

Patent Claims

1. 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.
2. The antibody according to claim 1, wherein the additional Fab fragment is fused to the C-terminus of the heavy chain by a peptidic linker.

3. The antibody according to any one of claims 1 and 2, wherein
- a) the 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 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.
4. The antibody according to anyone of claims 1 to 3, wherein the antibody is
- a) a full length antibody of the human subclass IgG1,
 - b) a full length antibody of the human subclass IgG4,
 - c) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G,
 - d) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G,
 - e) a full length antibody 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,
 - f) a full length antibody of the human subclass IgG4 with the mutations S228P 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,
 - g) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, I253A, H310A and H435A 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,

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- 5 h) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, M252Y, S254T and T256E 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, or
- 10 i) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, H310A, H433A and Y436A in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain.
5. The antibody according to any one of claims 1 to 4, wherein the bispecific antibody comprises
- 15 i) a light chain that has a sequence identity to SEQ ID NO: 01 of 70 % or more,
- ii) a heavy chain that has a sequence identity to SEQ ID NO: 02 of 70 % or more,
- iii) a light chain that has a sequence identity to SEQ ID NO: 03 of 70 % or more, and
- 20 iv) a heavy chain Fab fragment that has a sequence identity to SEQ ID NO: 04 of 70 % or more.
6. The antibody according to any one of claims 1 to 4, wherein the bispecific antibody comprises a light chain that has the amino acid sequence of SEQ ID NO: 01, a heavy chain that has the amino acid sequence of SEQ ID NO: 02, a 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.
- 25 7. The antibody according to any one of claims 1 to 6, wherein the antibody is monoclonal.
8. The antibody according to any one of claims 1 to 7, wherein the human A-beta binding site comprises the VH sequence as in SEQ ID NO: 18, including
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post-translational modifications of that sequence, and the VL sequence as in SEQ ID NO: 19, including post-translational modifications of that sequence.

- 5 9. The antibody according to any one of claims 1 to 8, wherein 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.
- 10 10. A pharmaceutical formulation comprising the antibody according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.
- 10 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 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.
- 15 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.
- 20 16. A method of treating an individual having Alzheimer's disease comprising administering to the individual an effective amount of the antibody according to any one of claims 1 to 9.
- 25 17. 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 antibody according to any one of claims 1 to 9 to inhibit/slow down the formation of plaques in the brain.