across the blood-brain-barrier into the brain. In certain examples, the blood-brain-barrier shuttle module is a monovalent binding entity that specifically binds to the transferrin receptor. The anti-transferrin receptor antibodies as reported herein when used as blood-brain-barrier shuttle module are useful, e.g., for the diagnosis or treatment of neurological disorders, such as Alzheimer's disease, Parkinson's Disease and Alzheimer's Disease with Parkinson's Disease co-morbidity.

Reported herein are anti-transferrin receptor antibodies that specifically bind to human transferrin receptor (huTfR) and cynomolgus transferrin receptor (cyTfR). In certain examples, the anti-transferrin receptor antibody

- binds to human transferrin receptor (huTfR) and cynomolgus transferrin receptor (cyTfR);
- has an off-rate for the human transferrin receptor that is equal to or less than (i.e. at most) that of the anti-transferrin receptor antibody 128.1 for the cynomolgus transferrin receptor, whereby the off-rates are determined by surface plasmon resonance, and whereby the anti-transferrin receptor antibody 128.1 has a heavy chain variable domain of SEQ ID NO: 64 and a light chain variable domain of SEQ ID NO: 65;
- binds with an off-rate for the human transferrin receptor that is between and including 0.1 1/s and 0.005 1/s.

Reported herein is an anti-transferrin receptor antibody that specifically binds to human transferrin receptor and cynomolgus transferrin receptor, which comprises

i) a humanized heavy chain variable domain derived from the heavy chain variable domain of SEQ ID NO: 01, and

ii) a humanized light chain variable domain derived from the light chain variable domain of SEQ ID NO: 26,

wherein the antibody has an off-rate for the human transferrin receptor that is equal to or less than (i.e. at most) the off-rate of the anti-transferrin receptor antibody 128.1 for the cynomolgus transferrin receptor,

whereby the off-rates are determined by surface plasmon resonance, and

whereby the anti-transferrin receptor antibody 128.1 has a heavy chain variable domain of SEQ ID NO: 64 and a light chain variable domain of SEQ ID NO: 65.

In one example the off-rate for the human transferrin receptor is between and including 0.1 1/s and 0.005 1/s.

In one example the antibody has in the light chain variable domain at position 80 a proline amino acid residue (P) (numbering according to Kabat).

In one example the antibody has in the light chain variable domain at position 91 an asparagine amino acid residue (N) (numbering according to Kabat).

In one example the antibody has in the light chain variable domain at position 93 an alanine amino acid residue (A) (numbering according to Kabat).

In one example the antibody has in the heavy chain variable domain at position 100g a serine amino acid residue (S) (numbering according to Kabat).

In one example the antibody has in the heavy chain variable domain at position 100g a glutamine amino acid residue (Q) (numbering according to Kabat).

In one example the antibody has in the heavy chain variable domain at position 65 a serine amino acid residue (S) (numbering according to Kabat).

In one example the antibody has in the heavy chain variable domain at position 105 a glutamine amino acid residue (Q) (numbering according to Kabat).

In one example the antibody the antibody has in the light chain variable domain at position 80 a proline amino acid residue (P), in the light chain variable domain at position 91 an asparagine amino acid residue (N), in the light chain variable domain at position 93 an alanine amino acid residue (A), in the heavy chain variable domain at position 100g a serine amino acid residue (S), in the heavy chain variable domain at position 65 a serine amino acid residue (S), and in the heavy chain variable domain at position 105 a glutamine amino acid residue (Q) (numbering according to Kabat).

In one example the antibody the antibody has in the light chain variable domain at position 80 a proline amino acid residue (P), in the light chain variable domain at position 91 an asparagine amino acid residue (N), in the light chain variable

domain at position 93 an alanine amino acid residue (A), in the heavy chain variable domain at position 100g a glutamine amino acid residue (Q), in the heavy chain variable domain at position 65 a serine amino acid residue (S), and in the heavy chain variable domain at position 105 a glutamine amino acid residue (Q) (numbering according to Kabat).

Reported herein is an anti-transferrin receptor antibody comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 66; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 68; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 71, 72 or 73; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 78.

In one aspect, reported herein is a humanized antibody that specifically binds to human transferrin receptor, wherein the antibody comprises

a) in the heavy chain variable domain the HVRs of SEQ ID NO: 66, 68 and 71, and in the light chain variable domain the HVRs of SEQ ID NO: 75, 76 and 78, or

b) in the heavy chain variable domain the HVRs of SEQ ID NO: 66, 68 and 73, and in the light chain variable domain the HVRs of SEQ ID NO: 75, 76 and 78.

In one preferred example the anti-transferrin receptor antibody comprises (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 66; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 68; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 72; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 78.

Reported herein is an anti-transferrin receptor antibody that specifically bind to human transferrin receptor (huTfR) comprising

i) a heavy chain variable domain (VH) sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 24, and

ii) a light chain variable domain (VL) having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 37,

wherein the antibody has about the same off-rate as an antibody comprising a heavy chain variable domain (VH) sequence of SEQ ID NO: 24 and a light chain variable domain (VL) sequence of SEQ ID NO: 37.

In one example the off-rate for the human transferrin receptor is between and including 0.1 1/s and 0.005 1/s.

Reported herein is an anti-transferrin receptor antibody that specifically bind to human transferrin receptor (huTfR) comprising

i) a heavy chain variable domain (VH) sequence having the amino acid sequence of SEQ ID NO: 24, and

ii) a light chain variable domain (VL) having the amino acid sequence of SEQ ID NO: 37.

In one example the antibody is a multispecific antibody having at least one binding specificity for the transferrin receptor and at least one binding specificity for a therapeutic target. In one example the antibody comprises a first antigen binding site which binds the transferrin receptor and a second antigen binding site which binds a brain antigen. In a further example the brain antigen is selected from the group consisting of human Abeta, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), human alpha-synuclein, human tau, which is phosphorylated at a tyrosine or serine residue, human CD20, amyloid precursor protein (APP), and human glucocerebrosidase. In one preferred example the multispecific antibody binds both

i) the transferrin receptor and Abeta, or
ii) the transferrin receptor and CD20, or
iii) the transferrin receptor and alpha-synuclein, or
iv) the transferrin receptor and phospho-tau, or
v) the transferrin receptor and HER2, or
vi) the transferrin receptor and glucocerebrosidase.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a heavy chain variable domain of SEQ ID NO: 81 and a light chain variable domain of SEQ ID NO: 82 binding site for human Abeta.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a heavy chain variable domain of SEQ ID NO: 79 and a light chain variable domain of SEQ ID NO: 80 binding site for human CD20. In one example, the heavy chain variable region comprises a replacement of the amino acid residue at Kabat position 11 with any amino acid but leucine. In one example, the substitution comprises a replacement of the amino acid residue at Kabat position 11 with a nonpolar amino acid. In one preferred example, the

substitution comprises a replacement of the amino acid residue at Kabat position 11 in the heavy chain variable domain of SEQ ID NO: 79 with an amino acid residue selected from the group consisting of valine, leucine, isoleucine, serine, and phenylalanine.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a heavy chain variable domain of SEQ ID NO: 83 and a light chain variable domain of SEQ ID NO: 84 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a humanized heavy chain variable domain derived from SEQ ID NO: 85 and a humanized light chain variable domain derived from SEQ ID NO: 86 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a humanized heavy chain variable domain derived from SEQ ID NO: 87 and a humanized light chain variable domain derived from SEQ ID NO: 88 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a humanized heavy chain variable domain derived from SEQ ID NO: 89 and a humanized light chain variable domain derived from SEQ ID NO: 90 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a humanized heavy chain variable domain derived from SEQ ID NO: 91 and a humanized light chain variable domain derived from SEQ ID NO: 92 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and at least one pair of a humanized heavy chain variable domain derived from SEQ ID NO: 93 and a humanized light chain variable domain derived from SEQ ID NO: 94 binding site for human alpha-synuclein.

In one example the antibody is a bispecific antibody comprising at least one pair of a heavy chain variable domain of SEQ ID NO: 24 and a light chain variable domain of SEQ ID NO: 37 forming a binding site for the transferrin receptor and a binding site for i) glucocerebrosidase that has the amino acid sequence of SEQ ID NO: 97, or ii) a functional variant of SEQ ID NO: 97 having at least 70 % sequence identity, or iii) a functional variant of SEQ ID NO: 97 having one or more amino acid mutations, deletions or insertions, or iv) a truncated functional variant of SEQ ID NO: 97 having at least one amino acid residue at the N-terminus or the C-termius or within the amino acid sequence deleted, or v) a combination of iii) and iv).

In one example the antibody comprises

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

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

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

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

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

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.

In one example the antibody is a CrossMab.

Reported herein is an anti-transferrin receptor antibody comprising

i) a heavy chain variable domain selected from the group consisting of SEQ ID NO: 52, 53, 54, 55, 56, 57 and 58, and a light chain variable domain selected from the group consisting of SEQ ID NO: 60, 61, 62 and 63,

or

ii) a heavy chain variable domain selected from the group consisting of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25, and a light chain variable domain selected from the group consisting of SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46 and 47.

In another aspect, reported herein is a humanized antibody that specifically binds to human transferrin receptor, wherein the antibody comprises

a) a heavy chain variable domain of SEQ ID NO: 23 and a light chain variable domain of SEQ ID NO: 37, or

b) a heavy chain variable domain of SEQ ID NO: 25 and a light chain variable domain of SEQ ID NO: 37, or

c) a heavy chain variable domain of SEQ ID NO: 55 and a light chain variable domain of SEQ ID NO: 60 or 61 or 62 or 63, or

d) a heavy chain variable domain of SEQ ID NO: 56 and a light chain variable domain of SEQ ID NO: 60 or 61 or 62 or 63.

Reported herein is a pharmaceutical formulation comprising an antibody as reported herein and a pharmaceutically acceptable carrier.

Reported herein is an antibody as reported herein for use as a medicament.

In another aspect, reported herein is a humanized antibody as reported herein coupled to a therapeutic compound for use as a medicament.

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

Reported herein is the use of an antibody as reported herein in the manufacture of a medicament for treating a neurological disorder.

In one example 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.

Reported herein is 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

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].

Figure 3: Off-rates of different anti-transferrin receptor antibodies determined at 37 °C using BIAcore; 1: 128.1; 2: 932; 3: 1026; 4: 1027; squares: binding to cynomolgus transferrin receptor; circle: binding to human transferrin receptor; y-axis: off-rate [1/s]

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

Herein is reported a humanized variant of the rabbit antibody 299 showing high transcytosis in an transcytosis assay according to Example 8, that has cross-reactivity to human and cynomolgus transferrin receptor, i.e. specifically binds to both orthologs of the transferrin receptor, that shows good cellular staining and that