

## **CLAIMS**

1. An isolated binding polypeptide comprising a modified IgG Fc domain comprising:
  - a) an aspartic acid (D) at amino acid position 256 and a phenylalanine (F) at amino acid position 434 or
  - b) a tyrosine (Y) at amino acid position 252 and an aspartic acid (D) at amino acid position 256,wherein amino acid positions are according to EU numbering.
  
2. An isolated binding polypeptide comprising a modified IgG Fc domain comprising:
  - a) a tryptophan (W) at position 307 and a phenylalanine (F) at amino acid position 434 or
  - b) 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.
  
3. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein modifications relative to a wild-type IgG Fc domain that together increase the FcRn-binding affinity of the modified 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, or
  - c) a tyrosine (Y) at amino acid position 252 and a glutamic acid (E) at amino acid position 256,

wherein amino acid positions are according to EU numbering.

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

- a) a tryptophan (W) at position 307 and a tyrosine (Y) at amino acid position 434,
- b) a tyrosine (Y) at amino acid position 252 and a tryptophan (W) at position 307,
- c) a glutamine (Q) at position 307 and a tyrosine (Y) at amino acid position 434, or
- d) a tyrosine (Y) at amino acid position 252 and a glutamine (Q) at position 307,

wherein amino acid positions are according to EU numbering.

5. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein the only modifications of the modified IgG Fc domain relative to a wildtype 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, or

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

wherein amino acid positions are according to EU numbering.

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

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

7. An isolated binding polypeptide comprising a modified 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;
- c) 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;
- d) 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
- e) 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 amino acid substitutions are according to EU numbering.

8. An isolated binding polypeptide comprising a modified IgG Fc domain comprising the double amino acid substitution M252Y/T256D, 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 amino acid substitutions are according to EU numbering.

9. An isolated binding polypeptide comprising a modified IgG Fc domain comprising:

a) a double amino acid substitution selected from the group consisting of 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 amino acid substitutions are according to EU numbering.

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

11. An isolated binding polypeptide comprising a modified Fc domain, wherein the only modifications of the modified Fc domain relative to a wildtype 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.
12. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein the modified 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.
13. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein modifications relative to a wild-type IgG Fc domain that together increase the FcRn-binding affinity of the modified 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.
14. An isolated binding polypeptide comprising a modified Fc domain, wherein the only modifications of the modified Fc domain relative to a wildtype 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.
15. The isolated binding polypeptide of any one of claims 1-14, wherein the isolated binding polypeptide has an increased serum half-life compared to a binding polypeptide comprising a wild-type IgG Fc domain.

16. The isolated binding polypeptide of any one of claims 1-15, wherein the isolated binding polypeptide has enhanced FcRn binding affinity compared to a binding polypeptide comprising a wild-type IgG Fc domain, optionally wherein the FcRn is a human FcRn.

17. The isolated binding polypeptide of claim 16, wherein the isolated binding polypeptide has enhanced FcRn binding affinity at an acidic pH compared to a binding polypeptide comprising a wild-type IgG Fc domain, optionally wherein the acidic pH is 6.0.

18. The isolated binding polypeptide of any one of claims 1-17, 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.

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

20. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein the modified IgG Fc domain comprises:

- 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, 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 phenylalanine (F) at amino acid position 434;

f) 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 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.

21. An isolated binding polypeptide comprising a modified 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, 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, 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;  
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.

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

wherein amino acid positions are according to EU numbering.

23. An isolated binding polypeptide comprising a modified IgG Fc domain comprising a quadruple amino acid substitution selected from the group consisting of

M252Y/T256D/T307Q/N434Y,

M252Y/T256E/T307W/N434Y,

M252Y/T256D/T307Q/N434F,

M252Y/T256D/T307W/N434Y, and

M252Y/T256D/T307W/N434F,

wherein amino acid substitutions are according to EU numbering.

24. An isolated binding polypeptide comprising a modified 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.

25. An isolated binding polypeptide comprising a modified 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.

26. An isolated binding polypeptide comprising a modified IgG Fc domain, wherein the modifications relative to a wild-type 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.

27. An isolated binding polypeptide comprising a modified 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.

28. An isolated binding polypeptide comprising a modified 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.

29. An isolated binding polypeptide comprising a modified IgG Fc domain comprising:  
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, wherein amino acid positions are according to EU numbering.

30. An isolated binding polypeptide comprising a modified IgG Fc domain comprising:  
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 amino acid positions are according to EU numbering.

31. An isolated binding polypeptide comprising a modified IgG Fc domain comprising the combination of amino acid substitutions M252Y/T256D/N434Y, wherein amino acid substitutions are according to EU numbering.

32. An isolated binding polypeptide comprising a modified IgG Fc domain comprising the combination of amino acid substitutions T256D/T307W/N434Y, wherein amino acid substitutions are according to EU numbering.

33. The isolated binding polypeptide of any one of claims 20-32, wherein the modified IgG Fc domain has enhanced FcRn binding affinity at an acidic pH and enhanced FcRn binding affinity at a non-acidic pH, compared to a wild-type 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.

34. The isolated binding polypeptide of any one of claims 20-33, wherein the modified IgG Fc domain has enhanced FcRn binding affinity at an acidic pH and enhanced FcRn binding affinity at a non-acidic pH, compared to a 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.

35. The isolated binding polypeptide of any one of claims 20-34, wherein the modified IgG Fc domain has reduced Fc $\gamma$ RIIIa binding affinity compared to a binding polypeptide comprising a wild-type IgG Fc domain, further optionally wherein the Fc $\gamma$ RIIIa is a human Fc $\gamma$ RIIIa.

36. The isolated binding polypeptide of any one of claims 20-35, wherein the modified IgG Fc domain has reduced Fc $\gamma$ RIIIa binding affinity compared to a IgG Fc domain comprising the five amino acid substitutions M252Y/S254T/T256E/H433K/N434F, further optionally wherein the Fc $\gamma$ RIIIa is a human Fc $\gamma$ RIIIa.

37. The isolated binding polypeptide of any one of claims 1-36, wherein the modified IgG Fc domain is a modified human Fc domain.
38. The isolated binding polypeptide of any one of claims 1-37, wherein the modified IgG Fc domain is a modified IgG1 Fc domain.
39. The isolated binding polypeptide of any one of claims 1-38, wherein the binding polypeptide has human FcRn binding affinity, and optionally rat FcRn binding affinity.
40. The isolated binding polypeptide of any one of claims 1-39, wherein the isolated binding polypeptide specifically binds one or more human targets.
41. The isolated binding polypeptide of any one of claims 1-40, wherein the isolated binding polypeptide is a monoclonal antibody.
42. The isolated binding polypeptide of claim 41, wherein the antibody is a chimeric, humanized, or human antibody.
43. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the isolated binding polypeptide of any one of claims 1-42.
44. An expression vector comprising the isolated nucleic acid molecule of claim 43.

45. A host cell comprising the expression vector of claim 44.
46. The host cell of claim 45, wherein the host cell is a mammalian cell.
47. A method of producing an isolated binding polypeptide, comprising  
culturing the host cell of claim 46 under conditions that allow expression of the binding polypeptide, and  
isolating the binding polypeptide from the culture.
48. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 1-42 and a pharmaceutically acceptable carrier.
49. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 40-42 for use in treating a disease or disorder in a subject in need thereof.
50. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 40-42 for use in treating a cancer in a subject in need thereof.
51. A pharmaceutical composition comprising the isolated binding polypeptide of any one of claims 40-42 for use in treating an autoimmune disorder in a subject in need thereof.