

CLAIMS

We claim:

1. An anti-CD98 antibody or antigen-binding fragment thereof for delivering an agent to the brain of a subject in need thereof, 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.
2. The anti-CD98 antibody or antigen-binding fragment thereof of claim 1, having 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.
3. The anti-CD98 antibody or antigen-binding fragment thereof of claim 1 or 2, comprising:
 - (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.

4. The anti-CD98 antibody or antigen-binding fragment thereof of any one of claims 1-3, being 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.

5. The anti-CD98 antibody or antigen-binding fragment thereof of any one of claims 1-3, being 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.

6. A conjugate comprising the anti-CD98 antibody or antigen-binding fragment thereof of any one of claims 1-5 coupled to a therapeutic or diagnostic agent, preferably, the conjugate is a multi-specific antibody comprising a first antigen binding region which binds the CD98 and comprises the antigen-binding fragment of any one of claims 1 to 5, and a second antigen binding region which binds a brain target, such as a brain target selected from the group consisting of beta-secretase 1 (BACE1), amyloid beta (Abeta), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, apolipoprotein E4 (ApoE4), alpha-synuclein, CD20, huntingtin, prion protein (PrP), leucine rich repeat kinase 2 (LRRK2), parkin, presenilin 1, presenilin 2, gamma secretase, death receptor 6 (DR6), amyloid precursor protein (APP), p75 neurotrophin receptor (p75NTR), and caspase 6.

7. A fusion construct comprising the anti-CD98 antibody or antigen-binding fragment thereof of any one of claims 1 to 5 covalently linked to a second antibody or an antigen binding fragment thereof that binds to a brain target, such as a brain target selected from the group consisting of beta-secretase 1 (BACE1), amyloid beta (Abeta), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, apolipoprotein E4 (ApoE4), alpha-synuclein, CD20, huntingtin, prion protein (PrP), leucine rich repeat kinase 2 (LRRK2), parkin, presenilin 1, presenilin 2, gamma secretase, death receptor 6 (DR6), amyloid precursor protein (APP), p75 neurotrophin receptor (p75NTR), and caspase 6.

8. The fusion construct of claim 7, 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 wherein the linker has the amino acid sequence of SEQ ID NO: 190 or SEQ ID NO: 191.

9. The fusion construct of claim 8, 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.

10. The fusion construct of claim 9, wherein 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, and wherein the numbering of amino acid residues is according to the EU index as set forth in Kabat.

11. The fusion construct of claim 10, wherein 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.

12. The fusion of any one of claims 7-11, wherein 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, more preferably the Fc has the M252Y/S254T/T256E (YTE) mutations, wherein the numbering of amino acid residues is according to the EU index as set forth in Kabat.

13. The fusion of any one of claims 7-12, wherein 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 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.

14. The fusion construct of any one of claims 7-13, 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.

15. The fusion construct of any one of claims 7-14, 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.

16. An isolated nucleic acid encoding the antibody or antigen-binding fragment of any one of claims 1-5, the conjugate of claim 6 or the fusion construct of any one of claims 7-15.

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

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

19. A method of producing the antibody or antigen-binding fragment of any one of claims 1-5, the conjugate of claim 6, or the fusion construct of any one of claims 7-15, comprising culturing a cell comprising a nucleic acid encoding the antibody or antigen-binding fragment, the conjugate or the fusion construct under conditions to produce the antibody or antigen-binding fragment, the conjugate or the fusion construct, and recovering the antibody or antigen-binding fragment, the conjugate or the fusion construct from the cell or cell culture.

20. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-5, the conjugate of claim 6, or the fusion construct of any one of claims 7-15, and a pharmaceutically acceptable carrier.

21. A method of treating or detecting a disorder, preferably a neurological disorder, in a subject in need thereof, comprising administering to the subject the antibody or antigen-binding fragment of any one of claims 1-5, the conjugate of claim 6, or the fusion construct of any one of claims 7-15, or the pharmaceutical composition of claim 20, preferably, the neurological disorder is selected from the group consisting of neurodegenerative diseases (such as Lewy body disease, postpoliomyelitis syndrome, Shy-Draeger syndrome, olivopontocerebellar atrophy, Parkinson's disease, multiple system atrophy, striatonigral degeneration, spinocerebellar ataxia, spinal muscular atrophy), tauopathies (such as Alzheimer disease and supranuclear palsy), prion

diseases (such as bovine spongiform encephalopathy, scrapie, Creutzfeldt-Jakob syndrome, kuru, Gerstmann-Straussler-Scheinker disease, chronic wasting disease, and fatal familial insomnia), bulbar palsy, motor neuron disease, and nervous system heterodegenerative disorders (such as Canavan disease, Huntington's disease, neuronal ceroid-lipofuscinosis, Alexander's disease, Tourette's syndrome, Menkes kinky hair syndrome, Cockayne syndrome, Halervorden-Spatz syndrome, lafora disease, Rett syndrome, hepatolenticular degeneration, Lesch-Nyhan syndrome, and Unverricht-Lundborg syndrome), 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).

22. The method of claim 21, wherein the antibody or antigen-binding fragment thereof, the conjugate, or the pharmaceutical composition is administered intravenously.

23. A method of delivering a therapeutic or diagnostic agent across the blood-brain barrier (BBB) of a subject in need thereof, comprising administering to the subject a complex comprising the therapeutic or diagnostic agent coupled to, preferably covalently conjugated to, the antibody or antigen-binding fragment thereof of any one of claims 1 to 5.

24. The method of any one of claims 21 to 24, wherein the administration reduces Fc-mediated effector function and/or does not induce rapid reticulocyte depletion.

25. A method of inducing antibody dependent phagocytosis (ADP) without stimulating secretion of a pro-inflammatory cytokine in a subject in need thereof, comprising administering to the subject a complex comprising a therapeutic antibody or antigen binding fragment thereof coupled to, preferably covalently conjugated to, the antigen-binding fragment thereof of any one of claims 1 to 5, wherein the therapeutic 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, wherein the numbering of amino acid residues is according to the EU index as set forth in Kabat.

26. The method of claim 25, wherein the therapeutic antibody or antigen binding fragment thereof binds specifically to tau aggregates.