

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 an antibody light chain and an 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 human IgGglutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the human IgGglutamine residue; Q124K mutation) (numbering according to Kabat),

5 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 human IgGlysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the human IgGlysine 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,

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

wherein 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
15 modifications of that sequence, and

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.

20 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.

25 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
30 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.

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:

- 5 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.

10 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.

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

As reported herein is the antibody as reported herein for use as a medicament.

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

20 As reported herein is the bispecific antibody as reported herein for use in treating 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.

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

5 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

Patent Claims

1. A bispecific antibody comprising
 - a) one antibody comprising two pairs each of an antibody light chain and an 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 human IgG glutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the human IgG 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 human IgG lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the human IgG 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,
- wherein the first antigen is human A-beta protein and the second antigen is human transferrin receptor,
- wherein 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, and

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.

- 5 2. The bispecific 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 bispecific antibody according to any one of claims 1 and 2, wherein
 - 10 a) the heavy chain that is fused to the additional Fab fragment 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,
15 or PGK.
4. The bispecific antibody according to anyone of claims 1 to 3, wherein the antibody is
 - 20 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,
 - 25 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,

- 5 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,
- 10 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
- 15 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.
- 20 5. The bispecific antibody according to any one of claims 1 to 4, wherein the bispecific antibody comprises
- 25 i) two copies of a light chain that has a sequence identity to SEQ ID NO: 01 of 70 % or more,
- ii) one copy of a heavy chain that has a sequence identity to SEQ ID NO: 02 of 70 % or more,
- iii) one copy of a light chain that has a sequence identity to SEQ ID NO: 03 of 70 % or more, and
- iv) one copy of a heavy chain that has a sequence identity to SEQ ID NO: 10 of 70 % or more.
- 30 6. The bispecific antibody according to any one of claims 1 to 4, wherein in the two pairs of the antibody light chains and the antibody heavy chains, the light chains have the amino acid sequence of SEQ ID NO: 01, one of the heavy chains has the amino acid sequence of SEQ ID NO: 02 and one of SEQ ID

NO: 10, and the light chain in the additional Fab fragment has the amino acid sequence of SEQ ID NO: 03.

7. The bispecific antibody according to any one of claims 1 to 6, wherein the bispecific antibody is monoclonal.
- 5 8. The bispecific 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 post-translational modifications of that sequence, and the VL sequence as in SEQ ID NO: 19, including post-translational modifications of that sequence.
- 10 9. The bispecific 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.
- 15 10. A pharmaceutical formulation comprising the bispecific antibody according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.
11. The bispecific antibody according to any one of claims 1 to 9 for use as a medicament.