CLAIMS

1. Binding protein, comprising

- a first moiety **M1**, which is a human transferrin receptor 1 (hTfR1) binding moiety comprising an immunoglobulin heavy chain variable region (VH) and an immunoglobulin light chain variable region (VL), said VH and VL regions forming a VH/VL pair comprising an antigen-binding surface, in which said antigen-binding surface provides the binding protein with the capacity to bind selectively to an epitope located in the protease-like domain of hTfR1 defined by amino acid residues 121-183 and 384-605 in SEQ ID NO:66, and
- a second moiety **M2** which comprises an antibody Fc domain, for example being selected from the group consisting of an antibody and an Fc fusion protein,

wherein M1 and M2 are connected to each other by at least one peptide linker between M1 and M2, said linker being arranged such that M2 elicits a reduced Fc-mediated response when administered to a human and when M1 binds to hTfR1 present on a cell.

2. Binding protein according to claim 1, wherein said epitope of M1 located in the protease-like domain of hTfR1 comprises or consists of the amino acid residues 150, 151, 154, 158, 159, 161, 163 and 385 in SEQ ID NO:66.

3. Binding protein according to any preceding claim, wherein said antigen-binding surface of M1 is composed of three complementarity-determining regions (CDRs) from said VH region and three CDRs from said VL region, and in which said CDRs comprise the following:

VHCDR1: **X1X2NMX3** (SEQ ID NO:1),
wherein
X1 is selected from D and A;
X2 is selected from Y and A; and
X3 is selected from D and A;

VHCDR2: **X4INPX5X6X7TTSX8NEKFKG** (SEQ ID NO:2),
wherein
X4 is selected from D and A;
X5 is selected from D and A;
X6 is selected from Y and A;
X7 is selected from D and A; and
X8 is selected from Y and A;

VHCDR3: **GGX9SGSSX10X11HPMX12X13** (SEQ ID NO:3)
wherein
X9 is selected from Y and A;
X10 is selected from Y and A;
X11 is selected from Y and A;
X12 is selected from D and A; and
X13 is selected from Y and A.

VLCDR1: **KSSQSLLX14STNQKNX15LA** (SEQ ID NO:4),
wherein
X14 is selected from Y and A; and
X15 is selected from Y and A;

VLCDR2: **X16ASTRES** (SEQ ID NO:5)
wherein
X16 is selected from W and A; and

VLCDR3: **QQX17FIX18PRT** (SEQ ID NO:6)
wherein
X17 is selected from Y and A; and
X18 is selected from Y and A.

4. Binding protein according to claim 3, in which the amino acid sequences of the six CDRs are the following:

VHCDR1: **DYNMD** (SEQ ID NO:7),
VHCDR2: **DINPDYDTTSYNEKFKG** (SEQ ID NO:8),
VHCDR3: **GGYSGSSYYHPMDY** (SEQ ID NO:9)
VLCDR1: **KSSQSLLYSTNQKNYLA** (SEQ ID NO:10),
VLCDR2: **WASTRES** (SEQ ID NO:11)
VLCDR3: **QQYFIYPRT** (SEQ ID NO:12)

5. Binding protein according to claim 3, in which the amino acid sequences of the six CDRs are the following:

VHCDR1:	**DYNMD**	(SEQ ID NO:7),
VHCDR2:	**DINPDADTTSYNEKFKG**	(SEQ ID NO:18),
VHCDR3:	**GGYSGSSYYHPMDY**	(SEQ ID NO:9)
VLCDR1:	**KSSQSLLYSTNQKNYLA**	(SEQ ID NO:10),
VLCDR2:	**WASTRES**	(SEQ ID NO:11)
VLCDR3:	**QQYFIYPRT**	(SEQ ID NO:12)

6. Binding protein according to claim 4, in which said VH region comprises SEQ ID NO:31 and said VL region comprises SEQ ID NO:45.

7. Binding protein according to claim 5, in which said VH region comprises SEQ ID NO:37 and said VL region comprises SEQ ID NO:45.

8. Binding protein according to any preceding claim, in which the VH/VL pair of the first moiety M1 form part of an scFv, in which the VH and VL regions are coupled together by a peptide scFv linker.

9. Binding protein according to claim 8, in which said scFv linker is attached to the N-terminal amino acid residue of the VH region and to the C-terminal amino acid residue of the VL region.

10. Binding protein according to any preceding claim, in which said Fc-mediated response elicited by said second moiety **M2** is an Fc-mediated cytotoxic response, for example selected from the group consisting of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC) and combinations thereof.

11. Binding protein according to any preceding claim, in which said at least one peptide linker between M1 and M2 is attached, on the M1 side, to the C-terminal amino acid residue of the VH region of M1 or to the N-terminal amino acid residue of the VL region of M1.

12. Binding protein according to claim 11, in which said peptide linker between M1 and M2 is attached, on the M2 side, to the C-terminal residue of a CH3 region of said

Fc domain, and, on the M1 side, to the N-terminal amino acid residue of the VL region of M1.

13. Binding protein according to any one of claims 1-11, in which M2 comprises an antibody having two antibody light chains and in which M1 and M2 are connected to each other via two peptide linkers,

the first linker being attached, on the M2 side, to the C-terminal amino acid residue of the first light chain of M2 and, on the M1 side, to the N-terminal amino acid residue of the VL region of M1, and

the second linker being attached, on the M2 side, to the N-terminal amino acid residue of the second light chain of M2 and, on the M1 side, to the C-terminal amino acid residue of the VH region of M1.

14. Binding protein according to any preceding claim, in which M2 is an antibody capable of selective binding to a target present in the brain of a mammal.

15. Binding protein according to claim 14, wherein said target is selected from the group consisting of amyloid-β peptide or derivatives or fragments thereof, alpha-synuclein or derivatives or fragments thereof, TAR DNA-binding protein 43 (TDP-43) or derivatives or fragments thereof, triggering receptor expressed on myeloid cells 2 (TREM2), beta-secretase 1 (BACE1), superoxide dismutase (SOD), huntingtin, transthyretin, P-secretase 1, epidermal growth factor, epidermal growth factor receptor 2, Tau, phosphorylated Tau or fragments thereof, apolipoprotein E4, CD20, prion protein, leucine rich repeat kinase 2, parkin, presenilin 2, gamma secretase, death receptor 6, amyloid-β precursor protein, p75 neurotrophin receptor, neuregulin and caspase 6.

16. Pharmaceutical composition, comprising a binding protein according to any preceding claim and a pharmaceutically acceptable carrier or excipient.

17. A binding protein according to any one of claims 1-15 or a composition according to claim 16 for use in treatment.

18. The binding protein or composition for use according to claim 17, wherein the treatment is therapeutic treatment or prophylactic treatment.

19. Use of a binding protein according to any one of claims 1-15 or a composition according to claim 16 in the manufacture of a medicament for the therapeutic or prophylactic treatment of a neurodegenerative disorder.

20. The use of claim 19, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, other disorders associated with Aβ protein aggregation, traumatic brain injury (TBI), Lewy body dementia (LBD), Down's syndrome (DS), amyotrophic lateral sclerosis (ALS), frontotemporal dementia, tauopathy, systemic amyloidosis, atherosclerosis, Parkinson's disease (PD), Parkinson's disease dementia (PDD), the Lewy body variant of Alzheimer's disease, multiple system atrophy, psychosis, schizophrenia, Creutzfeldt-Jakob disease, Huntington's disease, and familial amyloid neuropathy.