

CLAIMS

1. A conjugate or fusion construct comprising an anti-CD98 antibody or antigen-binding fragment thereof respectively coupled to or covalently linked to a second antibody or an antigen binding fragment thereof that binds a brain target, wherein the anti-CD98 antibody or antigen-binding fragment thereof binds to a CD98, preferably human CD98hc, with a dissociation constant K_D of at least 1 nM, preferably 1-500 nM, at neutral pH and an off-rate constant k_d of at least 10^{-4} sec^{-1} , preferably 10^{-4} to 10^{-1} sec^{-1} , at an acidic pH, preferably pH 5, and the anti-CD98 antibody or antigen-binding fragment thereof has an off-rate constant k_d of 2×10^{-2} to $2 \times 10^{-4} \text{ sec}^{-1}$, preferably $8 \times 10^{-3} \text{ sec}^{-1}$ at the neutral pH, wherein the second antibody or an antigen binding fragment thereof binds a brain target selected from Tau and a cancer of the central nervous system (CNS) or brain, more particularly, the brain target is selected from the group consisting of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, CD20, leucine rich repeat kinase 2 (LRRK2), parkin, death receptor 6 (DR6), p75 neurotrophin receptor (p75NTR), and caspase 6.

2. The conjugate or fusion construct of claim 1, wherein the anti-CD98 antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region comprising heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, and a light chain variable region comprising light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 have the amino acid sequences of:

- (i) SEQ ID NOs: 7, 8, 9, 10, 11 and 12, respectively;
- (ii) SEQ ID NOs: 67, 68, 69, 70, 71 and 72, respectively;
- (iii) SEQ ID NOs: 89, 90, 91, 92, 93 and 94, respectively;
- (iv) SEQ ID NOs: 113, 114, 115, 116, 117 and 118, respectively;
- (v) SEQ ID NOs: 123, 124, 125, 126, 127 and 128, respectively;
- (vi) SEQ ID NOs: 133, 134, 135, 136, 137 and 138, respectively;
- (vii) SEQ ID NOs: 150, 151, 152, 153, 154 and 155, respectively;
- (viii) SEQ ID NOs: 160, 161, 162, 163, 164 and 165, respectively;
- (ix) SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively;

- (x) SEQ ID NOs: 180, 181, 182, 183, 184 and 185, respectively;
 - (xi) SEQ ID NOs: 194, 195, 196, 197, 198 and 199, respectively; or
 - (xii) SEQ ID NOs: 204, 205, 206, 207, 208 and 209, respectively; or
- (2) a single variable domain on a heavy chain (VHH) comprising heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3 having the amino acid sequences of:
- (i) SEQ ID NOs: 29, 30 and 31, respectively;
 - (ii) SEQ ID NOs: 48, 49 and 50, respectively;
 - (iii) SEQ ID NOs: 143, 144 and 145, respectively.

3. The conjugate or fusion construct of claim 2, wherein the anti-CD98 antibody or antigen-binding fragment thereof is a VHH fragment comprising an amino acid sequence having at least 80%, such as at least 85%, 90%, 95% or 100%, sequence identity to SEQ ID NO: 28, SEQ ID NO: 47, or SEQ ID NO: 142.

4. The conjugate or fusion construct of claim 2, wherein the anti-CD98 antibody or antigen-binding fragment thereof is a single-chain variable fragment (scFv) comprising the heavy chain variable region covalently linked to the light chain variable region via a linker, preferably, the linker has the amino acid sequence of SEQ ID NO: 189, more preferably, the scFv comprises an amino acid sequence having at least 80%, such as at least 85%, 90%, 95% or 100%, sequence identity to the amino acid sequences of SEQ ID NO: 6, SEQ ID NO: 66, SEQ ID NO: 88, SEQ ID NO: 112, SEQ ID NO: 122, SEQ ID NO: 132, SEQ ID NO: 149, SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 193, or SEQ ID NO: 203.

5. The fusion construct of any one of claims 1-4, wherein the anti-CD98 antibody or antigen-binding fragment thereof is covalently linked to the carboxy terminus of only one of the two heavy chains of the second antibody or antigen binding fragment thereof via a linker, preferably the linker has the amino acid sequence of SEQ ID NO: 190 or SEQ ID NO: 191.

6. The fusion construct of claim 5, wherein each of the two heavy chains of the second antibody or antigen binding fragment thereof comprises one or more heterodimeric mutations, such as a modified heterodimeric CH3 domain, or one or more knob and hole mutations, as compared to a wild-type CH3 domain polypeptide; and/or the second antibody or

antigen binding fragment thereof comprises one or more mutations in the Fc domain that enhance binding of the fusion to the neonatal Fc receptor (RcRn), preferably the one or more mutations enhance the binding at an acidic pH; and/or the second antibody or antigen binding fragment thereof comprises one or more mutations in the Fc domain that reduce or eliminate the effector function,

preferably, the heterodimeric mutations comprise the modified heterodimeric CH3 domain of the first heavy chain comprises amino acid modifications at positions T350, L351, F405, and Y407, and the modified heterodimeric CH3 domain of the second heavy chain comprises amino acid modifications at positions T350, T366, K392 and T394, wherein the amino acid modification at position T350 is T350V, T350I, T350L or T350M; the amino acid modification at position L351 is L351Y; the amino acid modification at position F405 is F405A, F405V, F405T or F405S; the amino acid modification at position Y407 is Y407V, Y407A or Y407I; the amino acid modification at position T366 is T366L, T366I, T366V or T366M, the amino acid modification at position K392 is K392F, K392L or K392M, and the amino acid modification at position T394 is T394W; more preferably,

the modified heterodimeric CH3 domain of the first heavy chain comprises mutations T350V, L351Y, F405A and Y407V, and the modified heterodimeric CH3 domain of the second heavy chain comprises mutations T350V, T366L, K392L and T394W; and/or

the Fc has the M252Y/S254T/T256E (YTE) mutations; and/or the Fc has one or more amino acid modifications at positions L234, L235, D270, N297, E318, K320, K322, P331, and P329, such as one, two or three mutations of L234A, L235A and P331S,

wherein the numbering of amino acid residues is according to the EU index as set forth in Kabat.

7. The fusion construct of any one of claims 1-6, wherein the second antibody or antigen binding fragment thereof binds to Tau and comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 having the amino acid sequences of SEQ ID NOs: 213 to 218, respectively, preferably, the second antibody is a monoclonal antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 110 and a light chain having the amino acid sequence of SEQ ID NO: 111.

8. The fusion construct of claim 2, comprising:

- (1) a first heavy chain having an amino acid sequence that is at least 80%, such as at least 85%, 90%, 95% or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 16, 19, 22, 25, 32, 35, 38, 41, 44, 51, 54, 57, 60, 63, 73, 76, 79, 82, 85, 95, 98, 101, 104, 107, 119, 129, 139, 146, 156, 166, 176, 186, 200, 210, and 219;
 - (2) two light chains each independently having an amino acid sequence that is at least 80%, such as at least 85%, 90%, 95% or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 17, 20, 23, 26, 33, 36, 42, 45, 52, 55, 58, 61, 64, 74, 77, 80, 83, 86, 96, 99, 102, 105, 108, 120, 130, 140, 147, 157, 167, 177, 187, 201, 211, and 220, respectively; and
 - (3) a second heavy chain having an amino acid sequence that is at least 80%, such as at least 85%, 90%, 95% or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 18, 21, 24, 27, 34, 37, 43, 46, 53, 56, 59, 62, 65, 75, 78, 81, 84, 87, 97, 100, 103, 106, 109, 121, 131, 141, 148, 158, 168, 178, 188, 202, 212, and 221, respectively.
9. An isolated nucleic acid encoding the conjugate of any one of claims 1-4 or the fusion construct of any one of claims 1-8.
 10. A vector comprising the isolated nucleic acid of claim 9.
 11. A host cell comprising the nucleic acid of claim 9 or the vector of claim 10.
 12. A method of producing the conjugate of any one of claims 1-4, or the fusion construct of any one of claims 1-8, comprising culturing a cell comprising a nucleic acid encoding the conjugate or the fusion construct under conditions to produce the conjugate or the fusion construct, and recovering the conjugate or the fusion construct from the cell or cell culture.
 13. A pharmaceutical composition comprising the conjugate of any one of claims 1-4, or the fusion construct of any one of claims 1-8, and a pharmaceutically acceptable carrier.
 14. The conjugate of any one of claims 1-4, or the fusion construct of any one of claims 1-8, or the pharmaceutical composition of claim 13 for use in therapy.

15. Use of the conjugate of any one of claims 1-4, or the fusion construct of any one of claims 1-8, or the pharmaceutical composition of claim 13 in the manufacture of a medicament for the treatment or detection of a disorder, preferably a neurological disorder, preferably, the neurological disorder is selected from the group consisting of neurodegenerative diseases (such as Lewy body disease, Parkinson's disease, multiple system atrophy), tauopathies (such as Alzheimer disease and supranuclear palsy), motor neuron disease, dementia (such as Pick's disease, and spinocerebellar ataxia), and cancer of the CNS and/or brain (such as brain metastases resulting from cancer elsewhere in the body), preferably, the conjugate, the fusion construct or the pharmaceutical composition is to be administered intravenously, more preferably the medicament is for reducing Fc-mediated effector function and/or does not induce rapid reticulocyte depletion.

16. The use of claim 15, wherein the medicament is for delivering the second antibody or antigen binding fragment thereof across the blood-brain barrier (BBB) of a subject in need thereof.

17. The use of claim 15, wherein the medicament is for inducing antibody dependent phagocytosis (ADP) without stimulating secretion of a pro-inflammatory cytokine in a subject in need thereof, wherein the second antibody or antigen binding fragment thereof comprises one or more amino acid modifications at positions L234, L235, D270, N297, E318, K320, K322, P331, and P329, such as one, two or three mutations of L234A, L235A and P331S, and wherein the numbering of amino acid residues is according to the EU index as set forth in Kabat, preferably, the therapeutic antibody or antigen binding fragment thereof binds specifically to tau aggregates.