WHAT IS CLAIMED IS:

1. A Fc polypeptide comprising a modified CH3 domain that specifically binds to a human CD98hc protein and is capable of being transported across the blood-brain barrier (BBB).

2. The Fc polypeptide of claim 1, wherein the modified CH3 domain comprises:

(a) at least eleven, twelve, thirteen, fourteen, or fifteen substitutions in a set of amino acid positions consisting of 380, 382, 384, 385, 386, 387, 421, 422, 424, 426, 428, 436, 438, 440 and 442, according to EU numbering;

(b) at least eight, nine, ten, eleven, twelve, or thirteen substitutions in a set of amino acid positions consisting of 380, 382, 384, 385, 386, 387, 422, 424, 426, 428, 434, 438, and 440, according to EU numbering;

(c) at least eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, or nineteen substitutions in a set of amino acid positions consisting of 378, 380, 382, 383, 384, 385, 386, 387, 389, 421, 422, 424, 426, 428, 434, 436, 438, 440, and 442, according to EU numbering; or

(d) at least eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen substitutions in a set of amino acid positions consisting of 382, 383, 384, 385, 386, 387, 389, 421, 422, 424, 426, 428, 436, 438, and 440, according to EU numbering.

3. The Fc polypeptide of claim 2, wherein the modified CH3 domain comprises a sequence having at least 85%, 90%, or 95% sequence identity to amino acids 111-217 of the sequence of any one of SEQ ID NOS:28-43, wherein the modified CH3 domain comprises at least eleven, twelve, thirteen, fourteen, or fifteen substitutions in a set of amino acid positions consisting of a L at position 380, a N at position 382, a R, H, or Q at position 384, a F or Y at position 385, a V, L, I, F, Y, or E at position 386, a L at position 387, a E, Q, or A at position 421, a I, T, or P at position 422, an A at position 424, a N at position 426, a Y or W at position 428, a R or W at position 436, a F or W at position 438, a N at position 440, and an A, Q, K, R, H, or M at position 442.

4. The Fc polypeptide of claim 2 or 3, wherein the modified CH3 domain comprises:

(a) a L at position 380, a N at position 382, a H at position 384, a Y at position 385, a E at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(b) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an E at position 421, an I at position 422, an A at position 424,

a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(c) a L at position 380, a N at position 382, a H at position 384, a Y at position 385, a E at position 386, a L at position 387, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(d) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(e) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and a R at position 442;

(f) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and a H at position 442;

(g) a L at position 380, a N at position 382, a H at position 384, a Y at position 385, a E at position 386, a L at position 387, an E at position 421, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(h) a L at position 380, a N at position 382, a Q at position 384, a Y at position 385, a E at position 386, a L at position 387, an E at position 421, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(i) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(j) a L at position 380, a N at position 382, a Q at position 384, a Y at position 385, a E at position 386, a L at position 387, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(k) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a R at position 436, a F at position 438, a N at position 440, and a R at position 442;

(l) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and a K at position 442;

(m) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a W at position 436, a F at position 438, a N at position 440, and a R at position 442;

(n) a L at position 380, a N at position 382, a Q at position 384, a Y at position 385, a L at position 386, a L at position 387, an E at position 421, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(o) a L at position 380, a S at position 382, a R at position 384, a Y at position 385, a V at position 386, a L at position 387,an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(p) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an E at position 421, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442;

(q) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an E at position 421, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, and a N at position 440;

(r) a L at position 380, a N at position 382, a Q at position 384, a F at position 385, a H at position 386, a L at position 387, an I at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and a L at position 442; or

(s) a L at position 380, a N at position 382, a R at position 384, a F at position 385, a V at position 386, a L at position 387, an T at position 422, an A at position 424, a N at position 426, a Y at position 428, a F at position 438, a N at position 440, and an A at position 442.

5. The Fc polypeptide of any one of claims 2 to 4, wherein the modified CH3 domain comprises the sequence any one of SEQ ID NOs: 38, 29, 31, 32, 35, 36, 28, 30, 37, 41, 42, 43, 33, 34, 39, and 40.

6. The Fc polypeptide of claim 2, wherein the modified CH3 domain comprises:

(a) a D, M, N, P, F, or H at position 380, a R, Y, F, S, W, Y, K, or N at position 382, a L, Y, A, S, or F at position 384, a F, K, D, M, I, N, Y, L, or H at position 385, a T, P, E, K, A, V, D, T, or F at position 386, a N, L, Y, R, G, S, D, or T at position 387, a I, K, R, T, F, or H at position 422, a V, W, G, L, I, P, or Y at position 424, a D, A, Q, W, L, or P at position 426, a L at position 428, a S at position 434, a I, F, N, P, or S at position 438, and a K, T, I, or F at position 440;

(b) a S or V at position 378, a D at position 380, a R at position 382, a T at position 383, a Y at position 384, a K at position 385, a P at position 386, a Y at position 387, a T, Y, or F at

position 389, a D, E, or Q at position 421, an I at position 422, a V at position 424, a D at position 426, a L or Y at position 428, a S at position 434, a F at position 436, an I or V at position 438, a K at position 440, and a Q or M at position 442;

(c) a sequence having at least 85%, 90%, or 95% sequence identity to amino acids 111-217 of the sequence of any one of SEQ ID NOS:44-45, wherein the modified CH3 domain comprises at least eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen substitutions in a set of amino acid positions consisting of a R at position 382, a T at position 383, a Y at position 384, a K at position 385, a P at position 386, a Y at position 387, a T at position 389, a D at position 421, an I at position 422, a V at position 424, a D at position 426, a L at position 428, a F at position 436, a I at position 438, and a K at position 440;

(d) a R at position 382, a T at position 383, a Y at position 384, a K at position 385, a P at position 386, a Y at position 387, a T at position 389, a D at position 421, an I at position 422, a V at position 424, a D at position 426, a F at position 436, a I at position 438, and a K at position 440;

(e) a R at position 382, a T at position 383, a Y at position 384, a K at position 385, a P at position 386, a Y at position 387, a T at position 389, a D at position 421, an I at position 422, a V at position 424, a D at position 426, a L at position 428, a F at position 436, a I at position 438, and a K at position 440; or

(f) SEQ ID NO:44 or 45.

7. The Fc polypeptide of claim 1, wherein the modified CH3 domain comprises:

(a) (i) a first amino acid sequence of $LX_1NX_2X_3X_4X_5L$ (SEQ ID NO:46) at amino acid positions 382-389, wherein

X_1 is any amino acid,

X_2 is R, H, or Q,

X_3 is F or Y,

X_4 is V, L, I, F, Y, or E, and

X_5 is any amino acid;

(ii) a second amino acid sequence of $X_1X_2X_3AX_4X_5X_6X_7$ (SEQ ID NO:47) at amino acid positions 421-428, wherein

X_1 is E, N, Q, or A,

X_2 is I, V, T, or P,

X_3 and X_4 are any amino acid,

X_5 is N or S,

X_6 is any amino acid, and

X_7 is Y or W; and

(iii) a third amino acid sequence of $X_1X_2X_3X_4NX_5X_6$ (SEQ ID NO:48) at amino acid positions 436-442, wherein

X_1 is Y, R, or W,

X_2 is any amino acid,

X_3 is F or W,

X_4 and X_5 are any amino acid, and

X_6 is A, Q, K, R, H, M, or S; or

(b) (i) a first amino acid sequence of $X_1X_2YKPYX_3T$ (SEQ ID NO:49) at amino acid positions 382-389, wherein

X_1 is E or R, wherein X_2 is S or T, and

X_3 is any amino acid;

(ii) a second amino acid sequence of $X_1X_2X_3VX_4DX_5X_6$ (SEQ ID NO:50) at amino acid positions 421-428, wherein

X_1 is N or D, wherein X_2 is V or I,

X_3, X_4, and X_5 and are any amino acid, and

X_6 is M or L; and

(iii) a third amino acid sequence of $X_1X_2IX_3X_4$ (SEQ ID NO:51) at amino acid positions 436-440, wherein

X_1 is Y or F,

X_2 and X_3 are any amino acid, and

X_4 is S or K.

8. The Fc polypeptide of any one of claims 1 to 7, wherein:

(a) the Fc polypeptide binds the human CD98hc protein with an affinity of 15 nM to 5 μM;

(b) the Fc polypeptide has cyno CD98hc cross-reactivity; and/or

(c) the Fc polypeptide binds to cyno CD98hc with an affinity of 80 nM to 5 μM.

9. The Fc polypeptide of any one of claims 2 to 8, wherein the modified CH3 domain further comprises at least one modification that promotes heterodimerization.

10. The Fc polypeptide of claim 9, wherein the at least one modification that promotes heterodimerization comprises:

(a) a T366W substitution, according to EU numbering; or

(b) T366S, L368A, and Y407V substitutions, according to EU numbering.

11. The Fc polypeptide of any one of claims 1 to 2 and 6 to 10, wherein the Fc polypeptide comprises L at position 428 and S at position 434.

12. The Fc polypeptide of any one of claims 1 to 11, wherein the Fc polypeptide further comprises:

(a) one or more modifications that reduce effector function;

(b) Ala at position 234 and Ala at position 235, according to EU numbering;

(c) Gly or Ser at position 329, according to EU numbering;

(d) Ala at position 234, Ala at position 235, and Gly at position 329, according to EU numbering; or

(e) Ala at position 234, Ala at position 235, and Ser at position 329, according to EU numbering.

13. The Fc polypeptide of any one of claims 1 to 12, wherein the Fc polypeptide forms a dimer with a second Fc polypeptide.

14. The Fc polypeptide of claim 13, wherein the second Fc polypeptide:

(a) comprises a modified CH3 domain that specifically binds to a human CD98hc protein such that the dimer is bivalent for CD98hc binding; or

(b) does not comprise a modified CH3 domain that specifically binds to a human CD98hc protein such that the dimer is bivalent for CD98hc binding.

15. The Fc polypeptide of any one of claims 1 to 14, wherein the Fc polypeptide is further joined to a Fab.

16. The Fc polypeptide of any one of claims 1 to 15, wherein the C-terminal lysine of the Fc polypeptide is absent or removed.

17. The Fc polypeptide of any one of claims 1-16, wherein the Fc polypeptide is linked to a therapeutic agent.

18. A polynucleotide or vector comprising a nucleic acid sequence encoding the Fc polypeptide of any one of claims 1 to 17.

19. A host cell comprising the polynucleotide or vector of claim 18.

20. A pharmaceutical composition comprising the Fc polypeptide of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

21. Use of the Fc polypeptide of claim 17 in the manufacture of a medicament for:

(a) increasing transcytosis of the therapeutic agent across an endothelium or the BBB;

(b) delivering the therapeutic agent to brain parenchyma; or

(c) delivering the therapeutic agent to a biological target in the brain.

22. The use of claim 21, wherein wherein the biological target comprises:

(a) a cell surface target selected from the group consisting of TREM2, PILRA, CD33, CR1, ABCA1, ABCA7, MS4A4A, MS4A6A, MS4A4E, HLA-DR5, HLA-DR1, IL1RAP, TREML2, IL-34, SORL1, ADAM17, and Siglec11;

(b) a cell surface target on a hematological cancer cell;

(c) a cell surface target on a hematological cancer cell is selected from the group consisting of: B7H3, BCMA, CD125, CD166, CD19, CD20, CD205, CD22, CD25, CD30, CD37, CD39, CD73, and CD79b;

(d) a tumor cell;

(e) a cell surface target in a tumor cell selected from the group consisting of ALK, AXL, CD25, CD44v6, CD46, CD56 (NCAM), CDH6 (cadherin 6), CEACAM 5 (CD66E), EGFR, EGFR viii, ETBR, FGFR (1-4), Folate Receptor alpha, GAL-3BP (galectin binding protein), GD2, GD3, GloboH (globohexasylceramide), gp100, gpNMB, HER2, HER3, HER4, IGFR1, KIT, LIV1A, LRRC15 (leucine rich repeat containing 15), MET , NaPi2B, PDL1, PMEL17, PRAME, PSMA, PTK7 (CCK4; colon carcinoma kinase), RON, ROR1, TF (tissue factor), and TROP2;

(f) alpha-synuclein or a derivative or fragment thereof, amyloid-beta peptide or a derivative or fragment thereof, Tau or a derivative or fragment thereof, pTau, huntingtin, transthyretin, or TAR DNA-binding protein 43 (TDP-43);

(g) extracellular target in the brain; or

(h) an astrocyte, a microglia, an oligodendrocyte, a plaque, a tangle, or a non-neuronal target.

23. Use of the Fc polypeptide of claim 17 in the manufacture of a medicament for delivering the therapeutic agent to a peripheral CD98hc-expressing organ, wherein the peripheral CD98hc-expressing organ is kidney, testes, bone marrow, spleen, or pancreas.

24. Use of a monovalent molecule that binds to CD98hc with a binding affinity from about 20nM to about 550nM or a bivalent molecule that binds to CD98hc with a binding affinity from about 275nM to about 2100nM linked to a therapeutic agent, in the manufacture of a medicament for increasing brain exposure of the therapeutic agent.