according to the present invention for use in preventing, treating or alleviating amyloidosis.

In a seventh aspect, the present invention refers to a pharmaceutical composition comprising the humanized antibody or active fragment thereof according to the present invention for use in preventing, treating or alleviating Alzheimer's Disease.

In an eighth aspect, the present invention refers to a nucleic acid molecule comprising a nucleotide sequence encoding (a) the humanized antibody or active fragment thereof according to the present invention, or (b) the LCVR or light chain of the antibody, or the HCVR or heavy chain, of the humanized antibody or active fragment thereof according to the present invention.

In a ninth aspect, the present invention refers to a nucleic acid molecule comprising a nucleotide sequence encoding an antibody variable region comprising an HCVR and/or an LCVR of the humanized antibody or active fragment thereof according to the present invention.

In a tenth aspect, the present invention refers to an expression vector comprising the nucleotide sequence of the present invention.

In an eleventh aspect, the present invention refers to a cell comprising the nucleic acid molecule of the present invention or an expression vector of the present invention.

In a twelfth aspect, the present invention refers to a composition comprising the humanized antibody or active fragment thereof according to the present invention.

In a thirteenth aspect, the present invention refers to a mixture comprising a therapeutically effective amount of (a) the humanized antibody or active fragment thereof according to the present invention, and (b) one or more of the following: a biologically active substance, a pharmaceutically acceptable carrier, a diluent, or an excipient.

In a fourteenth aspect, the present invention refers to the use of the humanized antibody or active fragment thereof according to the present invention, or a pharmaceutical composition according to the present invention, and/or a composition according to the present invention, or a mixture according to the present invention, for the preparation of a medicament for preventing, treating or alleviating amyloidosis.

In a fifteenth aspect, the present invention refers to the use of the humanized antibody or active fragment thereof according to the present invention, or a pharmaceutical composition according to the present invention, and/or a composition according to the present invention, or a mixture according to the present invention, for the preparation of a medicament for preventing, treating or alleviating Alzheimer's disease in a subject.

In a sixteenth aspect, the present invention refers to a humanized antibody or an active fragment thereof according to the present invention, for use in protecting neurons from beta-amyloid-induced degradation.

In a seventeenth aspect, the present invention refers to a method of producing the humanized antibody or active fragment thereof, according to the present invention, comprising the step of culturing the cell of the present invention.

In an eighteenth aspect, the present invention refers to a method of producing the humanized antibody or active fragment thereof, according to the present invention, comprising the step of expressing one or more nucleic acid molecules independently selected from the nucleic acid molecules according to the present invention.

In a nineteenth aspect, the present invention refers to an *in vitro* method of detection of *amyloidosis in a patient comprising:*

(a) contacting a sample obtained from the patient suspected of containing beta-amyloid with a humanized antibody or active fragment thereof according to the present invention under conditions that allow binding of the antibody or active fragment thereof to beta-amyloid; and

(b) detecting the antibody or active fragment thereof bound to beta-amyloid;

such that the presence or absence of antibody or active fragment thereof bound to beta-amyloid indicates the presence or absence of beta-amyloid in the sample of the patient.

In a twentieth aspect, the present invention refers to an *in vitro* method of determining the extent of amyloidogenic plaque burden in a tissue sample and/or body fluid sample of a subject comprising:

(a) testing a tissue sample or body fluid sample that has been obtained from the subject under investigation for the presence of beta-amyloid with a humanized antibody or active fragment thereof according to the present invention;

(b) determining the amount of antibody or active fragment thereof bound to beta-amyloid; and

(c) calculating the plaque burden in the tissue sample or body fluid sample of the subject.

In one example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, and more particularly to at least three distinct binding sites on the β-amyloid protein wherein said one, said at least two and said at least three binding sites each comprise at least one or two consecutive amino acid residues predominantly involved in the binding of the antibody.

In particular, the chimeric antibody or a fragment thereof, or the humanized antibody or a fragment thereof according to the disclosure~~invention~~ binds to at least two, particularly to at least three distinct binding sites on the β-amyloid protein wherein at least two of the three distinct binding sites comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody and at least one of the three distinct binding sites comprise at least one amino acid residue.

The at least two distinct binding sites comprising at least two consecutive amino acid residues predominantly involved in the binding of the antibody are located in close proximity to each other on the antigen, separated and/or flanked by at least one amino acid residue not involved in antibody binding or to a significantly smaller extent as compared to said at least two consecutive amino acid residues, thus forming a conformational discontinuous epitope.

The at least three distinct binding sites comprising at least two consecutive amino acid residues and at least one amino acid residue, respectively, which are predominantly involved in the binding of the antibody are located in close proximity to each other on the epitope, separated and/or flanked by at least one amino acid residue not involved in antibody binding or to a significantly smaller extent as compared to the amino acid residues, which are predominantly involved in the binding of the antibody, thus forming a conformational discontinuous epitope.

In particular, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is disclosed~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein wherein said at least one or said at least two distinct binding sites each comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody, wherein the at least two consecutive amino acid residues representing a first binding site are –Phe-Phe- embedded within the following core sequence (SEQ ID NO: 9):

Xaa_3 - Phe – Phe – Xaa_4 – Xaa_5 – Xaa_6, wherein
Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile;
Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;
Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp,
Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp, and wherein said amino acid residues Xaa_3 Xaa_4, Xaa_5 and Xaa_6 are not involved in antibody binding or to a significantly smaller extent as compared to the –Phe-Phe- binding site.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is disclosed~~provided~~, wherein

Xaa_3 is Val or Leu, but particularly Val;

Xaa_4 is Ala or Val, but particularly Ala;

Xaa_5 is Glu or Asp, but particularly Glu;

Xaa_6 is Glu or Asp, but particularly Asp.

In particular, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is disclosed~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein wherein said distinct binding sites comprise at least one and at least two consecutive amino acid residues, respectively, predominantly involved in the binding of the antibody, wherein the at least two consecutive amino acid residues representing a first binding site are –Phe-Phe- and the at least one amino acid residue is –His- embedded within the following core sequence:

$-Xaa_1-His-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Phe-Phe-Xaa_7-Xaa_8-Xaa_9-$,

wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln, Lys and Arg

Xaa_3 is an amino acid residue selected from the group consisting of Asn and Gln

Xaa_4 is an amino acid residue selected from the group consisting of His, Asn, Gln, Lys and Arg

Xaa_5 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;

Xaa_6 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile

Xaa_7 is an amino acid residue selected from the group consisting of Ala, Val, Leu and Ile

Xaa_8 is an amino acid residue selected from the group consisting of Glu and Asp,

Xaa_9 is an amino acid residue selected from the group consisting of Glu and Asp, and wherein said amino acid residues Xaa_1, Xaa_3, Xaa_6, Xaa_7, Xaa_8 and Xaa_9, are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the –His- and the –Phe-Phe- binding site, respectively..

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is disclosed~~provided~~, wherein

Xaa_3 is Gln or Asn, but particularly Gln;

Xaa_4 is Lys

Xaa_5 is Leu

Xaa_6 is Val or Leu, but particularly Val;

Xaa_7 is Ala or Val, but particularly Ala;

Xaa_8 is Glu or Asp, but particularly Glu; and

Xaa_9 is Asp or Glu, but particularly Asp.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is disclosed~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein, wherein said at least one or said at least two distinct binding sites each comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody, wherein the at least two consecutive amino acid residues representing a second binding site are –Lys-Leu- embedded within the following core sequence (SEQ ID NO: 10):

$Xaa_1 - Xaa_2$ - Lys - Leu – Xaa_3 wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln Lys, and Arg;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile; and wherein said amino acid residues Xaa_2, Xaa_3, are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the –Lys-Leu- binding site.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein wherein said distinct binding sites comprise at least one and at least two consecutive amino acid residues, respectively, predominantly involved in the binding of the antibody, wherein the at least one and the at least two consecutive amino acids, which are separated by at least one amino acid residue not involved in antibody binding or to a significantly smaller extent as compared to the amino acid residues

predominantly involved in the binding of the antibody, are -His- and –Lys-Leu-, respectively, embedded within the following core sequence:

His – Xaa_2 - Lys - Leu – Xaa_3– Xaa_4– Xaa_5–Xaa_6- – Xaa_7 — Xaa_8 – wherein

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile;

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile

Xaa_5 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile

Xaa_6 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;

Xaa_7 is an amino acid residue selected from the group consisting of Glu and Asp,

Xaa_8 is an amino acid residue selected from the group consisting of Glu and Asp

and wherein said amino acid residues Xaa_2, Xaa_3, Xaa_6, Xaa_7, Xaa_8, are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the –His- and the –Lys-Leu- binding site, respectively.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, wherein

Xaa_2 is Gln or Asn, but particularly Gln;

Xaa_3 is Val or Leu, but particularly Val;

Xaa_4 is Phe

Xaa_5 is Phe

Xaa_6 is Ala or Val, but particularly Ala;

Xaa_7 is Glu or Asp, but particularly Glu; and

Xaa_8 is Asp or Glu, but particularly Asp.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, which recognizes and binds to at least two distinct binding sites on the β-amyloid protein wherein said at least two distinct binding sites each comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody, wherein the at least two consecutive amino acids are separated by at

least one amino acid residue not involved in antibody binding or to a significantly smaller extent than said consecutive amino acid residues, which are –Phe-Phe- and –Lys-Leu-, respectively, representing a first and second binding site embedded within the following core sequence:

Xaa_1 – Xaa_2 - Lys - Leu – Xaa_3 - Phe – Phe - Xaa_4 – Xaa_5 – Xaa_6, wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln Lys, and Arg;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile;

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp,

Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp and wherein said amino acid residues Xaa_2, Xaa_3, Xaa_4, Xaa_5 and Xaa_6 are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the –Lys-Leu- and –Phe-Phe- binding site, respectively.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein wherein said distinct binding sites comprise at least one and at least two consecutive amino acid residues, respectively, predominantly involved in the binding of the antibody, wherein the at least one and the at least two consecutive amino acids are separated by at least one amino acid residue not involved in antibody binding or to a significantly smaller extent as compared to the amino acid residues, which are predominantly involved in the binding of the antibody, and wherein said amino acid residues are –His- and –Phe-Phe- and –Lys-Leu-, respectively, embedded within the following core sequence:

His – Xaa_2 - Lys - Leu – Xaa_3 - Phe – Phe - Xaa_4 _ Xaa_5 _ Xaa_6, wherein

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile;

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp,

Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp, and wherein said amino acid residues Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the –His-, the –Lys-Leu- and the –Phe-Phe- binding site, respectively.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, wherein

Xaa_2 is Gln or Asn, but particularly Gln;

Xaa_3 is Val or Leu, but particularly Val;

Xaa_4 is Ala or Val, but particularly Ala;

Xaa_5 is Glu or Asp, but particularly Glu; and

Xaa_6 is Asp or Glu, but particularly Asp.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, which recognizes and binds to at least two distinct binding sites on the β-amyloid protein wherein said at least two distinct binding sites each comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody, wherein the at least two consecutive amino acids are separated by at least one amino acid residue not involved in antibody binding or to a significantly smaller extent than said consecutive amino acid residues, which are –Phe-Phe- and –Lys-Leu-, respectively, representing a first and second binding site embedded within the following core sequence:

$Xaa_1 – Xaa_2$ - Lys - Leu – Xaa_3 - Phe – Phe - $Xaa_4 – Xaa_5 – Xaa_6$, wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln, Lys and Arg;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln;

Xaa_3 is an amino acid residue selected from the group consisting of Val, Ala, Leu, Met, Phe, norleucine and Ile

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu and Ile;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp,

Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp, and wherein said amino acid residues Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, are not involved in antibody binding or to a smaller to significantly smaller extent as compared to the —Lys-Leu- and the –Phe- Phe binding site, respectively.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, wherein

Xaa_1 is His or Arg, but particularly His;

Xaa_2 is Gln or Asn, but particularly Gln;

Xaa_3 is Val or Leu, but particularly Val;

Xaa_4 is Ala or Val, but particularly Ala;

Xaa_5 is Glu or Asp, but particularly Glu; and

Xaa_6 is Asp or Glu, but particularly Asp.

In one example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is provided which recognizes and binds to at least two distinct binding sites on the β-amyloid protein wherein said at least two distinct binding sites each comprise at least two consecutive amino acid residues predominantly involved in the binding of the antibody, which are - Phe - Phe – Ala – Glu -, particularly - Phe - Phe – Ala –,but especially - Phe - Phe – and - Lys - Leu –, respectively, and wherein said at least two distinct binding sites exhibit amino acid sequence –Val - Phe - Phe - Ala - Glu – Asp - shown in SEQ ID NO: 7 and amino acid sequence His - Gln - Lys - Leu – Val - shown in SEQ ID NO: 8, respectively.

In one example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~, which recognizes and binds to at least one distinct binding site, particularly to a least two distinct binding sites, more particularly to at least three distinct binding sites on the β-amyloid protein wherein the said at least one or said at least two distinct binding sites comprise at least one and at least two consecutive amino acid residues, respectively, predominantly involved in the binding of the antibody, which are - Phe - Phe – and - Lys - Leu –, and –His-, respectively, wherein said distinct binding sites are embedded in the amino acid sequence –Val - Phe - Phe - Ala – Glu-, and amino acid sequence -His - Gln - Lys - Leu – Val -, respectively.

In another examplembodiment of the disclosureinvention, the chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof comprises an antigen recognition and binding site which recognizes and binds to at least two distinct binding sites on the β-amyloid protein wherein said at least two distinct binding sites each comprise at least two consecutive amino acid residues within the amino acid sequence given in SEQ ID NOs: 7 and 8, respectively, wherein said consecutive amino acid residues, particularly –Phe- Phe- and –Lys-Leu-, are predominantly involved in the binding of the β-amyloid protein.

In a further specific examplembodiment of the disclosureinvention, an antibody or a fragment thereof according to the disclosureinvention is describedprovided, which binds to 4 distinct binding sites on the β-amyloid protein wherein said 4 distinct binding sites include 2 binding sites each comprising one amino acid residue and 2 binding sites each comprising two consecutive amino acid residues, which residues are predominantly involved in the binding of the antibody, wherein said 4 distinct binding sites are located in close proximity to each other on the β-amyloid protein, and wherein said 4 binding sites are separated by at least one amino acid residue not involved in antibody binding or involved in binding but to a significantly smaller extent as compared to said one amino acid residue and said two consecutive amino acid residues of the 4 distinct binding sites thus forming a conformational discontinuous epitope.

In particular, the first of the two consecutive amino acid residues predominantly involved in the binding of the antibody is –Lys-Leu-, and the second of the at least two consecutive amino acid residues is –Phe-Phe-, the first of the single amino acid residues is -His- and the second of the single amino acid residues is -Asp- embedded within the following core sequence:

- Xaa_1– His – Xaa_2 – Lys – Leu –Xaa_3 – Phe – Phe – Xaa_4 – Xaa_5 – Asp – Xaa_6

wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln, Lys and Arg, but particularly His;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln, but particularly Gln ;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile, particularly Val;

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile, particularly Ala;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp, particularly Glu;

Xaa_6 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile, particularly Val; and wherein said amino acid residues Xaa_1, Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, are not involved in antibody binding or are involved in binding but to a significantly smaller extent as compared to the –His-, –Asp-, the -Lys-Leu, and the –Phe-Phe- binding site.

In one example~~embodiment~~, the disclosure~~invention~~ relates to an antibody or a fragment thereof according to the disclosure~~invention~~, which binds to 4 distinct binding sites on the β-amyloid protein, wherein said 4 distinct binding sites include two binding sites each comprising one amino acid residue and two binding sites each comprising two consecutive amino acid residues, wherein the first of the two consecutive amino acid residues predominantly involved in the binding of the antibody is –Lys-Leu-, and the second of the at least two consecutive amino acid residues is –Phe-Phe-, the first of the single amino acid residues is -His- and the second of the single amino acid residues is -Asp- embedded within the following core sequence:

- Xaa_1– His – Xaa_2 – Lys – Leu –Xaa_3 – Phe – Phe – Xaa_4 – Xaa_5 – Asp – Xaa_6

wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln, Lys and Arg, but particularly His;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln, but particularly Gln ;

Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile, particularly Val;

Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile, particularly Ala;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp, particularly Glu;

Xaa_6 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile, particularly Val; and wherein said amino acid residues Xaa_1, Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, are not involved in antibody binding or are involved in binding but to a significantly smaller extent as compared to the –His-, –Asp-, the -Lys-Leu, and the –Phe-Phe- binding site.

In a specific ~~example~~embodiment of the disclosure~~invention~~, the recognition and binding sites as defined herein before are forming a conformational discontinuous epitope localized in a region of the β-amyloid protein between amino acid residue 12 to 24, particularly between residues 14 to 23, more particularly between amino acid residues 14 and 20, wherein the at least two distinct recognition and binding sites each comprising at least 2 amino acid residues, are located at position 16 and 17 and at position 19 and 20, respectively, and wherein the at least one distinct recognition and binding site comprising at least 1 amino acid residue is located at position 14, which residues are predominantly involved in the binding of the β-amyloid protein and wherein said distinct recognition and binding sites are at least on one side flanked by amino acid residues, particularly residues 21 and 22, and separated by one amino acid residue located at position 15 and 18, which amino acid residues are not directly involved in the binding of the antigen or, at least, to a substantially smaller extent.

In still another ~~example~~embodiment of the disclosure~~invention~~ the said at least three distinct recognition and binding sites are flanked on both sides by amino acid residues, particularly residues 12 and 13, and residues 21 and 22 and are separated by one amino acid residue located at position 15 and 18, which amino acid residues are not directly involved in the binding of the antigen or, at least, to a substantially smaller extent.

In a specific ~~example~~embodiment, said consecutive amino acid residues, particularly –Lys-Leu- at position 16 and 17 and –Phe- Phe- at position 19 and 20, which are predominantly involved in the binding of the β-amyloid protein, are embedded into the following core region:

Val–	His–	His–	Gln–	Lys–	Leu–	Val–	Phe–	Phe–	Ala–	Glu–	Asp
12	13	14	15	16	17	18	19	20	21	22	23

In another specific ~~example~~embodiment, said amino acid residues, particularly –Lys-Leu- at position 16 and 17 and –Phe- Phe- at position 19 and 20, and –His- at position 14, which are predominantly involved in the binding of the β-amyloid protein, are embedded into the following core region:

Val–	His–	His–	Gln–	Lys–	Leu–	Val–	Phe–	Phe–	Ala–	Glu–	Asp–	Val–	Gly–
12	13	14	15	16	17	18	19	20	21	22	23	24	25

In another example~~embodiment~~ of the disclosure~~invention~~, a humanized antibody or a fragment thereof is described~~provided~~ which comprises in the light chain and heavy chain variable region, respectively, at least one CDR of non-human origin, particularly two CDRs of non-human origin, more particularly three CDR of non-human origin, embedded in one or more human- or primate-derived framework regions and, optionally, a constant region derived from a human or primate source antibody, which humanized antibody or fragment thereof is capable of specifically recognizing and binding β-amyloid protein, particularly a β-amyloid monomeric peptide, more particularly a β-amyloid polymeric peptide, even more particularly β-amyloid fibers, fibrils or filaments in isolation or as part of a β-amyloid plaque, at an epitope comprising the following amino acid sequence (SEQ ID NO: 11):

Xaa_1 – Xaa_2 - Lys - Leu – Xaa_3 - Phe – Phe- Xaa_4 – Xaa_5 – Xaa_6, wherein

Xaa_1 is an amino acid residue selected from the group consisting of His, Asn, Gln, but particularly His;

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln, but particularly Gln; and

Xaa_3 is an amino acid residue selected from the group consisting of Val, Leu, and Ile, but particularly Val;

Xaa_4 is an amino acid residue selected from the group consisting of Ala and Val, but particularly Ala;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp, but particularly Glu;

Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp, but particularly Asp.

In still another example~~embodiment~~ of the disclosure~~invention~~, a humanized antibody or a fragment thereof is described~~provided~~ which comprises in the light chain and heavy chain variable region, respectively, at least one CDR of non-human origin, particularly two CDRs of non-human origin, more particularly three CDR of non-human origin, embedded in one or more human- or primate-derived framework regions and, optionally, a constant region derived from a human or primate source antibody, which humanized antibody or fragment thereof is capable of specifically recognizing and binding β-amyloid protein, particularly a β-amyloid monomeric peptide, more particularly a β-amyloid polymeric peptide, even more particularly β-amyloid fibers, fibrils or

filaments in isolation or as part of a β-amyloid plaque, at an epitope comprising the following amino acid sequence:

His – Xaa_2 - Lys - Leu – Xaa_3 - Phe – Phe- Xaa_4 - Xaa_5 - Xaa_6, wherein

Xaa_2 is an amino acid residue selected from the group consisting of Asn and Gln, but particularly Gln; and

Xaa_3 is an amino acid residue selected from the group consisting of Val, Leu, and Ile, but particularly Val;

Xaa_4 is an amino acid residue selected from the group consisting of Ala and Val, but particularly Ala;

Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp, but particularly Glu;

Xaa_6 is an amino acid residue selected from the group consisting of Glu and Asp, but particularly Glu; and wherein said amino acid residues Xaa_2, Xaa_3, Xaa_4, Xaa_5, Xaa_6, are not involved in antibody binding or to a smaller extent as compared to the –His- and the –Lys-Leu- and the -Phe-Phe- binding site.

In a specific example~~embodiment~~ of the disclosure~~invention~~, the CDR of non-human origin is obtained from a donor antibody, but particularly from a murine donor antibody, raised against an antigen fragment which does not contain said distinct binding site. This shift in the epitopic region may have at least partially been caused by the use of a supramolecular antigenic construct comprising an antigenic peptide corresponding to the amino acid sequence of the β-amyloid peptide, particularly of β-amyloid peptide $A\beta_{1-16}$, modified with a hydrophilic moiety such as, for example, polyethylene glycol (PEG), wherein said hydrophilic moiety is covalently bound to each of the termini of the antigenic peptide through at least one, particularly one or two amino acids such as, for example, lysine, glutamic acid and cysteine or any other suitable amino acid or amino acid analogue capable of serving as a connecting device for coupling the hydrophilic moiety to the peptide fragment, as described herein below in the immunization process. When a PEG is used as the hydrophilic moiety, the free PEG termini are covalently bound to phosphatidylethanolamine or any other compound suitable to function as the anchoring element, for example, to embed the antigenic construct in the bilayer of a liposome as described herein.

In particular, the CDR of non-human origin is obtained from a murine donor antibody which exhibits the characteristic properties of ACI-01-Ab7C2 (also named "mC2" throughout the

application) deposited 01 December 2005 with the "Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ) in Braunschweig, Mascheroder Weg 1 B, 38124 Branuschweig, under the provisions of the Budapest Treaty under accession no DSM ACC2750).

In one examplembodiment of the disclosureinvention, the CDR of non-human origin is obtained from murine donor antibody ACI-01-Ab7C2 (also named "mC2" throughout the application) deposited 01 December 2005 with the "Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ) in Braunschweig, Mascheroder Weg 1 B, 38124 Branuschweig, under the provisions of the Budapest Treaty under accession no DSM ACC2750).

Also the use of lipid A as part of the immunization protocol may have contributed to a shift in the epitopic region.

In a specific examplembodiment, the disclosureinvention relates to a humanized antibody or a fragment thereof comprising integrated into human- or primate-derived framework regions at least one peptide with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 4 representing CDR1 of the Light Chain Variable Region (LCVR).

In another examplembodiment, the disclosureinvention relates to a humanized antibody or a fragment thereof, wherein said humanized antibody comprises integrated into human- or primate-derived heavy chain framework regions at least one peptide with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

In still another examplembodiment, the disclosureinvention relates to a humanized antibody or a fragment thereof, wherein said humanized antibody comprises integrated into human- or primate-derived light chain framework regions a peptide with an amino acid sequence of SEQ ID NO: 4 representing CDR1 of the Light Chain Variable Region (LCVR).

In particular, the disclosureinvention relates to a Light Chain Variable Region (LCVR) comprising integrated into human- or primate-derived framework regions at least one peptide with an amino acid sequence of SEQ ID NO: 4 representing CDR1 of the Light Chain Variable Region (LCVR).

In another specific examplembodiment, the disclosureinvention relates to a Heavy Chain Variable Region (HCVR) comprising integrated into human- or primate-derived framework regions at least one peptide with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

The disclosureinvention further relates to a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions at least two peptides, which peptides are different and exhibit an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR) wherein the same CDR cannot be present twice in the antibody. In particular, if the at least two CDRs present are both CDRs of the Light Chain Variable Region (LCVR), at least on of said CDRs must be CDR1 represented by SEQ ID NO: 4.

Also comprised by the disclosureinvention is a humanized antibody or a fragment thereof comprising integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR), but particularly a humanized antibody or a fragment thereof wherein the same CDR cannot be present twice in the antibody.

In particular, the disclosureinvention relates to a Heavy Chain Variable Region (HCVR) comprising integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

In a further examplembodiment, the disclosureinvention relates to a humanized antibody or a fragment thereof, comprising integrated into human- or primate-derived light chain framework regions at least two

peptides with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR).

In particular, the disclosure~~invention~~ relates to a Light Chain Variable Region (LCVR), which has integrated into human- or primate-derived light chain framework regions at least two peptides with an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR), wherein the same CDR cannot be present twice in the antibody and, in particular, at least on of said CDRs must be CDR1 represented by SEQ ID NO: 4.

The disclosure~~invention~~ also relates to a humanized antibody or a fragment thereof, comprising integrated into human- or primate-derived heavy chain framework regions peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR), particularly in the order indicated above.

In particular, the disclosure~~invention~~ relates to a Heavy Chain Variable Region (HCVR) comprising integrated into human- or primate-derived heavy chain framework regions peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR), particularly in the order indicated above.

Also comprised by the disclosure~~invention~~ is a humanized antibody or a fragment thereof comprising integrated into human- or primate-derived light chain framework regions peptides with an amino acid sequence of SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR), particularly in the order indicated above.

In particular, the disclosure~~invention~~ relates to a Light Chain Variable Region (LCVR) comprising integrated into human- or primate-derived light chain framework regions peptides with an amino acid sequence of SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and

SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR), particularly in the order indicated above.

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

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

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

In still anther example~~mbodiment~~, the disclosure~~invention~~ relates to a humanized antibody or a fragment thereof, which comprises integrated into human- or primate-derived framework regions peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1, SEQ ID NO: 2 representing CDR2

and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR) and SEQ ID NO: 4 representing CDR1, SEQ ID NO: 5 representing CDR2 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR).

In a specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Heavy Chain Variable Region (HCVR), or a fragment thereof, wherein said humanized antibody, Heavy Chain Variable Region (HCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least a peptide with an amino acid sequence of SEQ ID NO: 2 representing CDR2 of the Heavy Chain Variable Region (HCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Heavy Chain Variable Region (HCVR) or a fragment thereof, wherein said humanized antibody, Heavy Chain Variable Region (HCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least a peptide with an amino acid sequence of SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, Heavy Chain Variable Region (HCVR) or a fragment thereof, which antibody, Heavy Chain Variable Region (HCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1 and SEQ ID NO: 2 representing CDR2 of the Heavy Chain Variable Region (HCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Heavy Chain Variable Region (HCVR) or a fragment thereof, which antibody, Heavy Chain Variable Region (HCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence of SEQ ID NO: 1 representing CDR1 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Heavy Chain Variable Region (HCVR) or a fragment thereof, which antibody, Heavy Chain Variable Region (HCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain

framework regions at least two peptides with an amino acid sequence of SEQ ID NO: 2 representing CDR2 and SEQ ID NO: 3 representing CDR3 of the Heavy Chain Variable Region (HCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Light Chain Variable Region (LCVR) or a fragment thereof, which antibody, Light Chain Variable Region (LCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence of SEQ ID NO: 4 representing CDR1 and SEQ ID NO: 5 representing CDR2 of the Light Chain Variable Region (LCVR).

In another specific example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, a Light Chain Variable Region (LCVR) or a fragment thereof, which antibody, Light Chain Variable Region (LCVR) or fragment thereof comprises integrated into human- or primate-derived heavy chain framework regions at least two peptides with an amino acid sequence of SEQ ID NO: 4 representing CDR1 and SEQ ID NO: 6 representing CDR3 of the Light Chain Variable Region (LCVR).

Further comprised by the disclosure~~invention~~ is a humanized antibody or a fragment thereof, wherein both the Heavy Chain Variable Region (HCVR) and the Light Chain Variable Region (LCVR) of the mouse C2 antibody each contributes at least one of its CDR regions to the at least two CDR regions of the humanized antibody. The resulting humanized antibody or a fragment thereof thus may comprise

-at least an amino acid sequence of SEQ ID NO: 1 representing CDR1 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 4 representing CDR1 (LCVR);

-at least an amino acid sequence of SEQ ID NO: 2 representing CDR2 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 4 representing CDR1 (LCVR);

-at least an amino acid sequence of SEQ ID NO: 3 representing CDR3 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 4 representing CDR1 (LCVR);

-at least an amino acid sequence of SEQ ID NO: 1 representing CDR1 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 5 representing CDR2 (LCVR);

-at least an amino acid sequence of SEQ ID NO: 2 representing CDR2 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 5 representing CDR2 (LCVR);

-at least an amino acid sequence of SEQ ID NO:2 representing CDR2 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 6 representing CDR3 (LCVR);
-at least an amino acid sequence of SEQ ID NO:1 representing CDR1 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 6 representing CDR3 (LCVR);
-at least an amino acid sequence of SEQ ID NO: 3 representing CDR3 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 5 representing CDR2 (LCVR);
-at least an amino acid sequence of SEQ ID NO: 3 representing CDR3 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 6 representing CDR3 (LCVR).

In still another examplembodiment, the disclosureinvention relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof as described herein before, which antibody comprises a light chain and/or a heavy chain constant region of human or primate origin.

In a further examplembodiment, the disclosureinvention relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof, wherein at least one, particularly at least one but not more than 5, more particularly at least one but not more than 4, even more particularly at least one but not more than 3, but especially at least one but not more than 2, of the amino acids representative of the light chain and/or heavy chain CDR regions as given in SEQ ID NOs: 1 – 6 is changed through a conservative substitution such that the antibody maintains its full functionality.

In particular, the disclosureinvention relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof, wherein in CDR2 of the light chain variable region (LCVR) as given in SEQ ID NO: 5, the Lys at Kabat position 50 is replaced by an amino acid residue selected from the group consisting of Arg, Gln and Glu, particularly by Arg.

In particular, the disclosureinvention relates to a light chain variable region (LCVR) wherein in CDR2 as given in SEQ ID NO: 5, the Lys at Kabat position 50 is replaced by an amino acid residue selected from the group consisting of Arg, Gln and Glu, particularly by Arg.
In another examplembodiment, the disclosureinvention relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof, wherein in CDR2 of the light chain variable region (LCVR) as given in SEQ ID NO: 5, the Ser at Kabat position 53 is replaced by an amino acid residue selected from the group consisting of Asn or Thr, but particularly by Asn.

In particular, the disclosure~~invention~~ relates to a light chain variable region (LCVR) wherein in CDR2 as given in SEQ ID NO: 5, the Ser at Kabat position 53 is replaced by an amino acid residue selected from the group consisting of Asn or Thr, but particularly by Asn.

In one example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is provided, wherein the Heavy Chain Variable Region (HCVR) has an amino acid sequence that is 90%, particularly 95%, more particularly 98% identical to the sequence given in SEQ ID NO: 15 and 16, respectively.

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is provided, wherein the Light Chain Variable Region (LCVR) has an amino acid sequence that is 90%, particularly 95%, more particularly 98% identical to the sequence given in SEQ ID NO: 12 and 13, respectively.
In still another example~~embodiment~~ of the disclosure~~invention~~, a humanized antibody or a fragment thereof is provided, wherein at least two, but especially three, of the CDR regions of the Heavy Chain Variable Region (HCVR) have an amino acid sequence that is 90%, particularly 95%, more particularly 98% identical to the corresponding CDR region as given in SEQ ID NO: 1 – 3.

In a further example~~embodiment~~ of the disclosure~~invention~~, a humanized antibody or a fragment thereof is provided, wherein at least two, but especially three, of the CDR regions of the Light Chain Variable Region (LCVR) have an amino acid sequence that is 90%, particularly 95%, more particularly 98% identical to the corresponding CDR region as given in SEQ ID NO: 4 – 6.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present invention as described herein before wherein the Heavy Chain Variable Region (HCVR) has an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence given in SEQ ID NO: 15 and 16, respectively.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present invention as described herein before wherein the Light Chain Variable Region (LCVR) has an amino acid sequence that

is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence given in SEQ ID NO: 12 and 13, respectively.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present invention as described herein before, wherein at least one, particularly at least two, but especially three, of the CDR regions of the Heavy Chain Variable Region (HCVR) have an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the corresponding CDR region as given in SEQ ID NO: 1 – 3.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present invention as described herein before, wherein at least one, particularly at least two, but especially three, of the CDR regions of the Light Chain Variable Region (LCVR) have an amino acid sequence that is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the corresponding CDR region as given in SEQ ID NO: 4 – 6.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody according to the present invention and as described herein before, wherein at least one of the amino acids representative of the acceptor framework sequences obtained from human germline V_H and V_K sequences, respectively is changed through a substitution to an amino acid from the corresponding region of murine antibody ACI-01-Ab7C2 or a substitution conservative thereto.

In particular, the disclosure~~invention~~ relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Leu, norleucine, Ile, Val, Met, Ala, and Phe, particularly Leu and Ile, but especially Leu such as shown in SEQ ID NO: 15.

The disclosure~~invention~~ further relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Arg in Kabat position 94 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT

subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser such as shown in SEQ ID NO: 15.~~.~~

In still another ~~example~~embodiment, the disclosure~~invention~~ relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Leu, norleucine, Ile, Val, Met, Ala, and Phe, particularly Leu and Ile, but especially Leu and the Arg in Kabat position 94 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser such as shown in SEQ ID NO: 15.

The disclosure~~invention~~ further relates to a Light Chain Variable Region and to a humanized antibody comprising this Light Chain Variable Region, respectively,, wherein the Gln in Kabat position 45 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region is replaced by an amino acid selected from the group consisting of Lys, Arg, Gln, and Asn, particularly by Lys and Arg, but especially by Lys.

The disclosure~~invention~~ further relates to a Light Chain Variable Region and to a humanized antibody comprising this Light Chain Variable Region, respectively, wherein the Tyr in Kabat position 87 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region is replaced by an amino acid selected from the group consisting of Phe, Leu, Val, Ile, and Ala, particularly by Leu and Phe, but especially by Phe.

The disclosure~~invention~~ further relates to a Light Chain Variable Region and to a humanized antibody comprising this Light Chain Variable Region, respectively, wherein the Lys in Kabat position 50 in the CDR2 region obtained from a mouse monoclonal antibody, particularly murine antibody ACI-01-Ab7C2, such as shown in SEQ ID NO: 12 is replaced by an amino acid selected from the group consisting of Arg, Gln, His, and Asn, but especially by Arg.

In still another examplembodiment, the disclosureinvention relates to a Light Chain Variable Region and to a humanized antibody comprising this Light Chain Variable Region, respectively, wherein the Asn in Kabat position 53 in the CDR2 region obtained from a mouse monoclonal antibody, particularly murine antibody ACI-01-Ab7C2, such as shown in SEQ ID NO: 12 is replaced by an amino acid selected from the group consisting of Ala, Val, Leu, Ser and Ile; but especially Ser.

In still another examplembodiment, the disclosureinvention relates to a humanized antibody, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Leu, norleucine, Ile, Val, Met, Ala, and Phe, particularly Leu and Ile, but especially Leu and the Arg in Kabat position 94 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser as shown in SEQ ID NO: 15, and the Tyr in Kabat position 87 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region is replaced by an amino acid selected from the group consisting of Phe, Leu, Val, Ile, and Ala, particularly by Leu and Phe, but especially by Phe.

In still another examplembodiment, the disclosureinvention relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region as shown in SEQ ID NO: 15 is replaced by Leu.

In still another examplembodiment, the disclosureinvention relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Arg in Kabat position 94 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by Ser such as shown in SEQ ID NO: 15.

In still another examplembodiment, the disclosureinvention relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively,, wherein the

Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by Leu and Ile, but especially Leu and the Arg in Kabat position 94 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by Ser such as shown in SEQ ID NO: 15..

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a Light Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Tyr in Kabat position 87 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region is replaced by Phe.

In still another example~~embodiment~~, the disclosure~~invention~~ relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively,, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by Leu and Ile, but especially Leu and the Arg in Kabat position 94 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by Ser such as shown in SEQ ID NO: 15 and the Tyr in Kabat position 87 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region is replaced by Phe..

In one example~~embodiment~~, the disclosure~~invention~~ relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Leu, norleucine, Ile, Val, Met, Ala, and Phe, particularly Leu and Ile, but especially Leu and the Arg in Kabat position 94 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser such as shown in SEQ ID NO: 15 and wherein the Lys in Kabat position 50 in the CDR2 region obtained from a mouse monoclonal antibody, particularly murine antibody ACI-01-Ab7C2, is replaced by an amino acid selected from the group consisting of Arg, Gln, His, and Asn, but especially by Arg.

In one examplembodiment, the disclosureinvention relates to a Heavy Chain Variable Region and to a humanized antibody comprising this Heavy Chain Variable Region, respectively, wherein the Trp in Kabat position 47 in the acceptor framework sequence obtained from human germline V_H sequences of KABAT subgroup V_HIII of the Heavy Chain Variable Region is replaced by an amino acid selected from the group consisting of Leu, norleucine, Ile, Val, Met, Ala, and Phe, particularly Leu and Ile, but especially Leu and the Arg in Kabat position 94 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser such as shown in SEQ ID NO: 15 and wherein the Asn in Kabat position 53 in the CDR2 region obtained from a mouse monoclonal antibody, particularly murine antibody ACI-01-Ab7C2, is replaced by an amino acid selected from the group consisting of Ala, Val, Leu, Ser and Ile; but especially Ser.

In a specific examplembodiment, the disclosureinvention relates to the light chain variable region of SEQ ID NO: 12.

In another specific examplembodiment of the disclosureinvention, a humanized antibody is provided, which comprises the light chain variable region of SEQ ID NO: 12.

In a specific examplembodiment, the disclosureinvention relates to the light chain variable region including signal sequences as shown in SEQ ID NO: 13.

In another specific examplembodiment of the disclosureinvention, a humanized antibody is provided, which comprises the complete light chain variable region including signal sequences as shown in SEQ ID NO: 13.

In another specific examplembodiment of the disclosureinvention, a humanized antibody is provided, which comprises the light chain variable region of SEQ ID NO: 12 and the light chain constant region of SEQ ID NO: 14.

In another specific examplembodiment of the disclosureinvention, a humanized antibody is provided, which comprises the complete light chain variable region of SEQ ID NO: 13 and the light chain constant region of SEQ ID NO: 14.

In a specific ~~embodiment~~example, the ~~invention~~disclosure relates to the heavy chain variable region of SEQ ID NO: 15.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, a humanized antibody is described~~provided~~, which comprises the heavy chain variable region of SEQ ID NO: 15.

In a specific ~~embodiment~~example, the ~~invention~~disclosure relates to the heavy chain variable region including signal sequences as shown in SEQ ID NO: 16.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, a humanized antibody is provided, which comprises the complete heavy chain variable region including signal sequences as shown in SEQ ID NO: 16.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, a humanized antibody is provided, which comprises the heavy chain variable region of SEQ ID NO: 15 and the heavy chain constant region of SEQ ID NO: 17.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, a humanized antibody is provided, which comprises the heavy chain variable region of SEQ ID NO: 16 and the heavy chain constant region of SEQ ID NO: 17.

In one ~~embodiment~~example the humanized antibody according to the ~~invention~~disclosure and as described herein, upon co-incubation with an Aβ monomeric peptide having at least 30, particularly at least 35, more particularly at least 38, even more particularly at least 40 amino acid residues and/or an Aβ polymeric soluble amyloid peptide comprising a plurality of said Aβ monomeric units, but especially with an $A\beta_{1-42}$ monomeric and/or an Aβ polymeric soluble amyloid peptide comprising a plurality of said $A\beta_{1-42}$ monomeric units, particularly at a molar concentration ratio of antibody to Aβ1-42 of up to 1:1000, particularly of up to 1:500, more particularly of up to 1:300, even more particularly of up to 1:200, but especially at a molar concentration ratio of between 1:10 and 1:100, inhibits the aggregation of the Aβ monomers to high molecular polymeric fibrils.

In particular, the co-incubation of the antibody according to the disclosure~~invention~~ with amyloid monomeric and/or polymeric soluble amyloid peptides is carried out for 24 hours to 60 hours, particularly for 30 hours to 50 hours, more particularly for 48 hours, but especially 24 hours, at a temperature of between 28°C and 40°C, particularly of between 32°C and 38°C, more particularly at 37°C.

In a specific example~~embodiment~~ of the disclosure~~invention~~, co-incubation with amyloid monomeric and/or polymeric soluble amyloid peptides is accomplished for 24 hours at a temperature of 37°C.

In particular, the antibody, particularly the humanized antibody according to the disclosure~~invention~~ including any functionally equivalent antibody or functional parts thereof binds to $A\beta_{1-42}$ monomeric peptide and/or $A\beta$ polymeric soluble amyloid peptide comprising a plurality of said $A\beta_{1-42}$ monomeric units and, upon co-incubation with $A\beta_{1-42}$ monomeric peptide and/or $A\beta$ polymeric soluble amyloid peptide comprising a plurality of said $A\beta_{1-42}$ monomeric units inhibits the aggregation of the $A\beta$ monomers and/or polymers to high molecular polymeric fibrils.

In one example~~embodiment~~, the antibody, particularly the humanized antibody according to the disclosure~~invention~~ including any functionally equivalent antibody or functional parts thereof inhibits the aggregation of the $A\beta$ monomers and/or $A\beta$ soluble polymers comprising a plurality of said $A\beta$ monomeric units to high molecular polymeric fibrils by at least 50%, particularly by at least 60%, particularly by at least 65%, more particularly by at least 75%, even more particularly by at least 80%, but especially by at least 85%-90%, or more as compared to the respective amyloid peptide monomers incubated in buffer (control), at a molar concentration ratio of antibody to $A\beta$1-42 of up to 1:1000, particularly at a molar concentration ratio of between 1:10 and 1:100, but especially at a molar concentration ratio of 1:10.

In a specific example~~embodiment~~ of the disclosure~~invention~~, the antibody, particularly the humanized antibody according to the invention including any functionally equivalent antibody or functional parts thereof inhibits the aggregation of the $A\beta$ monomers and/or $A\beta$ soluble polymers comprising a plurality of said $A\beta$ monomeric units to high molecular polymeric fibrils by at least 30% at a molar concentration ratio of antibody to $A\beta$1-42 of 1:100.

In another specific examplembodiment of the disclosureinvention, the antibody, particularly the humanized antibody according to the disclosureinvention including any functionally equivalent antibody or functional parts thereof inhibits the aggregation of the Aβ monomers and/or Aβ soluble polymers comprising a plurality of said Aβ monomeric units to high molecular polymeric fibrils by at least 80% at a molar concentration ratio of antibody to Aβ1-42 of 1:10.

Binding of the antibodies according to the disclosureinvention and as described herein to amyloidogenic monomeric and/or polymeric peptides but, particularly, to the amyloid form (1-42) leads to inhibition of the aggregation of monomeric and/or polymeric amyloidogenic peptides to high molecular fibrils or filaments. Through the inhibition of the aggregation of amyloidogenic monomeric and/or polymeric peptides the antibodies according to the present invention are capable of preventing or slowing down the formation of amyloid plaques, particularly the amyloid form (1-42), which is know to become insoluble by change of secondary conformation and to be the major part of amyloid plaques in brains of diseased animals or humans.

The aggregation inhibition potential of the antibody according to the disclosureinvention may be determined by any suitable method known in the art, particularly by density-gradient ultracentrifugation followed by a SDS-PAGE sedimentation analysis on a preformed gradient and/or by a thioflavin T (Th-T) fluorescent assay.

In one examplembodiment, the disclosureinvention relates to an antibody, particularly a humanized antibody as described herein including any functionally equivalent antibody or functional parts thereof, which antibody, upon co-incubation, particularly at a molar concentration ratio of between 1:5 and 1:1000, particularly of between 1:10 and 1:500, more particularly at a ratio of 1:10 to 1:300, even more particularly at a ratio of between 1:10 and 1:100, with preformed high molecular polymeric amyloid fibrils or filaments formed by the aggregation of Aβ monomeric peptides having at least 30, particularly at least 35, more particularly at least 38, even more particularly at least 40 amino acid residues and, but especially $A\beta_{1-42}$ monomeric peptides, is capable of disaggregating the preformed polymeric fibrils or filaments by at least 20%, particularly by at least 30%, more particularly by at least 35%%, even more particularly by at least 40%, but especially by at least 50% or more.

In a specific examplembodiment of the disclosureinvention, the aggregation inhibition and the disaggregation potential of the antibody, respectively, is determined by density-gradient ultracentrifugation followed by a SDS-PAGE sedimentation analysis on a preformed gradient.

In another specific examplembodiment of the disclosureinvention, the aggregation inhibition and the disaggregation potential of the antibody, respectively, is determined by thioflavin T (Th-T) fluorescent assay.

In another specific examplembodiment, the antibody according to the disclosureinvention is co-incubated with amyloid preformed high molecular polymeric amyloid fibrils or filaments for 12 hours to 36 hours, particularly for 18 hours to 30 hours, more particularly for 24 hours at a temperature of between 28°C and 40°C, particularly of between 32°C and 38°C, more particularly at 37°C.

In particular, the co-incubation with preformed high molecular polymeric amyloid fibrils or filaments is done for 24 hours at a temperature of 37°C.

In a specific examplembodiment of the disclosureinvention, the antibody, particularly the humanized antibody according to the invention including any functionally equivalent antibody or functional parts thereof is capable of disaggregating the preformed polymeric fibrils or filaments by at least 24% at a molar concentration ratio of antibody to Aβ1-42 of 1:100.

In another specific examplembodiment of the disclosureinvention, the antibody, particularly the humanized antibody according to the invention including any functionally equivalent antibody or functional parts thereof is capable of disaggregating the preformed polymeric fibrils or filaments by at least 32% at a molar concentration ratio of antibody to Aβ1-42 of 1:10.

Through the disaggregation of amyloidogenic polymeric fibrils or filaments the antibodies according to the present disclosureinvention are capable of preventing or slowing down the formation of amyloid plaques which leads to an alleviation of the symptoms associated with the disease and a delay or reversal of its progression.

Accordingly, it is a further examplembodiment of the disclosureinvention to provide an antibody, particularly a humanized antibody, including any functionally equivalent antibody or functional parts thereof as described herein, which antibody is capable of decreasing the total amount of Aβ in the brain of an animal, particularly a mammal, but especially a human suffering from a disease or condition leading to increased concentration of Aβ in the brain.

In another examplembodiment, the disclosureinvention relates to a humanized antibody according to the invention and as described herein before, which antibody is bi-effective in that it exhibits both an

aggregation inhibition property as well as a disaggregation property, particularly paired with a high degree of conformational sensitivity.

In particular, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the invention and as described herein before, which antibody, upon co-incubation with amyloid monomeric and/or polymeric soluble amyloid peptides, particularly with β-amyloid monomeric peptides such as, for example, Aβ monomeric peptides 1-39; 1-40, 1-41, or 1-42, and/or a polymeric soluble β-amyloid peptide comprising a plurality of said Aβ monomeric units, but especially with an $A\beta_{1-42}$ monomeric and/or an Aβ polymeric soluble amyloid peptide comprising a plurality of said $A\beta_{1-42}$ monomeric units,, inhibits the aggregation of the Aβ monomers into high molecular polymeric fibrils or filaments and, in addition, upon co-incubation with preformed high molecular polymeric amyloid fibrils or filaments formed by the aggregation of amyloid monomeric peptides, particularly β-amyloid monomeric peptides such as, for example, Aβ monomeric peptides 1-39; 1-40, 1-41, or 1-42, but especially $A\beta_{1-42}$ monomeric peptides, is capable of disaggregating the preformed polymeric fibrils or filaments.

In another example~~aspect~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present invention and as described herein before, which antibody is capable of inducing a transition of the β-sheet conformation towards an α-helix and/or a random coil conformation, but particularly a random coil conformation, even more particularly a random coil conformation at a given location in the molecule, especially in the environment of Tyr 10 and Val12 of the Aβ protein, which leads to an increase of the random coil conformation at the expense of the β-sheet conformation and an improved solubilization of the preformed high molecular polymeric amyloid fibrils or filaments. In particular the decrease of the β-sheet conformation amounts to at least 30%, particularly to at least 35%, and more particularly to at least 40% and more as compared to the respective preformed amyloid polymeric fibrils or filaments incubated in buffer (control).

The antibody's potential in inducing a transition in the secondary structure is determined by solid state 13C NMR spectroscopy but, in particular, by measuring the integral intensities of the conformations of Tyr 10 and Val 12 Cβ in the $A\beta_{1-42}$ peptide.

In a further example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present disclosure~~invention~~ and as described herein before, is provided comprising at least one light chain or a fragment thereof or at least one heavy chain or a fragment thereof, wherein said antibody or fragment binds to an Aβ monomer with a high binding affinity with a K_D in a range of between at least about 1×10^{-7} M to at least about 1×10^{-12} M, particularly of at least about 1×10^{-8} M to at least about 1×10^{-11} M, more particularly of at least about 1×10^{-9} M to at least about 1×10^{-10} M, even more particularly of at least about 1×10^{-8} M to at least about 2×10^{-8} M, but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

In another example~~embodiment~~ of the disclosure~~invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present disclosure~~invention~~ and as described herein before, is provided comprising at least one light chain or a fragment thereof or at least one heavy chain or a fragment thereof, wherein said antibody or fragment binds to an Aβ fiber, fibril or filament with a high binding affinity with a K_D in a range of between at least about 1×10^{-7} M to at least about 1×10^{-12} M, particularly of at least about 1×10^{-8} M to at least about 1×10^{-11} M, more particularly of at least about 1×10^{-9} M to at least about 1×10^{-10} M, even more particularly of at least about 2×10^{-9} M to at least about 5×10^{-9} M, but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

In another example~~embodiment~~, the antibody according to the disclosure~~invention~~ and as described herein before or a fragment thereof, exhibits an binding affinity to an Aβ fiber, fibril or filament which is at least 2 times, particularly at least 4 times, particularly at least 10 times, particularly at least 15 times, more particularly at least 20 times, but especially at least 25 times higher than the binding affinity to an Aβ monomer.

In still another example~~embodiment~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~ as described herein before, which antibody substantially binds to aggregated Aβ, including Aβ plaques, in the mammalian, particularly the human brain but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

In another example~~aspect~~ of the disclosure~~invention~~, the chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is described~~provided~~ as described herein before, which antibody

substantially binds to soluble polymeric amyloid, particularly amyloid β (Aβ), including Aβ monomers, in the mammalian, particularly the human brain but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

Further provided is a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before, which antibody significantly reduces Aβ plaque burden in the mammalian, particularly the human brain. This can be achieved by either binding of the antibody to the plaque or by shifting the equilibrium between amyloid, particularly amyloid β (Aβ), in its insoluble and aggregated state towards its soluble form by disaggregating fibers to soluble poly- and monomeric forms by inducing a shift in conformation and binding and stabilizing the disaggregated and solubilized amyloid forms, particularly amyloid β (Aβ) forms, in the tissue and/or body fluids, particularly the brain. Through the activity of the antibody according to the disclosure~~invention~~ the peripheral clearing and catabolism is thus favored rather than deposition within the tissue and/or body fluids, particularly the brain. The beneficial effect of the antibody according to the invention can thus be obtained without binding of the antibody to the plaque.

Through this stabilizing activity, the antibody according to the disclosure~~invention~~ is able to neutralize the toxic effects of the polymeric and less aggregated soluble amyloid protein, particularly amyloid β (Aβ) protein, in the tissue and/or body fluids. In a specific example~~embodiment~~ of the disclosure~~invention~~ the antibody according to the disclosure~~invention~~ may thus achieve its beneficial effects without necessarily binding aggregated amyloid beta in the brain.

In a further example~~aspect~~ of the disclosure~~invention~~ a humanized antibody or a fragment thereof according to the present disclosure~~invention~~ and as described herein before, is provided comprising at least one light chain or a fragment thereof or at least one heavy chain or a fragment thereof incorporating at least one, particularly two and more particularly three CDR regions obtained form a mouse donor antibody, particularly from mouse antibody ACI-01-Ab7C2 (named "mC2" and hC2 for the humanized C2 antibody, throughout the application) deposited 01 December 2005 with the "Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ) in Braunschweig, Mascheroder Weg 1 B, 38124 Braunschweig, under accession no DSM ACC2750, wherein said antibody or fragment thereof has an affinity to the Aβ antigen which is at least 5 times,

particularly at least 8 times, more particularly at least 10 times, but especially at least 15 times higher than that of the mouse donor antibody.

The antibody of this disclosure~~invention~~ can be, in one embodiment, a whole antibody (e.g., with two full length light chains and two full length heavy chains) of any isotype and subtype (*e.g.*, IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgE, IgA1 and IgA2); but especially an antibody of the IgG4 isotype; alternatively, in another embodiment, it can be an antigen-binding fragment (e.g., Fab, $F(ab')_2$, and Fv) of a whole antibody.

The disclosure~~invention~~ thus also relates to antigen-binding fragments of the antibodies described herein. In one example~~mbodiment~~ of the disclosure~~invention~~, the fragment is selected from the group consisting of a Fab fragment, a Fab' fragment, a $F(ab)_2$fragment, and a F_v fragment, including the products of an Fab immunoglobulin expression library and epitope-binding fragments of any of the antibodies and fragments mentioned above.

In another example~~mbodiment~~, the antibody or antigen-binding fragment of the disclosure~~invention~~ is conjugated to polyethylene glycol. In yet another example~~mbodiment~~, the constant region of the antibody of the disclosure~~invention~~ is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified antibody. In still another example~~mbodiment~~, the antibody or antigen-binding fragment of the disclosure~~invention~~ comprises a Fc region having an altered effector function.

The disclosure~~invention~~ further relates to a nucleotide molecule comprising a nucleotide sequence encoding a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as disclosed herein before.

In particular, the disclosure~~invention~~ relates to a nucleotide molecule comprising a nucleotide sequence encoding a stretch of contiguous amino acid molecules as given in SEQ ID NO: 2 and 3, respectively, or the complementary sequence, representing the Complementarity Determining Regions (CDRs) 2 and 3 of the Heavy Chain Variable Region (HCVR).

More particularly, the disclosure~~invention~~ relates to a nucleotide molecule comprising a nucleotide sequence encoding a stretch of contiguous amino acid molecules as given in SEQ ID NO: 4, or

the complementary sequence, representing the Complementarity Determining Regions (CDRs) 1 of the Light Chain Variable Region (LCVR).

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence as given in SEQ ID NO: 18 and SEQ ID NO: 19, or the complementary sequence, encoding the amino acid sequence of CDR 2 and CDR 3, respectively, of the Heavy Chain Variable Region (HCVR).

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence as given in SEQ ID NO: 20, or the complementary sequence, encoding the nucleotide sequence of CDR 1 of the Light Chain Variable Region (LCVR).

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence of SEQ ID NO: 21, or the complementary sequence, encoding the light chain variable region.

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence of SEQ ID NO: 22, or the complementary sequence, encoding the complete light chain variable region including signal sequences.

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence encoding the light chain variable region of SEQ ID NO: 22 and the light chain constant region of SEQ ID NO: 23. The disclosure~~invention~~ also comprises the complementary strand of said nucleotide molecule.

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence of SEQ ID NO: 24 encoding the heavy chain variable region. The disclosure~~invention~~ also comprises the complementary strand of said nucleotide molecule.

In another example~~embodiment~~ of the disclosure~~invention~~ a nucleotide molecule is provided comprising a nucleotide sequence of SEQ ID NO: 25 encoding the complete heavy chain variable region including signal sequences. The disclosure~~invention~~ also comprises the complementary strand of said nucleotide molecule.

In another exampleembodiment of the disclosureinvention a nucleotide molecule is provided comprising a nucleotide sequence encoding the heavy chain variable region of SEQ ID NO: 25 and the heavy chain constant region of SEQ ID NO: 26 . The disclosureinvention also comprises the complementary strand of said nucleotide molecule.

Also comprised by the present disclosureinvention is a nucleotide sequence which hybridizes to one of the above-described antibody-encoding nucleotide sequences of the invention, particularly to the complementary strand thereof, either in isolation or as part of larger nucleotide molecule.

In particular, the disclosureinvention relates to a nucleotide sequence that hybridizes under conventional hybridization conditions, particularly under stringent hybridization conditions, to any of the nucleotide sequences given in SEQ ID NOs: 18-26 and 29 - 32, particularly to the complementary strand thereof.

In another exampleembodiment of the disclosureinvention an expression vector is provided comprising the nucleic acid molecule according to the disclosureinvention and as mentioned herein before.

In another exampleembodiment of the disclosureinvention a cell is provided comprising an expression vector comprising the nucleic acid according to the invention and as mentioned herein before.

In still another exampleembodiment, the disclosureinvention relates to a composition comprising the antibody according to the disclosureinvention, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosureinvention and as described herein before including any functionally equivalent antibody or any derivative or functional parts thereof, in a therapeutically effective amount, in particular a composition which is a pharmaceutical composition optionally further comprising a pharmaceutically acceptable carrier.

In another exampleembodiment of the disclosureinvention, said composition comprises the antibody in a therapeutically effective amount.

Further comprised by the disclosureinvention is a mixture comprising an antibody, particularly a monoclonal antibody according to the disclosureinvention, but particularly a chimeric antibody or a

fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before including any functionally equivalent antibody or any derivative or functional parts thereof, in a therapeutically effective amount and, optionally, a further biologically active substance and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

In particular, the disclosure~~invention~~ relates to a mixture, wherein the further biologically active substance is a compound used in the medication of amyloidosis, a group of diseases and disorders associated with amyloid or amyloid-like protein such as the Aβ protein involved in Alzheimer's disease.

In another example~~embodiment~~ of the disclosure~~invention~~, the other biologically active substance or compound may also be a therapeutic agent that may be used in the treatment of amyloidosis caused by amyloid β or may be used in the medication of other neurological disorders.

The other biologically active substance or compound may exert its biological effect by the same or a similar mechanism as the antibody according to the disclosure~~invention~~ or by an unrelated mechanism of action or by a multiplicity of related and/or unrelated mechanisms of action.

Generally, the other biologically active compound may include neutron-transmission enhancers, psychotherapeutic drugs, acetylcholine esterase inhibitors, calcium-channel blockers, biogenic amines, benzodiazepine tranquillizers, acetylcholine synthesis, storage or release enhancers, acetylcholine postsynaptic receptor agonists, monoamine oxidase-A or –B inhibitors, N-methyl-D-aspartate glutamate receptor antagonists, non-steroidal anti-inflammatory drugs, antioxidants, and serotonergic receptor antagonists.

More particularly, the disclosure~~invention~~ relates to a mixture comprising at least one compound selected from the group consisting of compounds effective against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepin and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), α-secretase activators, β- and γ–secretase inhibitors, tau proteins, neurotransmitter, β-sheet breakers, attractants for amyloid beta clearing / depleting cellular components, inhibitors of N-terminal truncated amyloid beta including pyroglutamated amyloid beta 3-42, anti-inflammatory molecules, or

cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine, M1 agonists and other drugs including any amyloid or tau modifying drug and nutritive supplements, and nutritive supplements, together with an antibody according to the present disclosure~~invention~~ and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

The disclosure~~invention~~ further relates to a mixture, wherein the compound is a cholinesterase inhibitor (ChEIs), particularly a mixture, wherein the compound is one selected from the group consisting of tacrine, rivastigmine, donepezil, galantamine, niacin and memantine.

In a further example~~embodiment~~, the mixtures according to the disclosure~~invention~~ may comprise niacin or memantine together with an antibody according to the present invention and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

In still another example~~embodiment~~ of the disclosure~~invention~~ mixtures are provided that comprise "atypical antipsychotics" such as, for example clozapine, ziprasidone, risperidone, aripiprazole or olanzapine for the treatment of positive and negative psychotic symptoms including hallucinations, delusions, thought disorders (manifested by marked incoherence, derailment, tangentiality), and bizarre or disorganized behavior, as well as anhedonia, flattened affect, apathy, and social withdrawal, together with an antibody, particularly a monoclonal antibody according to the invention, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the invention and as described herein and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

In a specific example~~embodiment~~ of the disIcosure~~invention~~, the compositions and mixtures according to the invention and as described herein before comprise the antibody and the biologically active substance, respectively, in a therapeutically effective amount.

Other compounds that can be suitably used in mixtures in combination with the antibody according to the present disclosure~~invention~~ are described in WO 2004/058258 (see especially pages 16 and 17) including therapeutic drug targets (page 36-39), alkanesulfonic acids and alkanolsulfuric acids (pages 39-51), cholinesterase inhibitors (pages 51-56), NMDA receptor antagonists (pages 56-58), estrogens (pages 58-59), non-steroidal anti-inflammatory drugs (pages 60-61),

antioxidants (pages 61-62), peroxisome proliferators-activated receptor (PPAR) agonists (pages 63-67), cholesterol–lowering agents (pages 68-75); amyloid inhibitors (pages 75-77), amyloid formation inhibitors (pages 77-78), metal chelators (pages 78-79), anti-psychotics and anti-depressants (pages 80-82), nutritional supplements (pages 83-89) and compounds increasing the availability of biologically active substances in the brain (see pages 89-93) and prodrugs (pages 93 and 94), which document is incorporated herein by reference.

In another example~~embodiment~~, the disclosure~~invention~~ relates to a mixture comprising the antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before and/or the biologically active substance in a therapeutically effective amount.

The disclosure~~invention~~ further relates to the use of an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before and/or a functional part thereof and/or a pharmaceutical composition, or a mixture comprising said antibody, for the preparation of a medicament for treating or alleviating the effects of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis such as diseases including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, and others, including macular degeneration.

Also comprised by the present disclosure~~invention~~ is a method for the preparation of an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before and/or a functional part thereof and/or a pharmaceutical composition, or a mixture comprising said antibody and/or a functional part

thereof, particularly in a therapeutically effective amount, for use in a method of preventing, treating or alleviating the effects of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis such as diseases including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, and others, including macular degeneration comprising formulating an antibody, particularly a monoclonal antibody according to the invention, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the invention in a pharmaceutically acceptable form.

Further comprised by the present disclosure~~invention~~ is a method for preventing, treating or alleviating the effects of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis such as diseases including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, and others, including macular degeneration by administering an antibody and/or a functional part thereof, but particularly a humanized antibody and/or a functional part thereof, or a composition or mixture comprising such an antibody and/or a functional part thereof, to a an animal or a human affected by such a disorder comprising administering the antibody in a therapeutically effective amount.

It is also an object of the disclosure~~invention~~ to describe~~provide~~ a method for the treatment of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), particularly a disease or condition characterized by a loss of

cognitive memory capacity by administering to an animal, particularly a mammal or a human, an antibody, particularly a pharmaceutical composition according to the disclosure~~invention~~ and as described herein.

In a specific ~~example~~~~embodiment~~ the disclosure~~invention~~ describes~~provides~~ a method for retaining or increasing cognitive memory capacity but, particularly, for restoring the cognitive memory capacity of an animal, particularly a mammal or a human, suffering from memory impairment by administering to an animal, particularly a mammal or a human, an antibody, particularly a pharmaceutical composition according to the disclosure~~invention~~ and as described herein before.

It is a further object of the disclosure~~invention~~ to describe~~provide~~ a therapeutic composition and a method of producing such a composition as well as a method for the treatment of amyloidosis, a group of diseases and disorders associated with amyloid plaque formation including secondary amyloidosis and age-related amyloidosis including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), particularly a disease or condition characterized by a loss of cognitive memory capacity, using an antibody according to the disclosure~~invention~~ and as described herein before.

In particular, the disclosure~~invention~~ relates to the treatment of an animal, particularly a mammal or a human, suffering from an amyloid-associated condition characterized by a loss of cognitive memory capacity leads to the retention of cognitive memory capacity.

The disclosure~~invention~~ further relates to a method of diagnosis of an amyloid-associated disease or condition in a patient comprising detecting the immunospecific binding of an antibody or an active fragment thereof to an epitope of the amyloid 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 amyloid protein into contact with an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the invention and as described herein before, and/or a functional part thereof, which antibody binds an epitope of the amyloid protein;

(b) allowing the antibody and/or a functional part thereof, to bind to the amyloid 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 amyloid protein in the sample or specific body part or area.

Also comprised is a method of determining the extent of amyloidogenic plaque burden in a tissue and/or body fluids comprising

(a) obtaining a sample representative of the tissue and/or body fluids under investigation;

(b) testing said sample for the presence of amyloid protein with an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before, and/or a functional part thereof;

(c) determining the amount of antibody bound to the protein; and

(d) calculating the plaque burden in the tissue and/or body fluids.

In particular, the disclosure~~invention~~ relates to a method of determining the extent of amyloidogenic plaque burden in a tissue and/or body fluids, wherein the formation of the immunological complex in step c) is determined such that presence or absence of the immunological complex correlates with presence or absence of amyloid protein.

In another example~~embodiment~~ of the disclosure~~invention~~, a test kit for detection and diagnosis of amyloid-associated diseases and conditions is provided comprising an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, but particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ and as described herein before, and/or a functional part thereof.

In particular, the disclosure~~invention~~ relates to a test kit for detection and diagnosis of amyloid-associated diseases and conditions comprising a container holding one or more antibodies according to the present disclosure~~invention~~, and/or a functional part thereof, and instructions for using the antibodies for the purpose of binding to amyloid protein 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 amyloid protein.

In another exampleaspect, the disclosureinvention provides an antibody comprising a variable region as recited in SEQ ID NO: 27, or a variant thereof. In one examplembodiment, a cell line expressing the antibody.

In another exampleaspect, the disclosureinvention describesprovides an antibody gene comprising a variable region as recited in SEQ ID NO: 29, or a variant thereof. In one examplembodiment, a cell line expresses the antibody.

In another exampleaspect, the disclosureinvention describesprovides a method for disaggregating preformed beta-amyloid fibers, comprising interacting an hC2 antibody with preformed beta-amyloid fibers.

In another exampleaspect, the disclosureinvention describesprovides a humanized antibody or a fragment thereof according to any of the preceding claims, wherein said antibody or fragment thereof protects neurons from Abeta-induced degradation.

In another exampleaspect, the disclosureinvention describesprovides a method of preventing Abeta-induced neuron degradation comprising treating neurons with an effective amount of a humanized antibody or a fragment thereof according to the disclosure herein.

In another exampleaspect, the disclosureinvention describesprovides use of a humanized antibody or a fragment thereof according to the description herein for the preparation of a medicament for preventing degeneration of neurons upon exposure to Abeta oligomer.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiment and the appended claims.

BRIEF DESCRIPTION OF FIGURES AND SEQUENCES

Figure 1 (Example 2): Expression Cassette of the mouse light chain variable region of the Chimeric Antibody

26. The nucleic acid molecule according to claim 23 or 24 encoding a light chain comprising the nucleotide sequence of SEQ ID NO: 22 and/or a heavy chain comprising the nucleotide sequence of SEQ ID NO: 25.

27. The nucleic acid molecule according to claim 23 or 24 encoding a light chain variable region and a light chain constant region comprising the nucleotide sequence of SEQ ID NO: 21 and the nucleotide sequence of SEQ ID NO: 23, respectively.

28. The nucleic acid molecule according to claim 23 or 24 encoding a heavy chain variable region and a heavy chain constant region comprising the nucleotide sequence of SEQ ID NO: 24 and the nucleotide sequence of SEQ ID NO: 26, respectively.

29. An expression vector comprising the nucleotide sequence of any one of claims 23-28.

30. A cell comprising the nucleic acid molecule of any one of claims 23-28 or an expression vector of claim 29.

31. A composition comprising the humanized antibody or active fragment thereof according to any one of claims 1-18.

32. A mixture comprising a therapeutically effective amount of (a) the humanized antibody or active fragment thereof according to any one of claims 1-18, and (b) one or more of the following: a biologically active substance, a pharmaceutically acceptable carrier, a diluent, or an excipient.

33. The mixture according to claim 32, wherein the biologically active substance is a compound used in the treatment of amyloidosis.

34. The mixture according to claim 33, further comprising at least one of the following compounds: an anti-oxidative stress compound; an anti-apoptotic compound; a metal chelator; a DNA repair inhibitor; 3-amino-1-propanesulfonic acid (3 APS); 1,3-propanedisulfonate (1,3PDS); an α-secretase activator; a β- and γ- secretase inhibitor; a tau protein; a neurotransmitter; a β-sheet breaker; an attractant for beta-amyloid clearing /

depleting cellular components~~;~~, an inhibitor of N-terminal truncated beta-amyloid~~;~~, an anti-inflammatory molecule~~;~~, a cholinesterase inhibitor (ChEI)~~;~~), an MI agonist; or another drug.

35. The mixture according to claim ~~33~~34, wherein the (i) DNA repair inhibitor is *pirenzepin, (ii) the inhibitor of N-terminal truncated beta-amyloid is pyroglutamated beta-amyloid* 3-42, (iii) the cholinesterase inhibitor (ChEI) is a tacrine, rivastigmine, donepezil, or galantamine, or (iv) the other drug is an amyloid- or tau-modifying drug or nutritive supplement.

36. The mixture according to claim 33, wherein the compound is tacrine, rivastigmine, donepezil, galantamine, niacin or memantine.

37. Use of the humanized antibody or active fragment thereof according to any one of claims 1-18, or a pharmaceutical composition according to any one of claims 19-22, and/or a composition according to claim 31, or a mixture according to any one of claims 32-36, for the preparation of a medicament for preventing, treating or alleviating amyloidosis.

38. The use according to claim 37, wherein the amyloidosis is secondary amyloidosis, age-related amyloidosis, Alzheimer's Disease (AD), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), progressive supranuclear palsy, multiple sclerosis, the Guam Parkinson-Dementia complex, Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes, senile cardiac amyloidosis, endocrine tumors, or macular degeneration.

39. Use of the humanized antibody or active fragment thereof according to any one of claims 1-18, or a pharmaceutical composition according to any one of claims 19-22, and/or a composition according to claim 31, or a mixture according to any one of claims 32-36, for the preparation of a medicament for preventing, treating or alleviating Alzheimer's disease in a subject.

40. The use according to claim 39, wherein the treatment of the subject leads to the retention of cognitive memory capacity.

Sequence Listing

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        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Ser
                85                  90                  95
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Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

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    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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35 40 45

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
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ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa ctccctgtac 240

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<210> 25
<211> 1317
<212> DNA
<213> artificial sequence

<220>
<223> artificial humanized C2 heavy chain

<400> 25
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catgaggctc tgcacaacca ctacacacag aagagcctct ccctgtctct gggtaaa 1317

<210> 26
<211> 981
<212> DNA
<213> Homo sapiens

<220>
<223> artificial humanized C2 heavy chain constant region

<400> 26
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tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc 240

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aaatatggtc ccccgtgtcc cccatgccca gcacctgagt tcctgggggg accatcagtc 360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg 420

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<210> 27
<211> 112
<212> PRT
<213> Mus musculus

<400> 27

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Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
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Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 28
<211> 112
<212> PRT
<213> Mus musculus

<400> 28

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Leu Val
35 40 45

Ala Ser Ile Asn Ser Asn Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Ser Gly Asp Tyr Trp Gly Gln Gly Ser Thr Leu Thr Val Ser Ser
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<210> 29
<211> 336
<212> DNA
<213> Mus musculus

<400> 29
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tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

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tggacgttcg gtggaggcac caagctagaa atcaaa 336

<210> 30
<211> 417
<212> DNA
<213> Mus musculus

<400> 30
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ctgcagaagc caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct 240

ggggtcccag acaggttcag tggcagtgga tcagggacag atttcacact caagatcagc 300

agagtggagg ctgaggatct gggagtttat ttctgctctc aaagtacaca tgttccttgg 360

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<210> 31
<211> 336
<212> DNA
<213> Mus musculus

<400> 31
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ccagacaaga ggctggaatt ggtcgcaagc atcaatagta atggtggtag cacctattat 180

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tactggggcc aaggctccac tctcacagtc tcctca 336

<210> 32
<211> 408
<212> DNA
<213> Mus musculus

<400> 32
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gacagtgtga agggccgatt caccatctcc agagacaatg ccaagaacac cctgtacctg 300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgcaag tggtgactac 360

tggggccaag gctccactct cacagtctcc tcagccaaaa caacaccc 408