

CLAIMS

1. An anti-human transferrin receptor antibody, wherein in the heavy chain variable region of the antibody,

(a) CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 62 or SEQ ID NO: 63,

(b) CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 13 or SEQ ID NO: 14, and

(c) CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 15 or SEQ ID NO: 16, and

in the light chain variable region of the antibody,

(a) CDR1 comprises the amino acid sequence set forth as SEQ ID NO: 6 or SEQ ID NO: 7,

(b) CDR2 comprises the amino acid sequence set forth as SEQ ID NO: 8 or SEQ ID NO: 9, or the amino acid sequence Lys-Val-Ser, and

(c) CDR3 comprises the amino acid sequence set forth as SEQ ID NO: 10.

2. The antibody according to claim 1, wherein the framework region 3 of the heavy chain comprises the amino acid sequence set forth as SEQ ID NO: 64.

3. The antibody according to claim 2, wherein the heavy chain variable region comprises the amino acid sequence set forth as SEQ ID NO: 65.

4. The antibody according to claim 3, wherein the heavy chain

comprises the amino acid sequence set forth as SEQ ID NO: 66 or SEQ ID NO: 68.

5. The antibody according to claim 1, wherein the light chain variable region of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 or SEQ ID NO: 22.

6. The antibody according to claim 1, wherein the light chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27 or SEQ ID NO: 29.

7. The antibody according to claim 1, wherein the antibody has an affinity to both the extracellular region of human transferrin receptor and the extracellular region of monkey transferrin receptor.

8. The antibody according to claim 7, wherein the dissociation constant of its complex with the extracellular region of human transferrin receptor is not greater than 1×10^{-10} M, and the dissociation constant of its complex with the extracellular region of monkey transferrin receptor is not greater than 1×10^{-9} M.

9. The antibody according to claim 1, wherein the antibody is Fab antibody, F(ab')₂ antibody, or F(ab') antibody.

10. The anti-human transferrin receptor antibody according to claim

1, wherein the antibody is a single-chain antibody selected from the group consisting of scFab, scF(ab'), scF(ab')₂ and scFv.

11. The antibody according to claim 10, wherein the light chain and the heavy chain of the antibody are linked via a linker sequence.

12. The antibody according to claim 11, wherein the heavy chain is linked, via a linker sequence, to the light chain on the C-terminal side of the light chain.

13. The antibody according to claim 10, wherein the light chain is linked, via a linker sequence, to the heavy chain on the C-terminal side of the heavy chain.

14. The antibody according to claim 11, wherein the linker sequence consists of 2 to 50 amino acid residues.

15. The antibody according to claim 14, wherein the linker sequence is selected from the group consisting of the amino acid sequence Gly-Ser, the amino acid sequence Gly-Gly-Ser, the amino acid sequence Gly-Gly-Gly, the amino acid sequences set forth as SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5, the amino acid sequence consisting of three consecutively linked amino acid sequences each set forth as SEQ ID NO: 3, and the amino acid sequences consisting of 2 to 10 repeats of any of the aforementioned sequences that are consecutively linked.

16. A fusion protein comprising an anti-human transferrin receptor antibody and a different protein (A),

wherein the anti-human transferrin receptor antibody is the antibody according to claim 1, and

wherein the protein (A) is linked to the light chain of the antibody on the C-terminal side or the N-terminal side of the light chain.

17. The fusion protein according to claim 16, wherein the protein (A) is linked, directly or via a linker, to the light chain on the C-terminal side or the N-terminal side of the light chain.

18. The fusion protein according to claim 16, wherein the protein (A) is linked, via a linker, to the light chain on the C-terminal side or the N-terminal side of the light chain.

19. The fusion protein according to claim 18, wherein the linker is a peptide consisting of 1 to 50 amino acid residues.

20. The fusion protein according to claim 19, wherein the linker is a peptide comprising an amino acid sequence selected from the group consisting of a single glycine, a single serine, the amino acid sequence Gly-Ser, the amino acid sequence Gly-Gly-Ser, the amino acid sequence set forth as SEQ ID NO: 3, the amino acid sequence set forth as SEQ ID NO: 4, the amino acid sequence set forth as SEQ ID NO: 5, and the amino acid sequences consisting of 2 to 10 of any of the aforementioned sequences that are consecutively linked.

21. A fusion protein of an anti-human transferrin receptor antibody and a different protein (A),

wherein the anti-human transferrin receptor antibody is the antibody according to claim 1, and

wherein the protein (A) is linked to the heavy chain of the antibody on the C-terminal side or the N-terminal side of the heavy chain.

22. The fusion protein according to claim 21, wherein the protein (A) is linked, directly or via a linker, to the heavy chain on the C-terminal side or the N-terminal side of the heavy chain.

23. The fusion protein according to claim 21, wherein the protein (A) is linked, via a linker, to the heavy chain on the C-terminal side or the N-terminal side of the heavy chain.

24. The fusion protein according to claim 23, wherein the linker sequence is a peptide consisting of 1 to 50 amino acid residues.

25. The fusion protein according to claim 24, wherein the linker is a peptide comprising an amino acid sequence selected from the group consisting of a single glycine, a single serine, the amino acid sequence Gly-Ser, the amino acid sequence Gly-Gly-Ser, the amino acid sequence set forth as SEQ ID NO: 3, the amino acid sequence set forth as SEQ ID NO: 4, the amino acid sequence set forth as SEQ ID NO: 5, and the amino acid sequences consisting of 2 to 10 of any of the aforementioned

sequences that are consecutively linked.

26. The fusion protein according to claim 16, wherein the protein (A) is a protein originating from human.

5

27. The fusion protein according to claim 16, wherein the protein (A) is selected from the group consisting of nerve growth factor (NGF), lysosomal enzymes, ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3, neurotrophin-4/5, neurotrophin-6, neuregulin-1, erythropoietin, darbepoetin, activin, basic fibroblast growth factor (bFGF), fibroblast growth factor 2 (FGF2), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), interferon α , interferon β , interferon γ , interleukin 6, granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), cytokines, tumor necrosis factor α receptor (TNF- α receptor), PD-L1, and PD-L2.

10

15

20

25

28. The fusion protein according to claim 16, wherein the protein (A) is a lysosomal enzyme, wherein the lysosomal enzyme is selected from the group consisting of α -L-iduronidase, iduronate 2-sulfatase, human acidic α -glucosidase, glucocerebrosidase, β -galactosidase, GM2 activator protein, β -hexosaminidase A, β -hexosaminidase B, N-acetylglucosamine-1-phosphotransferase, α -mannosidase, β -mannosidase, galactosylceramidase, saposin C, arylsulfatase A, α -L-fucosidase, aspartylglucosaminidase, α -N-acetylgalactosaminidase,

acidic sphingomyelinase, α -galactosidase A, β -glucuronidase, heparan
N-sulfatase, α -N-acetylglucosaminidase, acetyl CoA: α -glucosaminide
N-acetyltransferase, N-acetylglucosamine-6-sulfate sulfatase, acid
ceramidase, amylo-1,6-glucosidase, sialidase, palmitoyl protein
thioesterase 1, tripeptidyl-peptidase 1, hyaluronidase 1, CLN1 and
CLN2.

29. The fusion protein according to claim 16, wherein the protein (A)
is human iduronate 2-sulfatase, human acidic α -glucosidase, or human
 α -L-iduronidase.

30. The fusion protein according to claim 21, wherein the protein (A)
is human acidic α -glucosidase, wherein

(1) the light chain of the antibody comprises the amino acid
sequence set forth as SEQ ID NO: 23, and

(2) the heavy chain of the antibody is linked, on the C-terminal
side of the heavy chain and via the amino acid sequence Gly-Ser, to the
human acidic α -glucosidase, thereby forming the amino acid sequence
set forth as SEQ ID NO: 57 or SEQ ID NO: 58.

31. The fusion protein according to claim 21, wherein the protein (A)
is human acidic α -glucosidase, wherein

(1) the light chain of the antibody comprises the amino acid
sequence set forth as SEQ ID NO: 23, and

(2) the heavy chain of the antibody comprises the amino acid
sequence set forth as SEQ ID NO: 66 or SEQ ID NO: 68, and the heavy

chain is linked, on the C-terminal side of the heavy chain and via the amino acid sequence Gly-Ser, to the human acidic α -glucosidase having the amino acid sequence set forth as SEQ ID NO: 55 or 56.

5 32. The fusion protein according to claim 21, wherein the protein (A) is human acidic α -glucosidase, wherein the antibody is Fab antibody, and wherein

(1) the light chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 23, and

10 (2) the heavy chain of the antibody is linked, on the C-terminal side of the heavy chain and via the amino acid sequence consisting of three consecutively linked amino acid sequences each set forth as SEQ ID NO: 3, to the human acidic α -glucosidase, thereby forming the amino acid sequence set forth as SEQ ID NO: 89.

15 33. The fusion protein according to claim 21, wherein the protein (A) is human acidic α -glucosidase, wherein the antibody is Fab antibody, and wherein

20 (1) the light chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 23, and

(2) the heavy chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 61, and the heavy chain is linked, on the C-terminal side of the heavy chain and via the amino acid sequence consisting of three consecutively linked amino acid sequences each set forth as SEQ ID NO: 3, to the human acidic α -glucosidase having the amino acid sequence set forth as SEQ ID NO: 55 or 56.

25

34. The fusion protein according to claim 21, wherein the protein (A) is human α -L-iduronidase, wherein the antibody is Fab antibody, and wherein

(1) the light chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 23, and

(2) the heavy chain of the antibody is linked, on the C-terminal side of the heavy chain and via the amino acid sequence consisting of three consecutively linked amino acid sequences each set forth as SEQ ID NO: 3, to the human α -L-iduronidase, thereby forming the amino acid sequence set forth as SEQ ID NO: 93.

35. The fusion protein according to claim 21, wherein the protein (A) is human α -L-iduronidase, wherein the antibody is Fab antibody, and wherein

(1) the light chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 23, and

(2) the heavy chain of the antibody comprises the amino acid sequence set forth as SEQ ID NO: 61, and the heavy chain is linked, on the C-terminal side of the heavy chain and via the amino acid sequence consisting of three consecutively linked amino acid sequences each set forth as SEQ ID NO: 3, to the human α -L-iduronidase having the amino acid sequence set forth as SEQ ID NO: 75 or 76.

36. The fusion protein according to claim 16 or 21, wherein a human IgG Fc region or part of the human IgG Fc region is introduced between the protein (A) and the antibody.

37. The fusion protein according to claim 36, wherein the human IgG Fc region is linked, directly or via a linker sequence, to the protein (A) on the C-terminal side of the protein (A), and the heavy chain or the light chain of the antibody is linked, directly or via a linker sequence, to the human IgG Fc region on the C-terminal side of the human IgG Fc region.

38. The fusion protein according to claim 36, wherein the human IgG Fc region comprises the amino acid sequence set forth as SEQ ID NO: 70.

39. The fusion protein according to claim 38, wherein the human IgG Fc region is linked, via a linker sequence, to a Fab heavy chain consisting of the amino acid sequence set forth as SEQ ID NO: 61, and comprises the amino acid sequence set forth as SEQ ID NO: 71 formed thereby.

40. A DNA fragment encoding the amino acid sequence of the anti-human transferrin receptor antibody according to claim 1.

41. A DNA fragment encoding the amino acid sequence of the fusion protein according to claim 16.

42. An expression vector comprising the DNA fragment according to claim 40 that is incorporated therein.

43. A mammalian cell transformed with the expression vector according to claim 42.

44. Use of the anti-human transferrin receptor antibody according to one of claims 1 to 15 in the production of a pharmaceutical agent by linking thereto the molecule of a physiologically active protein or a pharmacologically active low-molecular-weight compound for the treatment of a disease condition of the central nervous system, wherein the pharmaceutical agent is to be parenterally administered.

45. Use of the fusion protein according to claim 28 for the production of a pharmaceutical agent for the treatment of a disease condition of the central nervous system accompanying Pompe's disease, wherein the pharmaceutical agent is to be parenterally administered.

46. Use of the fusion protein according to any one of claims 28, 29, 34 and 35, for the production of a pharmaceutical agent for the treatment of a disease condition of the central nervous system accompanying Hurler syndrome or Hurler-Scheie syndrome, wherein the pharmaceutical agent is to be parenterally administered.