Claims

Claim 1. An anti-transferrin receptor 1 (TFR1) antibody or an antigen-binding fragment thereof, comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises a VH CDR1, a VH CDR2 and a VH CDR3, wherein

the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 8,

the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 16, and

the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 24, 79, 80, 81 or 82.

Claim 2. The anti-TFR1 antibody or antigen-binding fragment of claim 1, wherein the heavy chain variable domain comprises:

(A) the amino acid sequence of SEQ ID NO: 52, 98, 99, 100 or 101; or

(B) an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 52, 98, 99, 100 or 101; or

(C) an amino acid sequence having amino acid addition, deletion and/or substitution of one or more amino acids in comparison with the amino acid sequence of SEQ ID NO: 52, 98, 99, 100 or 101, wherein preferably, the amino acid addition, deletion and/or substitution does not occur in a CDR region.

Claim 3. The anti-TFR1 antibody or antigen-binding fragment of claim 1 or 2, which

(1) binds to human TFR1 and non-human primate TFR1; and/or

(2) does not substantially affect the binding of transferrin to TFR1; and/or

(3) binds to the transferrin-TFR1 complex.

Claim 4. The anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-3, which is a single domain antibody or a heavy-chain-only antibody and optionally a fully human antibody.

Claim 5. The anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-4, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 59, 107, 108, 109 or 110.

Claim 6. A transferrin receptor 1 (TFR1)-binding agent comprising the anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-5 conjugated to an additional molecule, preferably,

wherein the additional molecule is a therapeutic agent for treating a disease or disorder selected from: cancer, central nervous system cancer, Alzheimer's disease, Parkinson's disease, Huntington's disease, hunter syndrome, schizophrenia, antidepressant, multiple sclerosis, amyotrophic lateral sclerosis, lysosomal storage disease accompanied by

encephalopathy, glycogenosis, muscular dystrophy, cerebral ischemia, a prion disease, traumatic central nervous system disorder, viral and bacterial central nervous system disease, or

wherein the additional molecule is an imaging agent selected from: a radionuclide, biotin, a fluorescent protein, a fluorophore, horseradish peroxidase and alkaline phosphatase.

Claim 7. A multispecific antibody, comprising a first antigen-binding moiety binding to TFR1, wherein the first antigen-binding moiety comprises the heavy chain variable domain as defined in any one of claims 1-5, and a second antigen-binding moiety binding to a second antigen.

Claim 8. A multispecific antibody, which is selected from:

(a) a multispecific antibody comprising a first antigen-binding moiety binding to TFR1 and a second antigen-binding moiety binding to BACE1, wherein

the first antigen-binding moiety comprises the heavy chain variable domain as defined in any one of claims 1-5,

the second antigen-binding moiety comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an HCDR1, an HCDR2 and an HCDR3, and the light chain variable region comprises an LCDR1, an LCDR2 and an LCDR3, wherein the HCDR1 comprises an amino acid sequence of SEQ ID NO: 67, the HCDR2 comprises an amino acid sequence of SEQ ID NO: 73, and the HCDR3 comprises an amino acid sequence of SEQ ID NO: 83; and the LCDR1 comprises an amino acid sequence of SEQ ID NO: 88, the LCDR2 comprises an amino acid sequence of SEQ ID NO: 91, and the LCDR3 comprises an amino acid sequence of SEQ ID NO: 95,

preferably, wherein

the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 102; and/or the light chain variable region comprises an amino acid sequence of SEQ ID NO: 104; and

(b) a multispecific antibody comprising a first antigen-binding moiety binding to TFR1 and a second antigen-binding moiety binding to amyloid beta (Aβ), wherein

the first antigen-binding moiety comprises the heavy chain variable domain as defined in any one of claims 1-5,

the second antigen-binding moiety comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an HCDR1, an HCDR2 and an HCDR3, and the light chain variable region comprises an LCDR1, an LCDR2 and an LCDR3, wherein the HCDR1 comprises an amino acid sequence of SEQ ID NO: 68, the HCDR2 comprises an amino acid sequence of SEQ ID NO: 74, and the HCDR3 comprises an amino acid sequence of SEQ ID NO: 84; and the LCDR1 comprises an amino acid sequence

of SEQ ID NO: 89, the LCDR2 comprises an amino acid sequence of SEQ ID NO: 92, and the LCDR3 comprises an amino acid sequence of SEQ ID NO: 96,

preferably, wherein

the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 103; and/or

the light chain variable region comprises an amino acid sequence of SEQ ID NO: 105.

Claim 9. The multispecific antibody of claim 7 or 8, wherein the second antigen-binding moiety comprises a dsFv, an scFv, an scdsFv, a di-scFv, an Fab, an scFab or an F(ab')2.

Claim 10. The multispecific antibody of any one of claims 7-9, which comprises only one heavy chain variable domain as defined in any one of claims 1-5.

Claim 11. The anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-5 or the multispecific antibody of any one of claims 7-10, further comprising an Fc region, and optionally the Fc region comprises one or more modifications to reduce the effector function and/or enhance the FcRn binding.

Claim 12. The multispecific antibody of claim 11, wherein the Fc region is a heterodimeric Fc region comprising a first Fc region subunit and a second Fc region subunit, wherein one of the first Fc region subunit and the second Fc region subunit comprises a knob mutation, and the other comprises a hole mutation, optionally wherein

the knob mutation comprises one or more mutations selected from S354C and T366W; and/or

the hole mutation comprises one or more mutations selected from Y349C, T366S, L368A and Y407V;

preferably, the knob mutation comprises S354C and T366W, and the hole mutation comprises Y349C, T366S, L368A and Y407V.

Claim 13. The multispecific antibody of claim 12, wherein the second antigen-binding moiety comprises a heavy chain variable region and a light chain variable region, and the multispecific antibody comprises:

(a) (1) a first polypeptide comprising the heavy chain variable region, a CH1 domain and a first Fc region subunit, (2) a second polypeptide comprising the light chain variable region and a light chain constant region, and (3) a third polypeptide comprising the heavy chain variable domain and a second Fc region subunit, or

(b) (1) a first polypeptide comprising the heavy chain variable region, a CH1 domain, a first Fc region subunit, an optional peptide linker and the heavy chain variable domain, (2) a second polypeptide comprising the heavy chain variable region, a CH1 domain and a second

Fc region subunit, and (3) a third polypeptide and a fourth polypeptide each comprising the light chain variable region and a light chain constant region,

wherein the first Fc region subunit and the second Fc region subunit form the heterodimeric Fc region.

Claim 14. The multispecific antibody of claim 8, which is selected from:

(a) a multispecific antibody comprising a first polypeptide having the amino acid sequence of SEQ ID NO: 122, a second polypeptide having the amino acid sequence of SEQ ID NO: 113, and a third polypeptide having the amino acid sequence of SEQ ID NO: 129, 130, 131, 132 or 133; and

(b) a multispecific antibody comprising a first polypeptide having the amino acid sequence of SEQ ID NO: 119, 125, 126, 127 or 128, a second polypeptide having the amino acid sequence of SEQ ID NO: 117, and a third polypeptide and a fourth polypeptide each having the amino acid sequence of SEQ ID NO: 115.

Claim 15. A pharmaceutical composition or a kit comprising the anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-5 and 11, the TFR1-binding agent of claim 6 or the multispecific antibody of any one of claims 7-14.

Claim 16. A nucleic acid encoding the anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-5 and 11, or the multispecific antibody of any one of claims 7-14.

Claim 17. A vector comprising the nucleic acid of claim 16.

Claim 18. A host cell, comprising the nucleic acid of claim 16 or the vector of claim 17.

Claim 19. Use of the anti-TFR1 antibody or antigen-binding fragment of any one of claims 1-5 in the manufacture of

(a) an agent for transporting a compound across the blood-brain barrier,

(b) a medicament for treating cancer, or

(c) a medicament for treating a neurological disease or disorder, wherein the anti-TFR1 antibody or antigen-binding fragment is conjugated to a therapeutic agent for treating the neurological disease or disorder.

Claim 20. Use of the multispecific antibody of any one of claims 8-14 in the manufacture of

(a) a medicament for treating a neurological disease or disorder; preferably, the neurological disease or disorder is selected from Alzheimer’s disease, Parkinson’s disease,

spinal cord injury, Amyotrophic Lateral Sclerosis (ALS), stroke, traumatic brain injury and glaucoma,

(b) an agent or a kit for diagnosing Alzheimer's disease, Parkinson's disease, spinal cord injury, Amyotrophic Lateral Sclerosis (ALS), stroke, traumatic brain injury or glaucoma, or

(c) a medicament for inhibiting and/or decreasing the formation of amyloid plaques in the brain.