

CLAIMS

What is claimed is:

1. An isolated binding polypeptide comprising a modified human IgG Fc domain, comprising:

a) an aspartic acid (D) or a glutamic acid (E) at amino acid position 256, and/or a tryptophan (W) or a glutamine (Q) at amino acid position 307, wherein amino acid position 254 is not threonine (T), and further comprising:

—— a phenylalanine (F) or at amino acid position 434,

—— b) a tyrosine (Y) at amino acid position 434; or

—— a tyrosine (Y) at amino acid position 252,

wherein amino acid positions are according to EU numbering.

2. An isolated binding polypeptide comprising a modified Fc domain comprising a combination of amino acid substitutions at positions selected from the group consisting of:

a) a tyrosine (Y) at amino acid position 252, and an aspartic acid (D) at amino acid position

256;

b) an aspartic acid (D) or a tryptophan (W) at amino acid position 256; 307 and a phenylalanine

(F) at amino acid position 434; or

c) an aspartic acid (D) at amino acid position 256, and a tyrosine (Y) at amino acid position 434;

—— d) a tryptophan (W) or glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434;

—— wherein amino acid positions are according to EU numbering.

2. An isolated binding polypeptide comprising a modified human IgG Fc domain, wherein modifications relative to a wild-type human IgG Fc domain that together increase the FcRn-binding affinity of the modified human IgG Fc domain consist of:

a) a glutamic acid (E) at amino acid position 256 and a phenylalanine (F) at amino acid position 434,

b) an aspartic acid (D) at amino acid position 256 and a tyrosine (Y) at amino acid position 434,

c) a tyrosine (Y) at amino acid position 252 and a glutamic acid (E) at amino acid position 256,

d) a tryptophan (W) at position 307 and a tyrosine (Y) at amino acid position 434,

e) a tyrosine (Y) at amino acid position 252, and a tryptophan (W) at position 307,

f) a glutamine (Q) at position 307 and a tyrosine (Y) at amino acid position 307,
wherein 434, or

g) a tyrosine (Y) ~~is not~~ at amino acid position 434; 252 and a glutamine (Q) at position 307,

wherein amino acid positions are according to EU numbering.

3. An isolated binding polypeptide comprising a modified human IgG Fc domain, wherein the only modifications of the modified human IgG Fc domain relative to a wildtype human IgG Fc domain consist of:

a) a glutamic acid (E) at amino acid position 256 and a phenylalanine (F) at amino acid position 434,

b) an aspartic acid (D) at amino acid position 256 and a tyrosine (Y) at amino acid position 434,

c) a tyrosine (Y) at amino acid position 252 and a glutamic acid (E) at amino acid position 256,

d) a tryptophan (W) at position 307 and a tyrosine (Y) at amino acid position 434,
e) a tyrosine (Y) at amino acid position 252 and a tryptophan (W) at position 307,
f) a glutamine (Q) at position 307 and a tyrosine (Y) at amino acid position 434, or
g) a tyrosine (Y) at amino acid position 252 and a glutamine (Q) at position 307,
wherein amino acid positions are according to EU numbering.

4. An isolated binding polypeptide comprising a modified human IgG Fc domain comprising a combination of amino acid residues selected from the group consisting of:

a) a tyrosine (Y) at amino acid position 252, and a tryptophan (W) at amino acid position 307, wherein a tyrosine (Y) is not at amino acid position 434;

b) an aspartic acid (D) at amino acid position 256, and a tryptophan (W) at amino acid position 307, wherein a tyrosine (Y) is not at amino acid position 434;

gc) an aspartic acid (D) at amino acid position 256, and a glutamine (Q) at amino acid position 307, wherein a tyrosine (Y) is not at amino acid position 434;

hd) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, and a glutamine (Q) at amino acid position 307, wherein a tyrosine (Y) is not at amino acid position 434; and

ie) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, and a glutamine (Q) at amino acid position 307, wherein a threonine (T) is not at amino acid position 254, a histidine (H) is not at amino acid position 311, and a tyrosine (Y) is not at amino acid position 434;

wherein ~~the~~ amino acid substitutions are according to EU numbering.

~~35.~~ An isolated binding polypeptide comprising a modified human IgG Fc domain comprising:

a) a double amino acid substitution selected from the group consisting of M252Y/T256D, M252Y/~~T256E~~, ~~M252Y~~/T307Q, M252Y/T307W, T256D/T307Q, T256D/T307W, T256E/T307Q, and T256E/T307W, wherein a threonine (T) is not at amino acid position 254, a histidine (H) is not at amino acid position 311, and a tyrosine (Y) is not at amino acid position 434; or

b) a triple amino acid substitution selected from the group consisting of M252Y/T256D/T307Q, M252Y/T256D/T307W, M252Y/T256E/T307Q, and M252Y/T256E/T307W, wherein a threonine (T) is not at amino acid position 254, a histidine (H) is not at amino acid position 311, and a tyrosine (Y) is not at amino acid position 434;

wherein ~~the~~ amino acid substitutions are according to EU numbering.

~~4. The~~6. An isolated binding polypeptide ~~of any one of claims 1-3~~comprising a modified human IgG Fc domain, wherein modifications relative to a wild-type human IgG Fc domain that together increase the FcRn-binding affinity of the modified ~~Fc domain is a modified~~ human ~~Fc domain~~.

~~5. The isolated binding polypeptide of any one of claims 1-4, wherein the modified~~IgG Fc domain ~~is a modified IgG1 Fc domain~~consist of an aspartic acid (D) at amino acid position 256 and a glutamine (Q) at amino acid position 307, according to EU numbering.

~~6. The~~7. An isolated binding polypeptide ~~of any one of claims 1-5~~comprising a modified human IgG Fc domain, wherein the modified human IgG Fc domain comprises an aspartic acid (D) at amino acid position 256 and a tryptophan (W) at amino acid position 307, according to EU numbering.

~~8. An isolated binding polypeptide comprising a modified human IgG Fc domain, wherein modifications relative to a wild-type human IgG Fc domain that together increase the binding polypeptide has human FcRn binding affinity~~FcRn-binding affinity of the modified human IgG Fc domain consist of a tyrosine (Y) at amino acid position 252 and an aspartic acid (D) at amino acid position 256, according to EU numbering.

~~7. The isolated binding polypeptide of any one of claims 1-5, wherein the binding polypeptide has rat FcRn binding affinity.~~

~~8. The isolated binding polypeptide of any one of claims 1-7, wherein the binding polypeptide has human and rat FcRn binding affinity.~~

~~9. The isolated binding polypeptide of any one of claims 2-8, wherein the isolated binding polypeptide has an altered serum half-life compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~10. The isolated binding polypeptide of claim 9, wherein the isolated binding polypeptide has an increased serum half-life compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~11.9.~~ The isolated binding polypeptide of any one of claims 1-8, wherein the isolated binding polypeptide has ~~altered FcRn binding affinity~~an increased serum half-life compared to a binding polypeptide comprising a wild-type human IgG Fc domain.

~~12.10.~~ The isolated binding polypeptide of ~~claim 11~~any one of claims 1-9, wherein the isolated binding polypeptide has enhanced FcRn binding affinity compared to a binding polypeptide comprising a wild-type human IgG Fc domain, optionally wherein the FcRn is a human FcRn.

11. The isolated binding polypeptide of claim 10, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising a wild-type human IgG Fc domain, optionally wherein the acidic pH is 6.0.

12. The isolated binding polypeptide of any one of claims 1-11, wherein the isolated binding polypeptide has higher FcRn binding affinity at an acidic pH compared to the FcRn binding affinity of the binding polypeptide at a non-acidic pH, optionally wherein the acidic pH is 6.0, and optionally wherein the non-acidic pH is 7.4.

13. The isolated binding polypeptide of any one of claims 1-12, wherein the isolated binding polypeptide has ~~enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~14. The isolated binding polypeptide of any one of claims 1-13, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to the FcRn binding affinity of the binding polypeptide at an elevated non-acidic pH.~~

~~15. The isolated binding polypeptide of any one of claims 12-14, wherein the enhanced FcRn binding affinity comprises a reduced FcRn binding off-rate.~~

~~16. The isolated binding polypeptide of any one of claims 13-15, wherein the acidic pH is about 6.0.~~

~~17. The isolated binding polypeptide of any one of claims 13-16, wherein the acidic pH is about 6.0 and the non-acidic pH is about 7.4.~~

~~18. The isolated binding polypeptide of any one of claims 1-17, wherein the isolated binding polypeptide has~~ altered FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type ~~Fc domain~~human IgG Fc domain, optionally wherein the FcγRIIIa is a human FcγRIIIa.

~~19. The isolated binding polypeptide of any one of claims 1-18, wherein the isolated binding polypeptide has reduced FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~20. The isolated binding polypeptide of any one of claims 1-18, wherein the isolated binding polypeptide has enhanced FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~21. The isolated binding polypeptide of any one of claims 1-18, wherein the isolated binding polypeptide has approximately the same FcγRIIIa binding affinity as a binding polypeptide comprising a wild-type Fc domain.~~

~~22. The isolated binding polypeptide of any one of claims 1-21, wherein the isolated binding polypeptide has approximately the same thermal stability as a binding polypeptide comprising a wild-type Fc domain.~~

~~23. The isolated binding polypeptide of any one of claims 1-21, wherein the isolated binding polypeptide has approximately the same thermal stability as a~~14. An isolated binding polypeptide comprising a modified ~~Fc domain~~ having the triple amino acid substitution M252Y/S254T/T256E, according to ~~EU~~ numbering.

~~24. The isolated binding polypeptide of any one of claims 1-23, wherein the isolated binding polypeptide is an antibody.~~

~~25. The isolated binding polypeptide of any one of claims 1-24, wherein the isolated binding polypeptide is a monoclonal antibody.~~

~~26. The isolated binding polypeptide of any one of claims 24-25, wherein the isolated antibody is a chimeric, humanized, or human antibody.~~

~~27. The isolated binding polypeptide of any one of claims 24-26, wherein the isolated antibody is a full-length antibody.~~

~~28. The isolated binding polypeptide of any one of claims 1-27, wherein the isolated binding polypeptide specifically binds one or more human targets.~~

~~29. An isolated nucleic acid molecule comprising a nucleic acid encoding the isolated polypeptide of any one of claims 1-28.~~

~~30. A vector comprising the isolated nucleic acid molecule of claim 29.~~

~~31. The vector of claim 30, wherein the vector is an expression vector.~~

~~32. A host cell comprising the vector of any one of claims 30-31.~~

~~33. The host cell of claim 32, wherein the host cell is of eukaryotic or prokaryotic origin.~~

~~34. The host cell of any one of claims 32-33, wherein the host cell is of mammalian origin.~~

~~35. The host cell of any one of claims 32-33, wherein the host cell is of bacterial origin.~~

~~36. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 1-28.~~

~~37. A pharmaceutical composition comprising the isolated antibody of any one of claims 24-27.~~

~~38. An isolated binding polypeptide comprising a IgG Fc domain, wherein the modified Fe domain, wherein the modified human IgG Fc domain comprises an aspartic acid (D) at amino acid position 256, and a glutamine (Q) at amino acid position 307, according to EU numbering.;~~

~~39. An isolated binding polypeptide comprising a modified Fc domain, wherein the modified Fc domain comprises an aspartic acid (D) at amino acid position 256, and a tryptophan (W) at amino acid position 307, according to EU numbering.~~

~~40. An isolated binding polypeptide comprising a modified Fc domain, wherein the modified Fc domain comprises a tyrosine (Y) at amino acid position 252, and an aspartic acid (D) at amino acid position 256, according to EU numbering.~~

~~41. The isolated binding polypeptide of any one of claims 38-40, wherein the modified Fc domain is a modified human Fc domain.~~

~~42. The isolated binding polypeptide of any one of claims 38-41, wherein the modified Fc domain is a modified IgG1 Fc domain.~~

~~43. The isolated binding polypeptide of any one of claims 38-42, wherein the binding polypeptide has human FcRn binding affinity.~~

~~44. The isolated binding polypeptide of any one of claims 38-42, wherein the binding polypeptide has rat FcRn binding affinity.~~

~~45. The isolated binding polypeptide of any one of claims 38-44, wherein the isolated binding polypeptide has an increased serum half-life compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~46. The isolated binding polypeptide of any one of claims 38-44, wherein the isolated binding polypeptide has enhanced FcRn binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~47. The isolated binding polypeptide of any one of claims 38-44, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~48. The isolated binding polypeptide of any one of claims 38-47, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to the FcRn binding affinity of the binding polypeptide at an elevated non-acidic pH.~~

~~49. The isolated binding polypeptide of any one of claims 46-48, wherein the enhanced FcRn binding affinity comprises a reduced FcRn binding off-rate.~~

~~50. The isolated binding polypeptide of claim 47 or 48, wherein the acidic pH is about 6.0.~~

~~51. The isolated binding polypeptide of claim 47, wherein the acidic pH is about 6.0 and the non-acidic pH is about 7.4.~~

~~52. The isolated binding polypeptide of claim 48, wherein the acidic pH is about 6.0.~~

~~53. The isolated binding polypeptide of any one of claims 38-52, wherein the isolated binding polypeptide has altered FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~54. The isolated binding polypeptide of any one of claims 38-53, wherein the isolated binding polypeptide is a monoclonal antibody.~~

~~55. The isolated binding polypeptide of any one of claims 38-54, wherein the antibody is a chimeric, humanized, or human antibody.~~

~~56. The isolated binding polypeptide of any one of claims 38-55, wherein the isolated binding polypeptide specifically binds one or more human targets.~~

~~57. An isolated nucleic acid molecule comprising a nucleic acid encoding the isolated polypeptide of any one of claims 38-56.~~

~~58. An expression vector comprising the isolated nucleic acid molecule of claim 57.~~

~~59. A host cell comprising the expression vector of claim 58.~~

~~60. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 38-58.~~

~~61. An isolated binding polypeptide comprising a modified Fc domain, wherein the modified Fc domain comprises a combination of at least four amino acid substitutions comprising:~~

~~—— an aspartic acid (D) or a glutamic acid (E) at amino acid position 256, and a tryptophan (W) or a glutamine (Q) at amino acid position 307, wherein amino acid position 254 is not threonine (T), and further comprising:~~

~~—— a phenylalanine (F) or a tyrosine (Y) at amino acid position 434; and~~

~~—— a tyrosine (Y) at amino acid position 252,~~

~~wherein amino acid positions are according to EU numbering.~~

~~62. An isolated binding polypeptide comprising a modified Fc domain having a combination of amino acid substitutions at positions selected from the group consisting of:~~

~~a) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~

~~b) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~

~~c) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~

~~da) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a ~~phenylalanine (F)~~tyrosine (Y) at amino acid position 434; ~~or~~~~

~~b) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~

~~c) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434;~~

~~d) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~

e)- a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a ~~tyrosine (Y)~~phenylalanine (F) at amino acid position 434;

~~wherein the~~ f) a tyrosine (Y) at amino acid substitution position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a phenylalanine (F) at amino acid position 434; and

g) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434;

wherein amino acid positions are according to EU numbering.

~~63.~~15. An isolated binding polypeptide comprising a modified human IgG Fc domain comprising:

a quadruple combination of amino acid ~~substitution~~residues selected from the group consisting of ~~M252Y/T256D/T307Q/N434Y, M252Y/T256E/T307W/N434Y, M252Y/T256E/T307Q/N434Y, M252Y/T256D/T307Q/N434F, and M252Y/T256D/T307W/N434Y;~~

~~wherein the amino acid substitutions are according to EU numbering.~~

~~64. The isolated binding polypeptide of any one of claims 61-63, wherein the modified Fc domain is a modified human Fc domain.~~

~~65. The isolated binding polypeptide of any one of claims 61-64, wherein the modified Fc domain is a modified IgG1 Fc domain.~~

~~66. The isolated binding polypeptide of any one of claims 61-65, wherein the binding polypeptide has human FcRn binding affinity.~~

~~67. The isolated binding polypeptide of any one of claims 61-65, wherein the binding polypeptide has rat FcRn binding affinity.~~

~~68. The isolated binding polypeptide of any one of claims 61-67, wherein the binding polypeptide has human and rat FcRn binding affinity.~~

~~69. The isolated binding polypeptide of any one of claims 61-68, wherein the isolated binding polypeptide has altered FcRn binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~70. The isolated binding polypeptide of claim 61-69, wherein the isolated binding polypeptide has enhanced FcRn binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~71. The isolated binding polypeptide of any one of claims 61-70, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~72. The isolated binding polypeptide of any one of claims 61-71, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~73. The isolated binding polypeptide of any one of claims 61-72, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at a non-acidic pH compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~74. The isolated binding polypeptide of any one of claims 61-73, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at a non-acidic pH compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~75. The isolated binding polypeptide of any one of claims 61-74, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH, and enhanced FcRn binding affinity at a non-acidic pH, compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~76. The isolated binding polypeptide of any one of claims 61-75, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH, and enhanced FcRn binding affinity at a non-acidic pH, compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~77. The isolated binding polypeptide of any one of claims 61-76, wherein the acidic pH is about 6.0.~~

~~78. The isolated binding polypeptide of any one of claims 61-77, wherein the non-acidic pH is about 7.4.~~

~~79. The isolated binding polypeptide of any one of claims 61-78, wherein the isolated binding polypeptide has an altered serum half-life compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~80. The isolated binding polypeptide of any one of claims 61-79, wherein the isolated binding polypeptide has a reduced serum half-life compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~81. The isolated binding polypeptide of any one of claims 61-80, wherein the isolated binding polypeptide has a reduced serum half-life compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~82. The isolated binding polypeptide of any one of claims 61-81, wherein the isolated binding polypeptide has altered FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~83. The isolated binding polypeptide of any one of claims 61-82, wherein the isolated binding polypeptide has reduced FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~84. The isolated binding polypeptide of any one of claims 61-83, wherein the isolated binding polypeptide has reduced FcγRIIIa binding affinity compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~85. The isolated binding polypeptide of any one of claims 61-84, wherein the isolated binding polypeptide has reduced thermal stability compared to a binding polypeptide comprising a wild-type Fc domain.~~

~~86. The isolated binding polypeptide of any one of claims 61-85, wherein the isolated binding polypeptide has reduced thermal stability compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~87. The isolated binding polypeptide of any one of claims 61-86, wherein the isolated binding polypeptide is an antibody.~~

~~88. The isolated binding polypeptide of any one of claims 61-87, wherein the isolated binding polypeptide is a monoclonal antibody.~~

~~89. The isolated binding polypeptide of any one of claims 61-88, wherein the isolated antibody is a chimeric, humanized, or human antibody.~~

~~90. The isolated binding polypeptide of any one of claims 61-89, wherein the isolated antibody is a full-length antibody.~~

~~91. The isolated binding polypeptide of any one of claims 61-90, wherein the isolated binding polypeptide specifically binds one or more targets.~~

~~92. An isolated nucleic acid molecule comprising a nucleic acid encoding the isolated polypeptide of any one of claims 61-91.~~

~~93. A vector comprising the isolated nucleic acid molecule of claim 92.~~

~~94. The vector of claim 93, wherein the vector is an expression vector.~~

~~95. A host cell comprising the vector of any one of claims 93-94.~~

~~96. The host cell of claim 95, wherein the host cell is of eukaryotic or prokaryotic origin.~~

~~97. The host cell of any one of claims 95-96, wherein the host cell is of mammalian origin.~~

~~98. The host cell of any one of claims 95-96, wherein the host cell is of bacterial origin.~~

~~99. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 61-92.~~

~~100. A pharmaceutical composition comprising the isolated antibody of any one of claims 87-90.~~

~~101. An isolated binding polypeptide comprising a modified Fc domain comprisinga) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to EU numbering.;~~

~~102. An isolated binding polypeptide comprising a modified Fc domain comprisingb) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to EU numbering.;~~

~~103. An isolated binding polypeptide comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to EU numbering.~~

~~104. An isolated binding polypeptide comprising a modified Fc domain comprisingc) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434, according to EU numbering.;~~

~~105. An isolated binding polypeptide comprising a modified Fc domain comprisingd) a~~
tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a
tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;~~;~~ and
e) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position
256, a tryptophan (W) at amino acid position 307, and a phenylalanine (F) at amino acid position
434,
wherein amino acid substitutions are according to EU numbering.

~~106. The isolated binding polypeptide of any one of claims 101-105, wherein the modified Fc domain is a modified human Fc domain.~~

~~107. The~~16. An isolated binding polypeptide comprising a modified human IgG Fc domain,
wherein modifications relative to a wild-type human IgG Fc domain that together increase the
FcRn-binding affinity of the modified human IgG Fc domain consist of a tyrosine (Y) at amino
acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid
position 307, and a tyrosine (Y) at amino acid position 434.

17. An isolated binding polypeptide comprising a modified human IgG Fc domain comprising a
quadruple amino acid substitution selected from the group consisting of any one of claims 101-
~~106,~~

M252Y/T256D/T307Q/N434Y,

M252Y/T256E/T307W/N434Y,

M252Y/T256D/T307Q/N434F,

M252Y/T256D/T307W/N434Y, and

M252Y/T256D/T307W/N434F,

wherein ~~the modified Fc domain is a modified IgG1 Fc domain.~~amino acid substitutions are according to EU numbering.

~~108. The~~18. An isolated binding polypeptide ~~of any one of claims 101-107, wherein the~~
comprising a modified human IgG Fc domain comprising a tyrosine (Y) at amino acid position
252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307,
and a tyrosine (Y) at amino acid position 434, according to EU numbering.

19. An isolated binding polypeptide ~~has human FcRn binding affinity~~comprising a modified
human IgG Fc domain comprising a tyrosine (Y) at amino acid position 252, a glutamic acid (E)
at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at
amino acid position 434, according to EU numbering.

~~109. The~~20. An isolated binding polypeptide ~~of any one of claims 101-108~~comprising a
modified human IgG Fc domain, wherein the modifications relative to a wild-type human IgG Fc
domain that together increase the FcRn-binding affinity of the modified human IgG Fc domain
consist of a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position
256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434,
according to EU numbering.

21. An isolated binding polypeptide ~~has a reduced serum half-life compared to a binding~~
~~polypeptide~~comprising a modified human IgG Fc domain comprising a tyrosine (Y) at amino

acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434, according to EU numbering.

22. An isolated binding polypeptide comprising a ~~wild-type Fc domain~~ modified human IgG Fc domain comprising a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to EU numbering.

~~110. The~~ 23. An isolated binding polypeptide of any one of claims 101-109, comprising a modified human IgG Fc domain comprising:

a) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, and a tyrosine (Y) at amino acid position 434, or

b) an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434,

wherein ~~the~~ amino acid positions are according to EU numbering.

24. An isolated binding polypeptide ~~has a reduced serum half-life compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~ comprising a modified human IgG Fc domain comprising a combination of amino acid substitutions selected from the group consisting of

~~M252Y/T256D/N434Y~~ and

T256D/T307W/N434Y,

wherein amino acid substitutions are according to EU numbering.

~~25.~~ The isolated binding polypeptide of any one of claims ~~101-110~~14-24, wherein the ~~isolated binding polypeptide~~modified human IgG Fc domain has enhanced FcRn binding affinity at an acidic pH₇ and enhanced FcRn binding affinity at a non-acidic pH, compared to a ~~binding polypeptide comprising a wild-type Fc domain~~wild-type human IgG Fc domain, optionally wherein the acidic pH is 6.0 and optionally wherein the non-acidic pH is 7.4, further optionally wherein the FcRn is a human FcRn.

~~112~~26. The isolated binding polypeptide of any one of claims ~~101-111~~14-25, wherein the ~~isolated binding polypeptide~~modified human IgG Fc domain has enhanced FcRn binding affinity at an acidic pH₇ and enhanced FcRn binding affinity at a non-acidic pH, compared to a ~~binding polypeptide~~human IgG Fc domain comprising the five amino acid substitutions M252Y/S254T/T256E/H433K/N434F, optionally wherein the acidic pH is 6.0 and optionally wherein the non-acidic pH is 7.4, further optionally wherein the FcRn is a human FcRn.

~~113.~~ The ~~isolated binding polypeptide of claim 111 or 112, wherein the acidic pH is about 6.0 and the non-acidic pH is about 7.4.~~

~~114~~27. The isolated binding polypeptide of any one of claims ~~101-113~~14-26, wherein the ~~isolated binding polypeptide~~modified human IgG Fc domain has reduced FcγRIIIa binding affinity compared to a binding polypeptide comprising a wild-type ~~Fc domain~~human IgG Fc domain, further optionally wherein the FcγRIIIa is a human FcγRIIIa.

~~115~~28. The isolated binding polypeptide of any one of claims ~~101-114~~14-27, wherein the ~~isolated binding polypeptide~~ modified human IgG Fc domain has reduced FcγRIIIa binding affinity compared to a ~~binding polypeptide~~ human IgG Fc domain comprising the five amino acid substitutions M252Y/S254T/T256E/H433K/N434F, further optionally wherein the FcγRIIIa is a human FcγRIIIa.

~~116~~29. The isolated binding polypeptide of any one of claims 1-28, wherein the modified human IgG Fc domain is a modified human IgG1 Fc domain.

30. The isolated binding polypeptide of any one of claims 1-29, wherein the binding polypeptide has human FcRn binding affinity, and optionally rat FcRn binding affinity.

31. The isolated binding polypeptide of any one of claims ~~101-115~~, wherein the isolated binding polypeptide has reduced thermal stability as a binding polypeptide comprising a wild-type Fc domain.

~~117. The isolated binding polypeptide of any one of claims 101-116, wherein the isolated binding polypeptide has reduced thermal stability compared to a binding polypeptide comprising M252Y/S254T/T256E/H433K/N434F.~~

~~118. The isolated binding polypeptide of any one of claims 101-117, wherein the isolated binding polypeptide is a monoclonal antibody.~~

~~119. The isolated binding polypeptide of claim 118, wherein the antibody is a chimeric, humanized, or human antibody.~~

~~120. The isolated binding polypeptide of any one of claims 101-119~~1-30, wherein the isolated binding polypeptide specifically binds one or more human targets.

42432. The isolated binding polypeptide of any one of claims 1-31, wherein the isolated binding polypeptide is a monoclonal antibody.

33. The isolated binding polypeptide of claim 32, wherein the antibody is a chimeric, humanized, or human antibody.

34. An isolated nucleic acid molecule comprising a ~~nucleic acid~~ nucleotide sequence encoding the isolated binding polypeptide of any one of claims ~~401-420~~ 1-33.

42235. An expression vector comprising the isolated nucleic acid molecule of claim ~~421~~ 34.

42336. A host cell comprising the expression vector of claim ~~422~~ 35.

42437. The host cell of claim 36, wherein the host cell is a mammalian cell.

38. A method of producing an isolated binding polypeptide, comprising culturing the host cell of claim 37 under conditions that allow expression of the binding polypeptide, and isolating the binding polypeptide from the culture.

39. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims ~~401-420~~ 1-32 and a pharmaceutically acceptable carrier.

~~125. A method of 40. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 1-32 for use in treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the isolated binding polypeptide of any one of claims 1-28, 38-58, 61-91, and 101-120, or administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of claims 36-37, 60, 99-100, and 124.~~

~~126. The method of claim 125, wherein the disease or disorder is a cancer.~~

~~127. The method of claim 126, wherein the cancer is a tumor.~~

~~128. The method of claim 125, wherein the disease or disorder is an autoimmune disorder.~~

~~129~~41. A method of treating a cancer in a subject in need thereof, pharmaceutical composition comprising administering to the subject a therapeutically effective amount of the isolated binding polypeptide of any one of claims 1-2813 and 38-58, or administering to the 29-33 for use in treating a cancer in a subject a therapeutically effective amount of thein need thereof.

42. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 36, 37, and 60.

~~130. A method of 14-33 for use in treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the isolated binding polypeptide of any one of claims 61-91 and 101-120, or administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of claims 99, 100, and 124.~~

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