wherein each of the (full length) antibody light chains comprises in the constant light chain domain (CL) at position 123 the amino acid residue arginine (instead of the wild-type glutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the wild-type glutamine residue; Q124K mutation) (numbering according to Kabat),

wherein each of the (full length) antibody heavy chains comprises in the first constant heavy chain domain (CH1) at position 147 an glutamic acid residue (instead of the wild-type lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the wild-type lysine amino acid residue; K213E mutation) (numbering according to Kabat EU index),

wherein the additional Fab fragment specifically binding to the second antigen comprises a domain crossover such that the constant light chain domain (CL) and the constant heavy chain domain 1 (CH1) are replaced by each other, and

wherein the first antigen is human A-beta protein and the second antigen is human transferrin receptor.

One aspect as reported herein is a bispecific antibody comprising

a) one antibody comprising two pairs each of a antibody light chain and a antibody heavy chain, wherein the binding sites formed by each of the pairs of the heavy chain and the light chain specifically bind to a first antigen, and

b) one additional Fab fragment, wherein the additional Fab fragment is fused to the C-terminus of one of the heavy chains of the antibody, wherein the binding site of the additional Fab fragment specifically binds to a second antigen,

wherein each of the antibody light chains comprises in the constant light chain domain (CL) at position 123 the amino acid residue arginine (instead of the wild-type glutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the wild-type glutamine residue; Q124K mutation) (numbering according to Kabat),

wherein each of the antibody heavy chains comprises in the first constant heavy chain domain (CH1) at position 147 an glutamic acid residue (instead of the wild-type lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the wild-type lysine amino acid residue; K213E mutation) (numbering according to Kabat EU index),

wherein the additional Fab fragment specifically binding to the second antigen comprises a domain crossover such that the constant light chain domain (CL) and the constant heavy chain domain 1 (CH1) are replaced by each other, and

wherein the first antigen is human A-beta protein and the second antigen is human transferrin receptor.

In one embodiment the additional Fab fragment is fused to the C-terminus of the heavy chain by a peptidic linker.

In one embodiment the N-terminus of the heavy chain variable domain of the Fab fragment is fused to the C-terminus of the full length heavy chain or the C-terminus of the peptidic linker.

In one embodiment

a) the full length heavy chain that is fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP wherein the proline thereof is directly fused to the first amino acid residue of the additional Fab fragment or of the peptidic linker via a peptide bond, and

b) the full length heavy chain that is not fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP, or SPG, or PGK.

In one embodiment

the full length antibody is of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain, and

the additional Fab fragment is fused to the C-terminus of the heavy chain comprising the mutation T366W, or to the C-terminus of the heavy chain comprising the mutations T366S, L368A, and Y407V.

In one embodiment, the human A-beta binding site comprises the VH sequence as in SEQ ID NO: 18, including post-translational modifications of that sequence, and the VL sequence as in SEQ ID NO: 19, including post-translational modifications of that sequence.

In one embodiment, the human transferrin receptor binding site comprises the VH sequence as in SEQ ID NO: 20, including post-translational modifications of that sequence, and the VL sequence as in SEQ ID NO: 21, including post-translational modifications of that sequence.

In one embodiment the bispecific antibody comprises

i) a light chain with an amino acid sequence that has a sequence identity to SEQ ID NO: 01 of 70 % or more,

ii) a heavy chain with an amino acid sequence that has a sequence identity to SEQ ID NO: 02 of 70 % or more,

iii) a light chain with an amino acid sequence that has a sequence identity to SEQ ID NO: 03 of 70 % or more, and

iv) a heavy chain Fab fragment with an amino acid sequence that has a sequence identity to SEQ ID NO: 04 of 70 % or more,

wherein

SEQ ID NO: 01 has the amino acid sequence DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLL IYGASSRATGVPARFSGSGSGTDFTLTISSLEPEDFATYYCLQIYNMPIT FGQGTKVEIKRTVAAPSVFIFPPSDRKLKSGTASVVCLLNNFYPREAK

VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC,

SEQ ID NO: 02 has the amino acid sequence
QVELVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE
WVSAINASGTRTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV
YYCARGKGNTHKPYGYVRYFDVWGQGTLVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVEDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDEKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLS
CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG,

SEQ ID NO: 03 has the amino acid sequence
AIQLTQSPSSLSASVGDRVTITCRASQSISSYLAWYQQKPGKAPKLLIY
RASTLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQNYASSNV
DNTFGGGTKVEIKSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDKKVEPKSC, and

SEQ ID NO: 04 has the amino acid sequence
QSMQESGPGLVKPSQTLSLTCTVSGFSLSSYAMSWIRQHPGKGLEWI
GYIWSGGSTDYASWAKSRVTISKTSTTVSLKLSSVTAADTAVYYCAR
RYGTSYPDYGDASGFDPWGQGTLVTVSSASVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

As reported herein is a bispecific antibody comprising a (full length) light chain that has the amino acid sequence of SEQ ID NO: 01, a (full length) heavy chain that has the amino acid sequence of SEQ ID NO: 02, a (full length) light chain that has the amino acid sequence of SEQ ID NO: 03, and an antibody Fab fragment comprising the amino acid sequences of SEQ ID NO: 04.

In one embodiment the bispecific antibody is monoclonal.

As reported herein is an isolated nucleic acid encoding the bispecific antibody as reported herein.

As reported herein is a host cell comprising the nucleic acid as reported herein encoding the bispecific antibody as reported herein.

As reported herein is a method of producing a bispecific antibody as reported herein comprising the following steps:

a) culturing the host cell as reported herein so that the bispecific antibody is produced, and

b) recovering the bispecific antibody from the cell or the cultivation medium and thereby producing the bispecific antibody as reported herein.

As reported herein is an immunoconjugate comprising the bispecific antibody as reported herein and a cytotoxic agent.

As reported herein is a pharmaceutical formulation comprising the bispecific antibody as reported herein and a pharmaceutically acceptable carrier.

Another aspect as reported herein is a pharmaceutical formulation comprising the antibody as reported herein and a pharmaceutically acceptable carrier.

Another aspect as reported herein is the antibody as reported herein for use as a medicament.

As reported herein is the bispecific antibody as reported herein for use in treating Alzheimer's disease.

Another aspect as reported herein is the antibody as reported herein for use in the treatment of Alzheimer's disease.

As reported herein is the bispecific antibody as reported herein for use in inhibiting/slowing down the formation of plaques in the brain.

As reported herein is the bispecific antibody as reported herein for use in disintegrating β-amyloid plaques.

As reported herein is the use of the bispecific antibody as reported herein in the manufacture of a medicament.

Another aspect as reported herein is use of the antibody as reported herein in the manufacture of a medicament.

In one embodiment the medicament is for the treatment of amyloid disorders.

In one embodiment the medicament for the prevention and/or treatment of a disease associated with amyloidogenesis and/or amyloid-plaque formation. In one embodiment the disease is selected from the group consisting of dementia, Alzheimer's disease, motor neuropathy, Down's syndrome, Creutzfeldt Jacob disease, hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's

disease, HIV-related dementia, ALS or neuronal disorders related to aging. In one preferred embodiment the medicament is for treatment of Alzheimer's disease.

In one embodiment the medicament is for inhibiting/slowing down the formation of plaques in the brain. In one embodiment the medicament is for medicament for the disintegration of β-amyloid plaques.

As reported herein is a method of treating an individual having a disease associated with amyloidogenesis and/or amyloid-plaque formation comprising administering to the individual an effective amount of the bispecific antibody as reported herein.

As reported herein is a method of treating an individual having Alzheimer's disease comprising administering to the individual an effective amount of the bispecific antibody as reported herein.

As reported herein is a method for the disintegration of β-amyloid plaques in the brain of an individual comprising administering to the individual an effective amount of the bispecific antibody as reported herein to disintegrate β-amyloid plaques in the brain.

As reported herein is a method of inhibiting/slowing down the formation of plaques in the brain of an individual comprising administering to the individual an effective amount of the bispecific antibody as reported herein to inhibit/slow down the formation of plaques in the brain.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The knobs into holes dimerization modules and their use in antibody engineering are described in Carter P.; Ridgway J.B.B.; Presta L.G.: Immunotechnology, Volume 2, Number 1, February 1996 , pp. 73-73. . The additional disulfide bridge in the CH3 domain is reported in Merchant, A.M., et al., Nat. Biotechnol. 16 (1998) 677-681.

General information regarding the nucleotide sequences of human immunoglobulins light and heavy chains is given in: Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991).

VL sequence as in SEQ ID NO: 21, including post-translational modifications of that sequence.

10. A pharmaceutical formulation comprising the antibody according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

11. The antibody according to any one of claims 1 to 9 for use as a medicament.

12. The antibody according to any one of claims 1 to 9 for use in the treatment of Alzheimer's disease.

13. Use of the antibody according to any one of claims 1 to 9 in the manufacture of a medicament.

14. The use of claim 13, wherein the medicament is for treatment of Alzheimer's disease

15. The use of claim 13, wherein the medicament is for inhibiting/slowing down the formation of plaques in the brain.