Claims

1. An antibody or a functional variant thereof, wherein the variable part of the light chain of said antibody comprises, consists essentially of or consists of an amino acid sequence of:

DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSDGKTYLNWFQQRPGQSPRRLTYLVSKLDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHFPFTFGGGTKVEIK (SEQ ID NO: 1),

and

wherein the variable part of heavy chain of said antibody comprises, consists essentially of or consists of an amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSS (SEQ ID NO: 2).

2. The antibody of claim 1, comprising the CDR regions:

V_L CDR1: SSQSLLYSDGKTYLN (SEQ ID NO: 3);
V_L CDR2: LVSKLDS (SEQ ID NO: 4); and
V_L CDR3: VQGTHFP (SEQ ID NO: 5)

in the light chain.

3. The antibody of claim 1, comprising the CDR regions:

V_H CDR1: GYSFTGHTMN (SEQ ID NO: 6);
V_H CDR2: LINPSDGVTRYNQKFQG (SEQ ID NO: 7); and
V_H CDR3: EAKREWDETY (SEQ ID NO: 8)

in the heavy chain.

4. The antibody according to any one of the preceding claims, wherein the light chain comprises, consists essentially of or consists of the amino acid sequence of:

DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSDGKTYLNWFQQRPGQSPRRLTYLVSKLDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHFPFTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 17).

5. The antibody according to any one of the preceding claims, wherein the heavy chain comprises, consists essentially of or consists of the amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 18).

6. The antibody according to any one of the preceding claims, wherein the heavy chain comprises, consists essentially of or consists of the amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 19).

7. The antibody according to any one of the preceding claims, wherein said humanized antibody specifically binds to the pyroglutamate carrying N-terminus of the Aβ N3pE epitope.

8. The antibody according to any one of the preceding claims, wherein said humanized antibody binds specifically to an epitope selected from the group consisting of

pEFRHDSGYEVHHQKLV (SEQ ID NO: 23),
pEFRHDSGYEVHHQKL (SEQ ID NO: 24),
pEFRHDSGYEVHHQK (SEQ ID NO: 25),
pEFRHDSGYEVHHQ (SEQ ID NO: 26),
pEFRHDSGYEVHH (SEQ ID NO: 27),
pEFRHDSGYEVH (SEQ ID NO: 28),
pEFRHDSGYEV (SEQ ID NO: 29),
pEFRHDSGYE (SEQ ID NO: 30),
pEFRHDSGY (SEQ ID NO: 31),
pEFRHDSG (SEQ ID NO: 32),
pEFRHDS (SEQ ID NO: 33),
pEFRHD (SEQ ID NO: 34)
pEFRH (SEQ ID NO: 35), and
pEFR (SEQ ID NO: 36).

9. The antibody according to any one of claims 1 to 6, wherein said humanized antibody of the invention binds to an Aβ N3pE variant, wherein the Aβ N3pE variant is defined as pE-Aβ_{3-x}, wherein x is defined as an integer between 19 and 42.

10. The antibody of claim 9, wherein the Aβ N3pE variant is selected from:

pE-Aβ_{3-38},
pE-Aβ_{3-40},
pE-Aβ_{3-42}.

11. The antibody according to any one of the preceding claims, wherein said antibody does not bind to epitopes that do not carry a pyroglutamate at the N-terminus.

12. A pharmaceutical composition comprising the antibody according to any one of the preceding claims.

13. The pharmaceutical composition of claim 12, further comprising a further biologically active substance and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

14. The pharmaceutical composition of claim 13, wherein said further biologically active substance is selected from 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.

15. The pharmaceutical composition of claim 14, wherein said further biologically active substance is 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 (3 APS), 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, such as inhibitors of glutaminyl cyclase, 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 drugs and nutritive supplements, cholinesterase inhibitors (ChEIs), memantine or glutaminyl cyclase inhibitors.

16. The antibody or the pharmaceutical composition according to any one of the preceding claims for use in the diagnosis,

treatment of amyloidosis, especially for use in the treatment of a neurodegenerative disease selected from the group consisting of mild cognitive impairment (MCI), Alzheimer's disease (AD), like for instance sporadic Alzheimer's disease (SAD) or Familial Alzheimer's dementias (FAD) like Familial British Dementia (FBD) and Familial Danish Dementia (FDD), neurodegeneration in Down Syndrome and clinical or pre-clinical cerebral amyloid angiopathy; and/or the treatment of a condition selected from prodromal AD, mild AD, moderate AD and severe AD and/or the slowing of cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy.

17. The antibody or the pharmaceutical composition for use according to claim 24, wherein the administration of said antibody or said pharmaceutical composition leads to the reversion of cognitive decline, improvement of cognition or the prevention of cognitive decline in a subject diagnosed with mild cognitive impairment (MCI), Alzheimer's disease (AD), like for instance sporadic Alzheimer's disease (SAD) or Familial Alzheimer's dementias (FAD) like Familial British Dementia (FBD) and Familial Danish Dementia (FDD), neurodegeneration in Down Syndrome and clinical or pre-clinical cerebral amyloid angiopathy and/or of a condition selected from prodromal AD, mild AD, moderate AD and severe AD; or

wherein the administration of said antibody or said pharmaceutical composition leads to the clearance or removal of Aβ N3pE from plaques or other biological complexes; or

wherein the administration of said antibody or said pharmaceutical composition leads to the reduction of the plaque load and/or the removal of complete plaques from the affected tissue, such as brain tissue.

Claims

1. An antibody, wherein the variable part of the light chain of said antibody comprises or consists of an amino acid sequence of:

DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSDGKTYLNWFQQRPGQSPRRLTYLVSKLDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHFPFTFGGGTKVEIK (SEQ ID NO: 1),

wherein the variable part of heavy chain of said antibody comprises or consists of an amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSS (SEQ ID NO: 2);

and wherein said antibody specifically binds to an epitope at the N-terminus of pyroglutamated amyloid beta (Aβ N3pE) peptide.

2. The antibody according to claim 1, wherein the light chain comprises or consists of the amino acid sequence of:

DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSDGKTYLNWFQQRPGQSPRRLTYLVSKLDSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHFPFTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 17).

3. The antibody according to any one of the preceding claims, wherein the heavy chain comprises or consists of the amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE

SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 18).

4. The antibody according to any one of the preceding claims, wherein the heavy chain comprises or consists of the amino acid sequence of:

QVQLVQSGAEVVKPGASVKVSCKASGYSFTGHTMNWVRQAPGQGLEWMGLINPSDGVTRYNQKF QGRVTITRDTSTTTVHMELTSLTSEDTATYYCTREAKREWDETYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 19).

5. The antibody according to any one of the preceding claims, wherein said humanized antibody binds specifically to an epitope selected from the group consisting of

pEFRHDSGYEVHHQKLV (SEQ ID NO: 23),
pEFRHDSGYEVHHQKL (SEQ ID NO: 24),
pEFRHDSGYEVHHQK (SEQ ID NO: 25),
pEFRHDSGYEVHHQ (SEQ ID NO: 26),
pEFRHDSGYEVHH (SEQ ID NO: 27),
pEFRHDSGYEVH (SEQ ID NO: 28),
pEFRHDSGYEV (SEQ ID NO: 29),
pEFRHDSGYE (SEQ ID NO: 30),
pEFRHDSGY (SEQ ID NO: 31),
pEFRHDSG (SEQ ID NO: 32), and
pEFRHDS (SEQ ID NO: 33).

6. The antibody according to any one of claims 1 to 5, wherein said humanized antibody of the invention binds to an Aβ N3pE

variant, wherein the Aβ N3pE variant is defined as pE-$A\beta_{3-x}$, wherein x is defined as an integer between 19 and 42.

7. The antibody of claim 6, wherein the Aβ N3pE variant is selected from:

$pE\text{-}A\beta_{3-38}$,
$pE\text{-}A\beta_{3-40}$,
$pE\text{-}A\beta_{3-42}$.

8. A pharmaceutical composition comprising the antibody according to any one of the preceding claims.

9. The pharmaceutical composition of claim 8, further comprising a further biologically active substance and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

10. The pharmaceutical composition of claim 9, wherein said further biologically active substance is selected from 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.

11. The pharmaceutical composition of claim 10, wherein said further biologically active substance is 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 (3 APS), 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, such as inhibitors of glutaminyl cyclase, anti-inflammatory molecules, or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine, Ml agonists and other drugs including any amyloid or tau modifying drugs and nutritive supplements, cholinesterase inhibitors (ChEIs), memantine or glutaminyl cyclase inhibitors.

12. Use of the antibody according to any one of claims 1 to 7 or the pharmaceutical composition according to any one of claims 8 to 11 in the manufacture of a medicament for the treatment of a neurodegenerative disease selected from the group consisting of mild cognitive impairment (MCI), Alzheimer's disease (AD), like for instance sporadic Alzheimer's disease (SAD) or Familial Alzheimer’s dementias (FAD) like Familial British Dementia (FBD) and Familial Danish Dementia (FDD), neurodegeneration in Down Syndrome and clinical or pre-clinical cerebral amyloid angiopathy; and/or the treatment of a condition se1ected from prodromal AD, mild AD, moderate AD and severe AD and/or the slowing of cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy.

13. The use according to claim 12, wherein the administration of said antibody or said pharmaceutical composition leads to the reversion of cognitive decline, improvement of cognition or the prevention of cognitive decline in a subject diagnosed with mild cognitive impairment (MCI), Alzheimer's disease (AD), like for instance sporadic Alzheimer's disease (SAD) or Familial Alzheimer’s dementias (FAD) like Familial British Dementia (FBD) and Familial Danish Dementia (FDD), neurodegeneration in Down Syndrome and clinical or pre-clinical cerebral amyloid angiopathy

and/or of a condition se1ected from prodromal AD, mild AD, moderate AD and severe AD; or

wherein the administration of said antibody or said pharmaceutical composition leads to the clearance or removal of Aβ N3pE from plaques or other biological complexes; or

wherein the administration of said antibody or said pharmaceutical composition leads to the reduction of the plaque load and/or the removal of complete plaques from the affected tissue, such as brain tissue.