CLAIMS

1. An Fc region comprising a modified CH3 domain that binds to a human transferrin receptor protein 1 (TfR1) and is capable of being transported across the blood-brain barrier (BBB).

2. The Fc region of claim 1, that competes for binding to a human TfR1 with a polypeptide comprising the amino acid sequence any one of SEQ ID NOs: 4-46, 236-299, 302, and 347-553.

3. The Fc region of claim 1 or 2, wherein the modified CH3 domain binds to the apical domain of the human TfR1.

4. The Fc region of any one of claims 1 to 3, wherein the modified CH3 domain binds to an epitope that comprises amino acid 208 of the human TfR1 having the sequence of SEQ ID NO: 235.

5. The Fc region of any one of claims 1 to 4, wherein the modified CH3 domain binds to the human TfR1 without inhibiting binding of transferrin to the human TfR1.

6. The Fc region of any one of claims 1 to 5, wherein the modified CH3 domain is joined to a Fab.

7. The Fc region of any one of claims 1 to 5, wherein the Fc region is joined to an antibody variable region or to a therapeutic polypeptide.

8. The Fc region of any one of claims 1 to 7, wherein a set of amino acids in a CH3 domain is substituted to generate the modified CH3 domain.

9. The Fc region of claim 8, wherein the set of amino acids includes solvent-exposed residues in the CH3 domain.

10. The Fc region of claim 8 or 9, wherein the modified CH3 domain comprises five, six, seven, eight, or nine substitutions in a set of amino acid positions comprising 157, 159, 160, 161, 162, 163, 186, 189, and 194; and wherein the substitutions and the positions are determined with reference to amino acids 114-220 of SEQ ID NO: 1.

11. The Fc region of claim 10, wherein the modified CH3 domain further comprises one, two, three, or four substitutions at positions comprising 153, 164, 165, and 188; and wherein the substitutions and the positions are determined with reference to amino acids 114-220 of SEQ ID NO: 1.

12. The Fc region of claim 11, wherein the modified CH3 domain comprises at least one substitution selected from the following: position 153 is Trp, Leu, or Glu; position 157 is Tyr or Phe; position 159 is Thr; position 160 is Glu; position 161 is Trp; position 162 is Ser, Ala, Val, or Asn; position 163 is Ser or Asn; position 186 is Thr or Ser; position 188 is Glu or Ser; position 189 is Glu; and position 194 is Phe.

13. The Fc region of claim 12, wherein position 153 is Glu, position 157 is Tyr or Phe, position 159 is Thr, position 160 is Glu, position 161 is Trp, position 162 is Val, Ser, or Ala, position 163 is Asn, position 186 is Thr or Ser, position 188 is Glu, position 189 is Glu, and position 194 is Phe.

14. The Fc region of claim 13, wherein the Fc region comprises a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of any one of SEQ ID NOs: 280, 281, 431, 240, and 279.

15. The Fc region of claim 13 or 14, further comprising:

(a) Trp at position 139, as numbered with reference to SEQ ID NO: 1;

(b) Ala at position 7, Ala at position 8, and Trp at position 139, as numbered with reference to SEQ ID NO: 1;

(c) Ala at position 7, Ala at position 8, Gly at position 102, and Trp at position 139, as numbered with reference to SEQ ID NO:1;

(d) Ala at position 7, Ala at position 8, Trp at position 139, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO: 1;

(e) Ala at position 7, Ala at position 8, Gly at position 102, Trp at position 139, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO:1;

(f) Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO: 1;

(g) Ala at position 7, Ala at position 8, Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO: 1;

(h) Ala at position 7, Ala at position 8, Gly at position 102, Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO:1;

(i) Ala at position 7, Ala at position 8, Ser at position 139, Ala at position 141, Val at position 180, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO: 1; or

(j) Ala at position 7, Ala at position 8, Gly at position 102, Ser at position 139, Ala at position 141, Val at position 180, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO:1.

16. The Fc region of claim 13 or 14, comprising:

A. a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of SEQ ID NO: 280, wherein the Fc region comprises Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Val at position 162, Asn at position 163, Thr at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO: 1;

B. a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of SEQ ID NO: 281, wherein the Fc region comprises Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ser at position 162, Asn at position 163, Ser at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO: 1;

C. a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of SEQ ID NO: 431, wherein the Fc region comprises Glu at position 153, Phe at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ser at position 162, Asn at position 163, Ser at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO: 1;

D. a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of SEQ ID NO:240, wherein the Fc region comprises Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ser at position 162, Asn at position 163, Thr at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO: 1; or

E. a sequence having at least 85%, 90%, or 95% sequence identity to the sequence of SEQ ID NO: 279, wherein the Fc region comprises Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ala at position 162, Asn at position 163, Thr at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO: 1.

17. The Fc region of claim 16, further comprising:

(a) Trp at position 139, as numbered with reference to SEQ ID NO: 1;

(b) Ala at position 7, Ala at position 8, and Trp at position 139, as numbered with reference to SEQ ID NO: 1;

(c) Ala at position 7, Ala at position 8, Gly at position 102, and Trp at position 139, as numbered with reference to SEQ ID NO:1;

(d) Ala at position 7, Ala at position 8, Trp at position 139, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO: 1;

(e) Ala at position 7, Ala at position 8, Gly at position 102, Trp at position 139, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO:1;

(f) Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO: 1;

(g) Ala at position 7, Ala at position 8, Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO: 1;

(h) Ala at position 7, Ala at position 8, Gly at position 102, Ser at position 139, Ala at position 141, and Val at position 180, as numbered with reference to SEQ ID NO:1;

(i) Ala at position 7, Ala at position 8, Ser at position 139, Ala at position 141, Val at position 180, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO: 1; or

(j) Ala at position 7, Ala at position 8, Gly at position 102, Ser at position 139, Ala at position 141, Val at position 180, Leu at position 201, and Ser at position 207, as numbered with reference to SEQ ID NO:1.

18. The Fc region of claim 16 or 17, wherein:

(a) the Fc region comprises the sequence of SEQ ID NO: 373;

(b) the Fc region comprises the sequence of SEQ ID NO: 374;

(c) the Fc region comprises the sequence of SEQ ID NO: 375;
(d) the Fc region comprises the sequence of SEQ ID NO: 500;
(e) the Fc region comprises the sequence of SEQ ID NO: 501;
(f) the Fc region comprises the sequence of SEQ ID NO: 379;
(g) the Fc region comprises the sequence of SEQ ID NO: 380;
(h) the Fc region comprises the sequence of SEQ ID NO: 381;
(i) the Fc region comprises the sequence of SEQ ID NO: 503;
(j) the Fc region comprises the sequence of SEQ ID NO: 504;
(k) the Fc region comprises the sequence of SEQ ID NO: 385;
(l) the Fc region comprises the sequence of SEQ ID NO: 386;
(m) the Fc region comprises the sequence of SEQ ID NO: 387;
(n) the Fc region comprises the sequence of SEQ ID NO: 507;
(o) the Fc region comprises the sequence of SEQ ID NO: 508;
(p) the Fc region comprises the sequence of SEQ ID NO: 391;
(q) the Fc region comprises the sequence of SEQ ID NO: 392;
(r) the Fc region comprises the sequence of SEQ ID NO: 393;
(s) the Fc region comprises the sequence of SEQ ID NO: 510;
(t) the Fc region comprises the sequence of SEQ ID NO: 511;
(u) the Fc region comprises the sequence of SEQ ID NO: 472;
(v) the Fc region comprises the sequence of SEQ ID NO: 473;
(w) the Fc region comprises the sequence of SEQ ID NO: 474;
(x) the Fc region comprises the sequence of SEQ ID NO: 549;
(y) the Fc region comprises the sequence of SEQ ID NO: 550;
(z) the Fc region comprises the sequence of SEQ ID NO: 478;
(aa) the Fc region comprises the sequence of SEQ ID NO: 479;
(ab) the Fc region comprises the sequence of SEQ ID NO: 480;
(ac) the Fc region comprises the sequence of SEQ ID NO: 552;
(ad) the Fc region comprises the sequence of SEQ ID NO: 553;
(ae) the Fc region comprises the sequence of SEQ ID NO: 409;
(af) the Fc region comprises the sequence of SEQ ID NO: 410;
(ag) the Fc region comprises the sequence of SEQ ID NO: 411;
(ah) the Fc region comprises the sequence of SEQ ID NO: 521;
(ai) the Fc region comprises the sequence of SEQ ID NO: 522;
(aj) the Fc region comprises the sequence of SEQ ID NO :415;

(ak) the Fc region comprises the sequence of SEQ ID NO: 416;

(al) the Fc region comprises the sequence of SEQ ID NO: 417;

(am) the Fc region comprises the sequence of SEQ ID NO: 524;

(an) the Fc region comprises the sequence of SEQ ID NO: 525;

(ao) the Fc region comprises the sequence of SEQ ID NO: 361;

(ap) the Fc region comprises the sequence of SEQ ID NO: 362;

(aq) the Fc region comprises the sequence of SEQ ID NO: 363;

(ar) the Fc region comprises the sequence of SEQ ID NO: 493;

(as) the Fc region comprises the sequence of SEQ ID NO: 494;

(at) the Fc region comprises the sequence of SEQ ID NO: 367;

(au) the Fc region comprises the sequence of SEQ ID NO: 368;

(av) the Fc region comprises the sequence of SEQ ID NO: 369;

(aw) the Fc region comprises the sequence of SEQ ID NO: 496; or

(ax) the Fc region comprises the sequence of SEQ ID NO: 497.

19. A polynucleotide comprising a nucleic acid sequence encoding the Fc region of any one of claims 1 to 18, or a vector or a host cell comprising the polynucleotide.

20. A method for producing an Fc region comprising a modified CH3 domain, comprising culturing a host cell under conditions in which the Fc region encoded by the polynucleotide of claim 19 is expressed.

21. A method for enhancing binding of an Fc region comprising a modified CH3 domain that comprises a non-native binding site to a human TfR1, the method comprising:

(a) introducing one or more substitutions at one or more positions within 10 Å of the non-native binding site; and

(b) testing the modified CH3 domain for binding the human TfR1.

22. The method of claim 21, wherein the non-native binding site comprises substitutions at one or more of the following positions: 157, 159, 160, 161, 162, 163, 186, 189, and 194; and wherein the substitutions and the positions are determined with reference to amino acids 114-220 of SEQ ID NO: 1.

23. A method for engineering a CH3 domain of an Fc region to bind to a human TfR1, the method comprising:

(a) modifying a polynucleotide that encodes the CH3 domain at a solvent-exposed surface patch;

(b) expressing a polypeptide comprising the modified CH3 domain; and

(c) determining whether the modified CH3 domain binds to the human TfR1.