

Claims

1. An isolated humanized antibody or antigen-binding fragment thereof that binds to a tau protein at an epitope of the tau protein consisting of or within the amino acid sequence of SEQ ID NO: 1, wherein the antibody or antigen-binding fragment thereof binds paired helical filament (PHF)-tau, preferably human PHF-tau, wherein the epitope of the tau protein comprises one or more of phosphorylated T427, phosphorylated S433 and phosphorylated S435 of the tau protein, but does not comprise all of phosphorylated T427, phosphorylated S433 and phosphorylated S435.
2. The isolated humanized antibody or antigen-binding fragment thereof of claim 1 comprising immunoglobulin heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 4, 5 and 6, respectively; and immunoglobulin light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 7 or 14, 8 and 9, respectively; wherein the isolated humanized antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 90% identical to SEQ ID NO: 12 or 18, or a light chain variable region having a polypeptide sequence at least 90% identical to SEQ ID NO: 13, 19, 23 or 59.
3. The isolated humanized antibody or antigen-binding fragment thereof of claim 2, comprising a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12 or 18, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 13, 19, 23 or 59.
4. The isolated humanized antibody or antigen-binding fragment thereof of any one of claims 1 to 3, comprising:
 - (a) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 13;
 - (b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 18, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 19;
 - (c) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 23; or

- (d) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 18, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 59.
5. The isolated humanized antibody or antigen-binding fragment thereof of any one of claims 1 to 4, comprising:
- (a) a first heavy chain having the polypeptide sequence of SEQ ID NOs: 15 or 20;
 - (b) two light chains each independently having the polypeptide sequence of SEQ ID NOs: 16, 21, 24 or 60; and
 - (c) a second heavy chain having the polypeptide sequence of SEQ ID NO: 17 or 22.
6. The isolated humanized antibody or antigen-binding fragment thereof of any one of claims 1 to 4, comprising:
- (a) a heavy chain having the polypeptide sequence of SEQ ID NO: 61 or 62; and
 - (b) a light chain having the polypeptide sequence of SEQ ID NO: 16 or 24, or 21 or 60, respectively.
7. A conjugate comprising the isolated humanized antibody or antigen-binding fragment thereof of any one of claims 1 to 6 coupled to an anti-CD98 or anti-TfR antibody or antigen-binding fragment thereof.
8. The conjugate of claim 7, wherein the anti-CD98 or anti-TfR antibody or antigen-binding fragment thereof binds to a CD98, preferably human CD98hc, or a TfR, preferably human TfR1, respectively, 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.
9. The conjugate of claim 7 or 8, wherein the anti-CD98 or anti-TfR 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.

10. The conjugate of any one of claims 7-9, wherein the anti-CD98 or anti-TfR antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising HCDR1, HCDR2 and HCDR3, and a light chain variable region comprising LCDR1, LCDR2 and LCDR3, wherein:

- (a) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 of the anti-CD98 antibody or antigen-binding fragment thereof have the amino acid sequences of SEQ ID NOs: 26, 27, 28 or 33, 29, 30 and 31, respectively; or
- (b) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 of the anti-TfR antibody or antigen-binding fragment thereof have the amino acid sequences of SEQ ID NOs: 35, 36, 37, 38, 39 and 40, respectively.

11. The conjugate of any one of claims 7-10, wherein the anti-CD98 or anti-TfR 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: 55 or 56, 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 sequence of SEQ ID NO: 25, SEQ ID NO: 32, SEQ ID NO: 34, or SEQ ID NO: 41.

12. A fusion construct comprising the conjugate of any one of claims 7-11, wherein the anti-CD98 or anti-TfR antibody or antigen-binding fragment thereof is covalently linked to the carboxy terminus of only one of the two heavy chains of the isolated humanized antibody or antigen-binding fragment thereof via a linker, preferably wherein the linker has the amino acid sequence of SEQ ID NO: 52.

13. The fusion construct of claim 12, wherein each of the two heavy chains of the isolated humanized 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.

14. The fusion construct of claim 13, wherein 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.

15. The fusion construct of claim 13, wherein the modified heterodimeric CH3 domain of the first heavy chain comprises mutation T366W, and the modified heterodimeric CH3 domain of the second heavy chain comprises mutations T366S, L368A and Y407V.

16. The fusion construct of any one of claims 12-15, wherein the isolated humanized 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.

17. The fusion construct of any one of claims 12-16, wherein the isolated humanized 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.

18. A fusion construct comprising:

- (a) a first heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 42-49;

- (b) two light chains each independently having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 21, 24 and 60; and
- (c) a second heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 22.

19. An isolated nucleic acid encoding the isolated humanized antibody or antigen-binding fragment thereof of any of claims 1-6, the conjugate of any one of claims 7-11, or the fusion construct of any one of claims 12-18.

20. A vector comprising the isolated nucleic acid of claim 19.