

The present disclosure relates to a pharmaceutical formulation comprising an antibody as reported herein and a pharmaceutically acceptable carrier.

The present disclosure relates to an antibody as reported herein for use as a medicament.

5 In another aspect, the present disclosure relates to a humanized antibody as reported herein coupled to a therapeutic compound for use as a medicament.

The present disclosure relates to the use of an antibody as reported herein in the manufacture of a medicament for treating a neurological disorder.

10 In another aspect, the present disclosure relates to a humanized antibody as reported herein conjugated to a neurological disorder drug for use in the treatment of a neurological disorder.

15 In one embodiment the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, CNS inflammation, Alzheimer's Disease, Parkinson's Disease, multiple sclerosis, CD20 positive cancer with brain metastases, and Her2 positive cancer with brain metastases.

20 The present disclosure relates to the use of an antibody as reported herein in the manufacture of a medicament for transporting one or more compounds across the blood-brain-barrier (BBB).

DESCRIPTION OF THE FIGURES

Figure 1: Scheme of transcytosis assay

25 **Figure 2:** Off-rates of different anti-transferrin receptor antibodies determined at 25 °C using BIAcore; 1: 128.1; 2: 128.1 fused to anti-pTau antibody mAb86; 3: 567; 4: 932; 5: 567 fused to anti-pTau antibody mAb86; 6: 1026; 7: 1027; squares: binding to cynomolgus transferrin receptor; circle: binding to human transferrin receptor; y-axis: off-rate [1/s].

Patent Claims

1. A humanized antibody that specifically binds to human transferrin receptor,
wherein the antibody comprises

in the heavy chain variable domain the HVRs of SEQ ID NO: 66, 68 and 72,

and

5 in the light chain variable domain the HVRs of SEQ ID NO: 75, 76 and 78.
2. The humanized antibody according to claim 1 comprising a heavy chain
variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ
ID NO: 37.
3. The humanized antibody according to any one of claims 1 to 2, wherein the
10 humanized antibody is effector function silent.
4. The humanized antibody according to any one of claims 1 to 3, wherein the
humanized antibody specifically binds to human transferrin receptor and to
cynomolgus transferrin receptor.
5. The humanized antibody according to any one of claims 1 to 4, wherein the
15 humanized antibody is a multispecific antibody having at least one binding
specificity for the human transferrin receptor and at least one binding
specificity for a therapeutic target.
6. The humanized antibody according to claim 5, wherein the humanized
antibody comprises a first antigen binding site which binds the human
20 transferrin receptor and a second antigen binding site which binds a brain
antigen.
7. The humanized antibody according to claim 6, wherein the brain antigen is
selected from the group consisting of Abeta, epidermal growth factor receptor
(EGFR), human epidermal growth factor receptor 2 (HER2), alpha-synuclein,
25 CD20, amyloid precursor protein (APP) and glucocerebrosidase.
8. The humanized antibody according to any one of claims 5 to 7, wherein the
multispecific antibody binds both

i) the human transferrin receptor and Abeta, or

- ii) the human transferrin receptor and CD20, or
- iii) the human transferrin receptor and alpha-synuclein, or
- iv) the human transferrin receptor and phospho-tau, or
- v) the human transferrin receptor and glucocerebrosidase.

5 9. The humanized antibody according to any one of claims 1 to 8, wherein the humanized antibody is a bispecific antibody comprising

- i) a first binding site comprising a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37,

and

10 ii) a second binding site selected from

- a) a heavy chain variable domain of SEQ ID NO: 81 and a light chain variable domain of SEQ ID NO: 82, or

- b) a heavy chain variable domain of SEQ ID NO: 83 and a light chain variable domain of SEQ ID NO: 84, or

15 c) a heavy chain variable domain of SEQ ID NO: 85 and a light chain variable domain of SEQ ID NO: 86, or

- d) a heavy chain variable domain of SEQ ID NO: 87 and a light chain variable domain of SEQ ID NO: 88, or

20 e) a heavy chain variable domain of SEQ ID NO: 91 and a light chain variable domain of SEQ ID NO: 92, or

- f) a heavy chain variable domain of SEQ ID NO: 89 and a light chain variable domain of SEQ ID NO: 90, or

- g) a heavy chain variable domain of SEQ ID NO: 93 and a light chain variable domain of SEQ ID NO: 94, or

25 h) a heavy chain variable domain of SEQ ID NO: 79 and a light chain variable domain of SEQ ID NO: 80.

10. The humanized antibody according to any one of claims 1 to 9, wherein the humanized antibody is
- a) a full length antibody of the human subclass IgG1, or
 - b) a full length antibody of the human subclass IgG4, or
 - 5 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 optionally P329G,
 - 10 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, or
 - 15 f) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and optionally 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.
11. The humanized antibody according to any one of claims 1 to 9, wherein the humanized antibody comprises
- 20 i) a homodimeric Fc-region of the human IgG1 subclass optionally with the mutations P329G, L234A and L235A, or
 - ii) a homodimeric Fc-region of the human IgG4 subclass optionally with the mutations P329G, S228P and L235E, or
 - iii) a heterodimeric Fc-region whereof
 - 25 a) one Fc-region polypeptide comprises the mutation T366W, and the other Fc-region polypeptide comprises the mutations T366S, L368A and Y407V, or
 - b) one Fc-region polypeptide comprises the mutations T366W and Y349C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V, and S354C, or

- c) one Fc-region polypeptide comprises the mutations T366W and S354C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V and Y349C,

or

- 5 iv) a heterodimeric Fc-region of the human IgG4 subclass whereof both Fc-region polypeptides comprise the mutations P329G, L234A and L235A and

- 10 a) one Fc-region polypeptide comprises the mutation T366W, and the other Fc-region polypeptide comprises the mutations T366S, L368A and Y407V, or

- b) one Fc-region polypeptide comprises the mutations T366W and Y349C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V, and S354C, or

- 15 c) one Fc-region polypeptide comprises the mutations T366W and S354C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V and Y349C,

or

- 20 v) a heterodimeric Fc-region of the human IgG4 subclass whereof both Fc-region polypeptides comprise the mutations P329G, S228P and L235E and

- a) one Fc-region polypeptide comprises the mutation T366W, and the other Fc-region polypeptide comprises the mutations T366S, L368A and Y407V, or

- 25 b) one Fc-region polypeptide comprises the mutations T366W and Y349C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V, and S354C, or

- c) one Fc-region polypeptide comprises the mutations T366W and S354C, and the other Fc-region polypeptide comprises the mutations T366S, L368A, Y407V and Y349C.

12. A humanized antibody according to any one of claims 1 to 11 coupled to a therapeutic compound for use as a medicament.
13. A humanized antibody according to any one of claims 1 to 11 conjugated to a neurological disorder drug for use in the treatment of a neurological disorder.
- 5 14. The humanized antibody according to claim 13, wherein the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure

disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.