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 (LBD), 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 other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation. Said pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

SUMMARY OF THE INVENTION

[0038a] In a first aspect, the present invention refers to the use of a humanized antibody or fragment thereof which binds to beta-amyloid in the preparation of a medicament for reducing the plaque load in the retinal ganglion cell layer of an animal suffering from cortical visual deficits, glaucoma, optic neuritis, ocular amyloidosis, or lattice dystrophy, wherein the humanized antibody or fragment thereof comprises: I. (A) (i) a heavy chain variable region (HCVR) comprising (a) a complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 1, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and (ii) a light chain variable region (LCVR) comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 12; or (B) (i) a light chain variable region (LCVR) comprising (a) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 5, or the amino acid sequence RVSNRFS, or the amino acid sequence KVSSRFS, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 6; and (ii) a heavy chain variable region comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 15; and II. a human IgG1 Fc region which comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the IgG1 Fc region.

[0038b] In a second aspect, the present invention refers to the use of a humanized antibody or fragment thereof which binds to beta-amyloid in the preparation of a medicament for reducing the amount of plaques in the retinal ganglion cell layer of an animal suffering from cortical visual deficits, glaucoma, optic neuritis, ocular amyloidosis, or lattice dystrophy, wherein the humanized antibody or fragment thereof comprises: I. (A) (i) a heavy chain variable region (HCVR) comprising (a) a complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 1, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and (ii) a light chain variable region comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 12; or (B) (i) a light chain variable region (LCVR) comprising (a) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 5, or the amino acid sequence RVSNRFS, or the amino acid sequence KVSSRFS, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 6; and (ii) a heavy chain variable region comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 15; and II. a human IgG1 Fc region which comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the IgG1 Fc region.

[0038c] In a third aspect, the present invention refers to the use of a humanized antibody or fragment thereof which binds to beta-amyloid in the preparation of a medicament for decreasing the total amount of soluble beta-amyloid in the retinal ganglion cell layer of an animal suffering from cortical visual deficits, glaucoma, optic neuritis, ocular amyloidosis, or lattice dystrophy, wherein the humanized antibody or functional fragment thereof comprises: I. (A) (i) a heavy chain variable region (HCVR) comprising (a) a complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 1, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and (ii) a light chain variable region comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 12; or (B) (i) a light chain variable region (LCVR) comprising (a) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4, (b) a CDR2 comprising the amino acid sequence of SEQ ID NO: 5, or the amino acid sequence RVSNRFS, or the amino acid sequence KVSSRFS, and (c) a CDR3 comprising the amino acid sequence of SEQ ID NO: 6; and (ii) a heavy chain variable region comprising an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 15; and II. a human IgG1 Fc region which comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the IgG1 Fc region.

[0039] In one example~~embodiment~~, the disclosure~~invention~~ relates to a chimeric antibody or a fragment thereof, 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.

[0040] 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 the three distinct binding sites comprise at least one amino acid residue.

[0041] 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.

[0042] 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.

[0043] In particular, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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):

[0044] Xaa_3 - Phe – Phe – Xaa_4 – Xaa_5 – Xaa_6, wherein:

[0045] Xaa_3 is an amino acid residue selected from the group consisting of Ala, Val, Leu, norleucine, Met, Phe, and Ile;

[0046] Xaa_4 is an amino acid residue selected from the group consisting of Ala, Val, Leu, Ser and Ile;

[0047] Xaa_5 is an amino acid residue selected from the group consisting of Glu and Asp;

[0048] 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.

[0049] In another example~~embodiment of the invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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.

[0050] In particular, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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 invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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.

[0051] In another example~~embodiment of the 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 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.

[0052] In another example~~embodiment of the 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 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.

[0053] In another example~~embodiment of the invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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.

[0054] In another example~~embodiment of the 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, 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.

[0055] In another example~~embodiment of the 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 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.

[0056] In another example~~embodiment of the invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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.

[0057] In another example~~embodiment of the 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, 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.

[0058] In another example~~embodiment of the invention~~, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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.

[0059] In another example~~embodiment of the 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.

[0060] In another example~~embodiment of the 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 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.

[0061] In another example~~embodiment of the invention~~, a 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.

[0062] In a specific example~~embodiment of the 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.

[0063] In still another example~~embodiment of the 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.

[0064] 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

[0065] 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

[0066] In another example~~embodiment of the invention~~, a humanized antibody or a fragment thereof is 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.

[0067] In still another example~~embodiment of the invention~~, a humanized antibody or a fragment thereof is 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.

[0068] In a specific example~~embodiment of the 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.

[0069] 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).

[0070] In one example~~embodiment of the invention~~, 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).

[0071] Also the use of lipid A as part of the immunization protocol may have contributed to a shift in the epitopic region.

[0072] In a specific example~~embodiment~~, the disclosure~~invention~~ 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).

[0073] In another example~~embodiment~~, the disclosure~~invention~~ 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).

[0074] In still another example~~embodiment~~, the disclosure~~invention~~ 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).

[0075] In particular, the disclosure~~invention~~ 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).

[0076] In another specific example~~embodiment~~, the disclosure~~invention~~ 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).

[0077] The disclosure~~invention~~ 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.

[0078] Also comprised by the disclosure~~invention~~ 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.

[0079] In particular, the disclosure~~invention~~ 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).

[0080] In a further example~~embodiment~~, the disclosure~~invention~~ 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).

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] In still anther example~~embodiment~~, 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.

[0089] In still anther example~~embodiment~~, 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).

[0090] 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).

[0091] 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).

[0092] 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).

[0093] 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).

[0094] 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).

[0095] 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).

[0096] 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).

[0097] 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 CDR2 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 5 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: 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 CDR3 (HCVR) in combination with an amino acid sequence of SEQ ID NO: 6 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: 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).

[0098] *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 as described herein before, which antibody comprises a light chain and/or a heavy chain constant region of human or primate origin.*

[0099] In a further example~~embodiment~~, the disclosure~~invention~~ 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.

[0100] In particular, the disclosure~~invention~~ 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.

[0101] In particular, the disclosure~~invention~~ 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.

[0102] In another example~~embodiment~~, the disclosure~~invention~~ 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.

[0103] 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.

[0104] In one example~~embodiment of the 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.

[0105] In another example~~embodiment of the 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.

[0106] In still another example~~embodiment of the 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.

[0107] In a further example~~embodiment of the 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] In particular, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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.

[0114] The disclosure~~invention~~ further relates to a humanized antibody, 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 as shown in SEQ ID NO: 15 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser.

[0115] In still another example~~embodiment~~, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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.

[0116] The disclosure~~invention~~ further relates to a humanized antibody, 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 as shown in SEQ ID NO: 12 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.

[0117] The disclosure~~invention~~ further relates to a humanized antibody, wherein the Leu in Kabat position 50 in the acceptor framework sequence obtained from human germline

V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region as shown in SEQ ID NO: 12 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.

[0118] The disclosure~~invention~~ further relates to a humanized antibody, 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 as shown in SEQ ID NO: 12 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.

[0119] In still another example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, wherein the Asn in Kabat position 53 in the acceptor framework sequence obtained from human germline V_K sequences of KABAT subgroup V_KII of the Light Chain Variable Region as shown in SEQ ID NO: 12 may be replaced by an amino acid selected from the group consisting of Gln, His, Lys and Arg, but especially by His and Gln.

[0120] In still another example~~embodiment~~, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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 as shown in SEQ ID NO: 15 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser, 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 as shown in SEQ ID NO: 12 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.

[0121] In still another example~~embodiment~~, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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.

[0122] In still another example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, 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 as shown in SEQ ID NO: 15 is replaced by an amino acid selected from the group consisting of Ser and Thr, but especially by Ser.

[0123] In still another example~~embodiment~~, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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 as shown in SEQ ID NO: 15 is replaced by Ser.

[0124] In still another example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody, 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 as shown in SEQ ID NO: 12 is replaced by Phe.

[0125] *In still another example~~embodiment~~, the disclosure~~invention~~ 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 as shown in SEQ ID NO: 15 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 as shown in SEQ ID NO: 15 is replaced by Ser 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 as shown in SEQ ID NO: 12 is replaced by Phe.

[0126] In a specific example~~embodiment~~, the disclosure~~invention~~ relates to the light chain variable region of SEQ ID NO: 12.

[0127] In another specific example~~embodiment of the invention~~, a humanized antibody is provided, which comprises the light chain variable region of SEQ ID NO: 12.

[0128] In a specific example~~embodiment~~, the disclosure~~invention~~ relates to the light chain variable region including signal sequences as shown in SEQ ID NO: 13.

[0129] In another specific example~~embodiment of the invention~~, a humanized antibody is provided, which comprises the complete light chain variable region including signal sequences as shown in SEQ ID NO: 13.

[0130] In another specific example~~embodiment of the invention~~, 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.

[0131] In another specific example~~embodiment of the invention~~, 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.

[0132] In a specific example~~embodiment~~, the disclosure~~invention~~ relates to the heavy chain variable region of SEQ ID NO: 15.

[0133] In another specific example~~embodiment of the invention~~, a humanized antibody is provided, which comprises the heavy chain variable region of SEQ ID NO: 15.

[0134] In a specific example~~embodiment~~, the disclosure~~invention~~ relates to the heavy chain variable region including signal sequences as shown in SEQ ID NO: 16.

[0135] In another specific example~~embodiment of the invention~~, a humanized antibody is provided, which comprises the complete heavy chain variable region including signal sequences as shown in SEQ ID NO: 16.

[0136] In another specific example~~embodiment of the invention~~, 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.

[0137] In another specific example~~embodiment of the invention~~, 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.

[0138] In one example~~embodiment~~ the humanized antibody according to the disclosure~~invention~~ 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, 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.

[0139] 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.

[0140] In a specific example~~embodiment of the invention~~, co-incubation with amyloid monomeric and/or polymeric soluble amyloid peptides is accomplished for 24 hours at a temperature of 37°C.

[0141] 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 Aβ 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 Aβ 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.

[0142] In one examplembodiment, the antibody, particularly the humanized antibody according to the disclosureinvention 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.

[0143] In a specific examplembodiment of the invention, the antibody, particularly the humanized antibody according to the disclosureinvention 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.

[0144] In another specific examplembodiment of the 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 80% at a molar concentration ratio of antibody to $A\beta$1-42 of 1:10.

[0145] 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 disclosureinvention 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.

[0146] The aggregation inhibition potential of the antibody according to the disclosure~~invention~~ may be determined by any suitable method known in the art, particularly by density-gradient ultracentrifugation followed by an SDS-PAGE sedimentation analysis on a preformed gradient and/or by a thioflavin T (Th-T) fluorescent assay.

[0147] In one example~~embodiment~~, the disclosure~~invention~~ 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 1:10 and 1:1000, more particularly at a ratio of 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.

[0148] In a specific example~~embodiment of the invention~~, 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.

[0149] In another specific example~~embodiment of the invention~~, the aggregation inhibition and the disaggregation potential of the antibody, respectively, is determined by thioflavin T (Th-T) fluorescent assay.

[0150] In another specific example~~embodiment~~, the antibody according to the disclosure~~invention~~ 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.

[0151] 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.

[0152] In a specific example~~embodiment of the invention~~, the antibody, particularly the humanized antibody according to the disclosure~~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.

[0153] In another specific example~~embodiment of the invention~~, the antibody, particularly the humanized antibody according to the disclosure~~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.

[0154] Through the disaggregation of amyloidogenic polymeric fibrils or filaments the antibodies according to the present disclosure~~invention~~ 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.

[0155] Accordingly, it is a further example~~embodiment of the invention~~ 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.

[0156] In another example~~embodiment~~, the disclosure~~invention~~ relates to a humanized antibody according to the disclosure~~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.

[0157] 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 disclosure~~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.

[0158] In another exampleaspeet, the disclosureinvention relates to a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present disclosureinvention 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).

[0159] 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.

[0160] In a further examplembodiment of the invention, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present

disclosureinvention 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 binding affinity of at least about 1 x 10^{-7} to at least about 1 x 10^{-12}, particularly of at least about 1 x 10^{-8} to at least about 1 x 10^{-11}, more particularly of at least about 1 x 10^{-9} to at least about 1 x 10^{-10}, even more particularly of at least about 1 x 10^{-8} to at least about 2 x 10^{-8}, but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

[0161] In another exampleembodiment of the invention, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the present disclosureinvention 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 binding affinity of at least about 1 x 10^{-7} to at least about 1 x 10^{-12}, particularly of at least about 1 x 10^{-8} to at least about 1 x 10^{-11}, more particularly of at least about 1 x 10^{-9} to at least about 1 x 10^{-10}, even more particularly of at least about 2 x 10^{-9} to at least about 5 x 10^{-9}, but, preferably, does not show any significant cross-reactivity with amyloid precursor protein (APP).

[0162] In another exampleembodiment, the antibody according to the disclosureinvention and as described herein before or a fragment thereof, exhibits an binding affinity to an Aβ fiber, fibril or filament which is 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.

[0163] In still another exampleembodiment, a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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).

[0164] In another aspect of the disclosureinvention, the chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof is 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).

[0165] 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 of a subject, particularly a mammal, and even more particularly a human, and in particular in the brain of the subject. 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 of the subject, particularly the brain. The beneficial effect of the antibody according to the disclosure~~invention~~ can thus be obtained without binding of the antibody to the plaque.

[0166] 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 of a subject, particularly a mammal, and even more particularly a human, and in particular in the brain of the subject. In a specific example~~embodiment of the invention~~ the antibody according to the disclosure~~invention~~ may thus achieve its beneficial effects without necessarily binding aggregated amyloid beta in the brain of the subject.

[0167] In a further example~~aspect of the 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.

[0168] 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 example~~embodiment~~, it can be an antigen-binding fragment (e.g., Fab, $F(ab')_2$, and Fv) of a whole antibody.

[0169] The disclosure~~invention~~ thus also relates to antigen-binding fragments of the antibodies described herein. In one example~~embodiment of the 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.

[0170] In another example~~embodiment~~, the antibody or antigen-binding fragment of the invention is conjugated to polyethylene glycol. In yet another example~~embodiment~~, the constant region of the antibody of the invention is modified to reduce at least one constant region-mediated biological effector function relative to an unmodified antibody. In still another example~~embodiment~~, the antibody or antigen-binding fragment of the invention comprises an Fc region having an altered effector function.

[0171] 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.

[0172] 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).

[0173] 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).

[0174] In another example~~embodiment of the 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).

[0175] In another example~~embodiment of the 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).

[0176] In another example~~embodiment of the 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.

[0177] In another example~~embodiment of the 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.

[0178] In another example~~embodiment of the 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.

[0179] In another example~~embodiment of the 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.

[0180] In another example~~embodiment of the 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.

[0181] In another example~~embodiment of the invention~~ 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 disclosure~~invention~~ also comprises the complementary strand of said nucleotide molecule.

[0182] Also comprised by the present disclosure~~invention~~ 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.

[0183] In particular, the disclosure~~invention~~ 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.

[0184] In another example~~embodiment of the invention~~ an expression vector is provided comprising the nucleic acid molecule according to the disclosure~~invention~~ and as mentioned herein before.

[0185] In another example~~embodiment of the invention~~ a cell is provided comprising an expression vector comprising the nucleic acid according to the disclosure~~invention~~ and as mentioned herein before.

[0186] In still another example~~embodiment~~, the disclosure~~invention~~ relates to a composition comprising the 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 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 or therapeutic composition, optionally further comprising a pharmaceutically acceptable carrier.

[0187] In another example~~embodiment of the invention~~, said composition comprises the antibody in a therapeutically effective amount.

[0188] Further comprised by the disclosure~~invention~~ is a composition comprising 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 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.

[0189] In particular, the disclosure~~invention~~ relates to a composition or 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.

[0190] In another example~~embodiment of the 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.

[0191] 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.

[0192] 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.

[0193] More particularly, the disclosure~~invention~~ relates to a composition or 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.

[0194] The disclosure~~invention~~ further relates to a composition or 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.

[0195] In a further example~~embodiment~~, the compositions according to the disclosure~~invention~~ may comprise niacin or memantine together with an antibody according to the present disclosure~~invention~~ and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

[0196] In still another example~~embodiment of the invention~~ compositions are provided that comprise "atypical antipsychotics" such as 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 disclosure~~invention~~, more 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, and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

[0197] In a specific example~~embodiment of the invention~~, the compositions and mixtures according to the disclosure~~invention~~ and as described herein before comprise the antibody and the biologically active substance, respectively, in a therapeutically effective amount.

[0198] 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.

[0199] In another example~~embodiment~~, the disclosure~~invention~~ relates to a composition comprising the antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, more 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.

[0200] The disclosure~~invention~~ further relates to the use of an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, more 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, and neurological disorders, such as Alzheimer's Disease (AD), Lewy body dementia (LBD), 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 other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation. Said pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

[0201] 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~~, more 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, comprising formulating an antibody, particularly a monoclonal antibody according to the disclosure~~invention~~, more particularly a chimeric antibody or a fragment thereof, or a humanized antibody or a fragment thereof according to the disclosure~~invention~~ in a pharmaceutically acceptable form, 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, and neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia (LBD), 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 other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation. The pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

[0202] 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, and neurological disorders such as Alzheimer's Disease (AD), Lewy body dementia (LBD), 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 other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation, wherein the pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular

amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy, by administering an antibody and/or a functional part thereof, more 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 subject, including a mammal, or a human affected by such a disorder, in a therapeutically effective amount.

[0203] Also disclosed herein is~~It is also an object of the invention to 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), and other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation, wherein the pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy, by administering to the subject, particularly a mammal or a human affected by such a disorder, an antibody, particularly a pharmaceutical composition according to the disclosure~~invention~~ and as described herein.

[0204] In a specific example~~embodiment the invention~~ provides a method for retaining or increasing cognitive memory capacity but, particularly, for restoring the cognitive memory capacity of a subject, particularly a mammal or a human, suffering from memory impairment by administering to the subject, particularly a mammal or a human in need thereof, an antibody, particularly a pharmaceutical or therapeutic composition according to the disclosure~~invention~~ and as described herein before.

[0205] Also disclosed herein is~~It is a further object of the invention to 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) and other diseases, including ocular diseases associated with pathological abnormalities/changes in the tissues of the visual system, particularly associated with amyloid-beta-related pathological abnormalities/changes in the tissues of the visual system, such as neuronal degradation. The pathological abnormalities may occur, for example, in different tissues of the eye, such as the visual cortex leading to cortical visual deficits; the anterior chamber and the optic nerve leading to glaucoma; the lens leading to cataract due to beta-amyloid deposition; the vitreous leading to ocular amyloidosis; the retina leading to primary retinal degeneration and macular degeneration, for example age-related macular degeneration; the optic nerve leading to optic nerve drusen, optic neuropathy and optic neuritis; and the cornea leading to lattice dystrophy.

[0206] The disclosure~~invention~~ further relates to a method of diagnosis of an amyloid-associated disease or condition 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 disclosure~~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 of the subject.

[0207] 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~~, more 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.

[0208] In particular, the disclosure~~invention~~ relates to a method of determining the extent of amyloidogenic plaque burden in a tissue and/or body fluids in need thereof, 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.

[0209] In another example~~embodiment of the invention~~, a test kit for detection and diagnosis of amyloid-associated diseases and conditions in a subject 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.

[0210] 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.

[0211] In another exampleaspect, the disclosureinvention provides methods and compositions for preventing, treating, or detecting a disease associated with amyloidosis in a subject in need thereof using immunoglobulins as described herein that further comprise a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region. The Fc region mediates the effector function of the antibody or fragment thereof. By modulating the ability of the Fc portion of the antibody or fragment thereof to bind to or activate its receptor, it is possible to abrogate or enhance the effector function of the antibody or fragment thereof.

[0212] Thus, in another exampleaspect, the disclosureinvention provides an antibody or fragment thereof of the disclosureinvention further comprising a variant Fc region comprising at least one amino acid mutation which decreases effector function. In one such exampleaspect, the at least one amino acid mutation decreases glycosylation of the antibody or fragment thereof. In another such exampleaspect, the at least one amino acid mutation decreases binding to a cognate Fc receptor. In another such exampleaspect, the at least one amino acid mutation decreases activation of a cognate Fc receptor upon binding of the antibody or fragment thereof. In one such exampleaspect, the variant Fc region is a variant IgG1 Fc region. In one such exampleaspect, the antibody or fragment thereof comprises a D265A mutation in the Fc region.

[0213] In another exampleaspect, the disclosureinvention provides an antibody or fragment thereof of the disclosureinvention further comprising a variant Fc region comprising at least one amino acid mutation which increases effector function. In one such exampleaspect, the at least one amino acid mutation enhances glycosylation of the antibody or fragment thereof. In another such exampleaspect, the at least one amino acid mutation increases binding to a cognate Fc receptor. In another such exampleaspect, the at least one amino acid mutation increases activation of a cognate Fc receptor upon binding of the antibody or fragment thereof. These and other objects, features and advantages of the present disclosureinvention

SEQUENCE LISTING:

<110> AC Immune

<120> Humanized Antibody

<130> 089667-0156

<141> 2008-10-03

<150> US 60/960,617

<151> 2007-10-05

<160> 32

<170> PatentIn version 3.3

<210> 1
<211> 10
<212> PRT
<213> Mus musculus

<220>
<223> C2 HuVH AF 4 humanised heavy chain variable region (CDR1)

<400> 1

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5 10

<210> 2
<211> 17
<212> PRT
<213> Mus musculus

<220>
<223> C2 HuVH AF 4 humanised heavy chain variable region (CDR2)

<400> 2

Ser Ile Asn Ser Asn Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
1 5 10
15

Gly

<210> 3
<211> 3
<212> PRT

<213> Mus musculus

<220>
<223> C2 HuVH AF 4 humanised heavy chain variable region (CDR3)

<400> 3

Gly Asp Tyr
1

<210> 4
<211> 16
<212> PRT
<213> Mus musculus

<220>
<223> C2 HuVK 1 humanised light chain variable region (CDR1)

<400> 4

Arg Ser Ser Gln Ser Leu Val Tyr Ser Asn Gly Asp Thr Tyr Leu His
1 5 10
15

<210> 5
<211> 7
<212> PRT
<213> Mus musculus

<220>
<223> C2 HuVK 1 humanised light chain variable region (CDR2)

<400> 5

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 6
<211> 9
<212> PRT
<213> Mus musculus

<220>
<223> C2 HuVK 1 humanised light chain variable region (CDR3)

<400> 6

Ser Gln Ser Thr His Val Pro Trp Thr
1 5

<210> 7
<211> 6
<212> PRT

<213> Homo sapiens

<220>
<223> Aβ epitope, region 2

<400> 7

Val Phe Phe Ala Glu Asp
1 5

<210> 8
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<223> Aβ epitope, region 1

<400> 8

His Gln Lys Leu Val
1 5

<210> 9
<211> 6
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be Ala, Val, Leu, norleucine, Met, Phe, or Ile

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa can be Ala, Val, Leu, Ser or Ile

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa can be Glu or Asp

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa can be Glu or Asp

<400> 9

Xaa Phe Phe Xaa Xaa Xaa
1 5

<210> 10
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be His, Asn, Gln Lys, or Arg

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa can be Asn or Gln

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa can be Ala, Val, Leu, norleucine, Met, Phe, or Ile

<400> 10

Xaa Xaa Lys Leu Xaa
1 5

<210> 11
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be His, Asn, Gln Lys, or Arg

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa can be Asn or Gln

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa can be Ala, Val, Leu, norleucine, Met, Phe, or Ile

<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa can be Ala, Val, Leu, Ser or Ile

<220>

<221> misc_feature
<222> (9)..(9)
<223> Xaa can be Glu or Asp

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa can be Glu or Asp

<400> 11

Xaa Xaa Lys Leu Xaa Phe Phe Xaa Xaa Xaa
1 5 10

<210> 12
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> artificial humanized C2 HuVK 1 variable light chain

<400> 12

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10
15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
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

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

<210> 13
<211> 219
<212> PRT
<213> artificial sequence

<220>
<223> artificial humanized C2 light chain

<400> 13

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10
15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

Asn Gly Asp Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
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

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

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155
160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170
175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 14
<211> 107
<212> PRT
<213> artificial sequence

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

<400> 14

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10
15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75
80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

85 90

95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

100 105

<210> 15

<211> 112

<212> PRT

<213> artificial sequence

<220>

<223> artificial humanized C2 HuVH AF 4 variable heavy chain

<400> 15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10

15

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

20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly 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 Ser Leu Tyr

65 70 75
80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90
95

Ala Ser Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105 110

<210> 16
<211> 439
<212> PRT
<213> artificial sequence

<220>
<223> artificial humanized C2 heavy chain

<400> 16

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly 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 Ser Leu Tyr
65 70 75
80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90
95

Ala Ser Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
115 120 125

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
130 135 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145 150 155
160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
165 170
175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
180 185 190

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
195 200 205

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
210 215 220

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235
240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250
255

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
275 280 285

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu

305 310 315
320

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
325 330
335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395
400

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
405 410
415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Leu Gly Lys

435

<210> 17

<211> 326

<212> PRT

<213> Homo sapiens

<220>
<223> IG GAMMA-4 CHAIN C REGION - modified

<400> 17

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10
15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75
80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90
95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro

100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155
160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170
175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235
240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250
255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315
320

Leu Ser Leu Ser Leu Gly
325

<210> 18
<211> 51
<212> DNA
<213> Mus musculus

<220>
<223> C2 HuVH AF 4 humanised heavy chain variable region (CDR2)

<400> 18
agcatcaata gtaatggtgg tagcacctat tatccagaca gtgtgaaggg c
51

<210> 19
<211> 9
<212> DNA
<213> Mus musculus

<220>
<223> C2 HuVH AF 4 humanised heavy chain variable region (CDR3)

<400> 19
ggtgactac
9

<210> 20
<211> 49
<212> DNA
<213> Mus musculus

<220>
<223> C2 HuVK 1 humanised light chain variable region (CDR1)

<400> 20
agatctagtc agagccttgt atatagtaat ggagacacct atttacatt
49

<210> 21
<211> 635
<212> DNA
<213> artificial sequence

<220>
<223> artificial humanized C2 Hu VK 1 variable light chain

<400> 21
gatattgtga tgacccaatc tccactctcc ctgcctgtca ctcctggtga gcctgcctcc
60

atctcttgca gatctagtca gagccttgta tatagtaatg gagacaccta tttacattgg
120

tacctgcaga agccaggcca gtctccacag ctcctgatct acaaagtttc caaccgattt
180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
240

agcagagtgg aggctgagga tgtgggagtt tattactgct ctcaaagtac acatgttcct
300

tggacgttcg gccaaggcac caaggtggaa atcaaa
336

<210> 22
<211> 657
<212> DNA
<213> artificial sequence

<220>
<223> artificial humanized C2 light chain

<400> 22
gatattgtga tgacccaatc tccactctcc ctgcctgtca ctcctggtga gcctgcctcc
60

atctcttgca gatctagtca gagccttgta tatagtaatg gagacaccta tttacattgg
120

tacctgcaga agccaggcca gtctccacag ctcctgatct acaaagtttc caaccgattt
180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
240

agcagagtgg aggctgagga tgtgggagtt tattactgct ctcaaagtac acatgttcct
300

tggacgttcg gccaaggcac caaggtggaa atcaaaagga ctgtggctgc accatctgtc
360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg
420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa
480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt
657

<210> 23
<211> 321
<212> DNA
<213> Homo sapiens

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

<400> 23
aggactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct
60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag
120

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac
180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag
240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag
300

agcttcaaca ggggagagtg t
321

<210> 24
<211> 798
<212> DNA
<213> artificial sequence

<220>
<223> artificial humanized C2 HuVH AF variable heavy chain

<400> 24
gaggtgcagc tggtcgagtc tgggggaggc ttagtgcagc ctggagggtc cctgagactc
60

tcctgtgcag cctctggatt cactttcagt agctatggca tgtcttgggt tcgccaggct
120

ccaggcaagg gtctcgaatt ggtcgcaagc atcaatagta atggtggtag cacctattat
180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa ctccctgtac
240

ctgcaaatga acagtctgag agctgaggac accgccgtgt attactgtgc aagtggtgac
300

tactggggcc aaggcaccac tgtcacagtc tcctca
336

<210> 25
<211> 1317
<212> DNA

<213> artificial sequence

<220>
<223> artificial humanized C2 heavy chain

<400> 25
gaggtgcagc tggtcgagtc tgggggaggc ttagtgcagc ctggagggtc cctgagactc
60

tcctgtgcag cctctggatt cactttcagt agctatggca tgtcttgggt tcgccaggct
120

ccaggcaagg gtctcgaatt ggtcgcaagc atcaatagta atggtggtag cacctattat
180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa ctccctgtac
240

ctgcaaatga acagtctgag agctgaggac accgccgtgt attactgtgc aagtggtgac
300

tactggggcc aaggcaccac tgtcacagtc tcctcagctt ccaccaaggg cccatccgtc
360

ttccccctgg cgccctgctc cagatcgacc tccgagagca cagccgccct gggctgcctg
420

gtcaaggact acttccccga accggtgacg gtgtcgtgga actcaggcgc cctgaccagc
480

ggcgtgcaca ccttcccggc tgtcctacag tcctcaggac tctactccct cagcagcgtg
540

gtgaccgtgc cctccagcag cttgggcacg aagacctaca cctgcaacgt agatcacaag
600

cccagcaaca ccaaggtgga caagagagtt gagtccaaat atggtccccc gtgtccccca
660

tgcccagcac ctgagttcct gggggggacca tcagtcttcc tgttcccccc aaaacccaag
720

gacactctca tgatctcccg gacccctgag gtcacgtgcg tggtggtgga cgtgagccag
780

gaagaccccg aggtccagtt caactggtac gtggatggcg tggaggtgca taatgccaag
840

acaaagccgc gggaggagca gttcaacagc acgtaccgtg tggtcagcgt cctcaccgtc
900

ctgcaccagg actggctgaa cggcaaggag tacaagtgca aggtctccaa caaaggcctc
960

ccgtcctcca tcgagaaaac catctccaaa gccaaagggc agccccgaga gccacaggtg
1020

tacaccctgc ccccatccca ggaggagatg accaagaacc aggtcagcct gacctgcctg
1080

gtcaaaggct tctaccccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag
1140

aacaactaca agaccacgcc tcccgtcctc gattccgacg gctccttctt cctctacagc
1200

aggctaaccg tggacaagag caggtggcag gaggggaatg tcttctcatg ctccgtgatg
1260

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
gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccagatc gacctccgag
60

agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacgaagacc
240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc
300

aaatatggtc ccccgtgtcc cccatgccca gcacctgagt tcctgggggg accatcagtc
360

ttcctgttcc ccccaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg
420

tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat
480

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac
540

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag
600

tgcaaggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa
660

gggcagcccc gagagccaca ggtgtacacc ctgccccat cccaggagga gatgaccaag
720

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag
780

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt cctcgattcc
840

gacggctcct tcttcctcta cagcaggcta accgtggaca agagcaggtg gcaggagggg
900

aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc
960

ctctccctgt ctctgggtaa a
981

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

<400> 27

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10
15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

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
100 105 110

<210> 29
<211> 336
<212> DNA

<213> Mus musculus

<400> 29
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
60

atctcttgca gatctagtca gagccttgta tatagtaatg gagacaccta tttacattgg
120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt
180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttcct
300

tggacgttcg gtggaggcac caagctagaa atcaaa
336

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

<400> 30
atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcctgcttc cagcagtgat
60

gttgtgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc
120

tcttgcagat ctagtcagag ccttgtatat agtaatggag acacctattt acattggtac
180

ctgcagaagc caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct
240

ggggtcccag acaggttcag tggcagtgga tcagggacag atttcacact caagatcagc
300

agagtggagg ctgaggatct gggagtttat ttctgctctc aaagtacaca tgttccttgg
360

acgttcggtg gaggcaccaa gctagaaatc aaacgggctg atgctgcacc aactgta
417

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

<400> 31
gaggtgcagc tggtggagtc tgggggaggc ttagtgcagc ctggagggtc cctgaaactc
60

tcctgtgcag cctctggatt cactttcagt agctatggca tgtcttgggt tcgccagact
120

ccagacaaga ggctggaatt ggtcgcaagc atcaatagta atggtggtag cacctattat
180

ccagacagtg tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgtac
240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagtggtgac
300

tactggggcc aaggctccac tctcacagtc tcctca
336

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

<400> 32
atgrasttsg ggytcagmtt grttttcctt gcccttattt taaaaggtgt ccaatgtgag
60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaactctcc
120

tgtgcagcct ctggattcac tttcagtagc tatggcatgt cttgggttcg ccagactcca
180

gacaagaggc tggaattggt cgcaagcatc aatagtaatg gtggtagcac ctattatcca
240

gacagtgtga agggccgatt caccatctcc agagacaatg ccaagaacac cctgtacctg
300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgcaag tggtgactac
360

tggggccaag gctccactct cacagtctcc tcagccaaaa caacaccc
408