CLAIMS

1. An Fc region variant, wherein the variant comprises alteration of amino acid at position 238 of the Fc region according to EU numbering and any one of the amino acids of (a) to (k) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:
(a) amino acid at position 235 of the Fc region according to EU numbering;
(b) amino acid at position 237 of the Fc region according to EU numbering;
(c) amino acid at position 241 of the Fc region according to EU numbering;
(d) amino acid at position 268 of the Fc region according to EU numbering;
(e) amino acid at position 295 of the Fc region according to EU numbering;
(f) amino acid at position 296 of the Fc region according to EU numbering;
(g) amino acid at position 298 of the Fc region according to EU numbering;
(h) amino acid at position 323 of the Fc region according to EU numbering;
(i) amino acid at position 324 of the Fc region according to EU numbering;
(j) amino acid at position 330 of the Fc region according to EU numbering; and
(k) at least two amino acids selected from (a) to (j).

2. The variant of claim 1, wherein at least two amino acids selected in (k) of claim 1 are any one of the following amino acid combinations (1) to (3):
(1) amino acids at positions 241, 268, 296, and 324 of the Fc region according to EU numbering;
(2) amino acids at positions 237, 241, 296, and 330 of the Fc region according to EU numbering; and
(3) amino acids at positions 235, 237, 241, and 296 of the Fc region according to EU numbering.

3. An Fc region variant, wherein the amino acid at position 238 of the Fc region according to EU numbering is Asp, and wherein the variant comprises any one of the amino acids of (a) to (k) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:
(a) Phe at amino acid position 235 of the Fc region according to EU numbering;
(b) Gln or Asp at amino acid position 237 of the Fc region according to EU numbering;
(c) Met or Leu at amino acid position 241 of the Fc region according to EU numbering;
(d) Pro at amino acid position 268 of the Fc region according to EU numbering;

(e) Met or Val at amino acid position 295 of the Fc region according to EU numbering;
(f) Glu, His, Asn, or Asp at amino acid position 296 of the Fc region according to EU numbering;
(g) Ala or Met at amino acid position 298 of the Fc region according to EU numbering;
(h) Ile at amino acid position 323 of the Fc region according to EU numbering;
(i) Asn or His at amino acid position 324 of the Fc region according to EU numbering;
(j) His or Tyr at amino acid position 330 of the Fc region according to EU numbering; and
(k) at least two amino acids selected from (a) to (j).

4. An Fc region variant, wherein the amino acid at position 238 of the Fc region according to EU numbering is Asp, and wherein the variant comprises the amino acids of any one of (1) to (3) below:
(1) Met at amino acid position 241, Pro at amino acid position 268, Glu at amino acid position 296, and His at amino acid position 324 of the Fc region according to EU numbering;
(2) Gln or Asp at amino acid position 237, Met at amino acid position 241, Glu at amino acid position 296, and His at amino acid position 330 of the Fc region according to EU numbering; and
(3) Phe at amino acid position 235, Gln or Asp at amino acid position 237, Met at amino acid position 241, and Glu at amino acid position 296 of the Fc region according to EU numbering.

5. An Fc region variant, wherein the variant comprises alterations of amino acids at positions 238 and 271 of the Fc region according to EU numbering and any one of the amino acids of (a) to (h) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:
(a) amino acid at position 234 of the Fc region according to EU numbering;
(b) amino acid at position 235 of the Fc region according to EU numbering;
(c) amino acid at position 236 of the Fc region according to EU numbering;
(d) amino acid at position 237 of the Fc region according to EU numbering;
(e) amino acid at position 239 of the Fc region according to EU numbering;
(f) amino acid at position 265 of the Fc region according to EU numbering;
(g) amino acid at position 267 of the Fc region according to EU numbering; and
(h) amino acid at position 297 of the Fc region according to EU numbering.

6. The variant of claim 5, wherein the amino acid alteration is a combination of amino acid alterations of any one of (1) to (3) below:

(1) amino acids at positions 233, 238, 264, 267, 268, and 271 of the Fc region according to EU numbering;
(2) amino acids at positions 233, 237, 238, 264, 267, 268, 271, 296, 297, 330, and 396 of the Fc region according to EU numbering; and
(3) amino acids at positions 233, 238, 264, 267, 268, 271 and 296 of the Fc region according to EU numbering.

7. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, and wherein the variant comprises any one of the amino acids of (a) to (h) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:
(a) Ala, His, Asn, Lys, or Arg at amino acid position 234 of the Fc region according to EU numbering;
(b) Ala at amino acid position 235 of the Fc region according to EU numbering;
(c) Gln at amino acid position 236 of the Fc region according to EU numbering;
(d) Arg or Lys at amino acid position 237 of the Fc region according to EU numbering;
(e) Lys at amino acid position 239 of the Fc region according to EU numbering;
(f) Lys, Asn, Arg, Ser, or Val at amino acid position 265 of the Fc region according to EU numbering;
(g) Lys, Arg, or Tyr at amino acid position 267 of the Fc region according to EU numbering; and
(h) Ala at amino acid position 297 of the Fc region according to EU numbering.

8. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, and wherein the variant comprises the amino acids of any one of (1) to (3) below:
(1) Asp at amino acid position 233, Asp at amino acid position 238, Ile at amino acid position 264, Arg at amino acid position 267, Glu at amino acid position 268, and Gly at amino acid position 271 of the Fc region according to EU numbering;
(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Ile at amino acid position 264, Ala at amino acid position 267, Glu at amino acid position 268, Gly at amino acid position 271, Asp at amino acid position 296, Ala at amino acid position 297, Arg at amino acid position 330, and Met at amino acid position 396 of the Fc region according to EU numbering; and
(3) Asp at amino acid position 233, Asp at amino acid position 238, Ile at amino acid position

264, Arg at amino acid position 267, Pro at amino acid position 268, Gly at amino acid position 271, and Glu at amino acid position 296 of the Fc region according to EU numbering.

9. The Fc region variant of any one of claims 1 to 8, wherein its complement-binding is also decreased.

10. The Fc region variant of claim 9, wherein the Fc region variant with decreased complement-binding comprises an amino acid alteration at position 322 of the Fc region according to EU numbering, or amino acid alterations at positions 327, 330, and 331 of the Fc region according to EU numbering.

11. The Fc region variant of claim 9, wherein the amino acid at position 322 is Ala or Glu in the Fc region according to EU numbering; or the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering.

12. An Fc region variant, wherein the variant comprises alterations of amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region.

13. The variant of claim 12, wherein the variant further comprises an amino acid alteration of any one of (a) to (e) below:
(a) the amino acid at position 233 of the Fc region according to EU numbering;
(b) the amino acid at position 237 of the Fc region according to EU numbering;
(c) the amino acid at position 264 of the Fc region according to EU numbering;
(d) the amino acid at position 267 of the Fc region according to EU numbering; and
(e) the amino acid at position 268 of the Fc region according to EU numbering.

14. The variant of claim 13, wherein the amino acid alteration is a combination of amino acid alterations of any one of (1) to (4) below:
(1) amino acids at positions 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;
(2) amino acids at positions 233, 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;
(3) amino acids at positions 238, 267, 268, 271, 327, 330, and 331 of the Fc region according to

EU numbering; and
(4) amino acids at positions 238, 264, 267, 271, 327, 330, and 331 of the Fc region according to EU numbering.

15. An Fc region variant, wherein the amino acid at position 238 is Asp, the amino acid at position 271 is Gly, the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region.

16. The variant of claim 15, wherein the variant further comprises any one of the amino acids of (a) to (e) below:
(a) Asp at amino acid position 233 of the Fc region according to EU numbering;
(b) Asp at amino acid position 237 of the Fc region according to EU numbering;
(c) Ile at amino acid position 264 of the Fc region according to EU numbering;
(d) Ala at amino acid position 267 of the Fc region according to EU numbering; and
(e) Asp or Glu at amino acid position 268 of the Fc region according to EU numbering.

17. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, wherein the variant also comprises the amino acids of any one of (1) to (4) below:
(1) Asp at amino acid position 237, Asp at amino acid position 238, Asp or Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering;
(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Asp at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and, Ser at amino acid position 331 of the Fc region according to EU numbering;
(3) Asp at amino acid position 238, Ala at amino acid position 267, Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering; and
(4) Asp at amino acid position 238, Ile at amino acid position 264, Ala at amino acid position 267, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering.

18. The Fc region variant of any one of claims 1 to 17, wherein the variant has an FcγRIIb-

binding activity that is at least 80% of the binding amount of a native IgG Fc region, and has an FcγRIIaR-binding activity that is 30% or less of the binding amount of the native IgG Fc region.

19. The Fc region variant of any one of claims 1 to 18, wherein a ratio of the FcγRIIb-binding activity of the variant relative to the binding activity of a polypeptide comprising the native IgG Fc region is at least 0.75, and the ratios of the binding activities to all activating FcγRs are 0.2 or less.

20. The Fc region variant of claim 19, wherein additionally a ratio of an FcγRIIaR-binding activity of the variant relative to the binding activity of a polypeptide comprising the native IgG Fc region is 0.1 or less.

21. A polypeptide comprising the Fc region variant of any one of claims 1 to 20.

22. The polypeptide of claim 21, wherein the polypeptide comprising the Fc region variant is an IgG antibody.

23. The polypeptide of claim 21, wherein the polypeptide comprising the Fc region variant is an Fc fusion protein molecule.

24. A pharmaceutical composition comprising the polypeptide of any one of claims 21 to 23, and a medically acceptable carrier.

25. The polypeptide of claim 21, which further comprises an antigen-binding domain whose antigen-binding activity changes depending on an ion concentration condition.

26. The polypeptide of claim 25, wherein the ion concentration condition is a calcium ion concentration condition.

27. The polypeptide of claim 26, wherein the aforementioned antigen-binding domain has a lower antigen-binding activity under a low calcium ion concentration condition than under a high calcium ion concentration condition.

28. The polypeptide of any one of claims 25 to 27, wherein the ion concentration condition is a pH condition.

29. The polypeptide of claim 28, wherein the antigen-binding domain has a lower antigen-binding activity in an acidic pH range condition than under a neutral pH range condition.

30. The polypeptide of any one of claims 25 to 29, wherein the polypeptide comprising the Fc region variant is an IgG antibody.

31. The polypeptide of any one of claims 25 to 29, wherein the polypeptide comprising the Fc region variant is an Fc fusion protein molecule.

32. A pharmaceutical composition comprising the polypeptide of any one of claims 25 to 31 and a medically acceptable carrier.

33. The pharmaceutical composition of claim 32 for promoting elimination of an antigen from plasma, wherein the antigen binds to the antigen-binding domain of the polypeptide of any one of claims 25 to 31, and is in the plasma.

34. Use of the polypeptide of any one of claims 25 to 31 for promoting elimination of an antigen from plasma, wherein the antigen binds to the antigen-binding domain of the polypeptide, and is in the plasma.

35. A method of reducing bindings of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity of the polypeptide, which comprises altering the amino acid at position 238 of the Fc region according to EU numbering and at least one amino acid selected from the amino acids at positions 235, 237, 241, 268, 295, 296, 298, 323, 324, and 330 of the Fc region according to EU numbering to other amino acids.

36. The method of claim 35, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 235 with Phe, a substitution of the amino acid at position 237 with Gln, a substitution of the amino acid at position 241 with Met or Leu, a substitution of the amino acid at position 268 with Pro, a substitution of the amino acid at position 295 with Met or Val, a substitution of the amino acid at position 296 with Glu, His, Asn, or Asp, a substitution of the amino acid at position 298 with Ala or Met, a substitution of the amino acid at position 323 with Ile, a substitution of the amino acid at position 324 with Asn or His, and a substitution of the amino acid at position 330 with His or Tyr according to EU numbering.

37. A method of producing a polypeptide comprising an Fc region variant, wherein the method comprises altering the amino acid at position 238 of the Fc region according to EU numbering and at least one amino acid selected from the amino acids at positions 235, 237, 241, 268, 295, 296, 298, 323, 324, and 330 of the Fc region according to EU numbering to other amino acids, wherein bindings to all activating FcγRs are decreased while an FcγRIIb-binding activity is maintained as compared to those of the polypeptide before the altering.

38. The method of claim 37, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, substitution of the amino acid at position 235 with Phe, substitution of the amino acid at position 237 with Gln, substitution of the amino acid at position 241 with Met or Leu, substitution of the amino acid at position 268 with Pro, substitution of the amino acid at position 295 with Met or Val, substitution of the amino acid at position 296 with Glu, His, Asn, or Asp, substitution of the amino acid at position 298 with Ala or Met, substitution of the amino acid at position 323 with Ile, substitution of the amino acid at position 324 with Asn or His, and substitution of the amino acid at position 330 with His or Tyr according to EU numbering.

39. A method of reducing binding activities of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity at a similar level in comparison to those of a native IgG, wherein the method comprises combining and introducing an amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of a native IgG Fc region, and an amino acid alteration(s) that decreases the binding activities to all FcγRs.

40. The method of claim 39, wherein the amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of the native IgG Fc region is an amino acid alteration(s) of Table 11.

41. The method of claim 39 or 40, wherein the amino acid alteration(s) that decreases the binding activities to all FcγRs is an alteration(s) of at least one amino acid selected from the amino acids at positions 234, 235, 236, 237, 239, 265, 267, and 297 of the Fc region according to EU numbering to another amino acid.

42. The method of any one of claims 39 to 41, wherein the amino acid alteration(s) of the Fc region is a substitution of the amino acid at position 234 with Ala, His, Asn, Lys, or Arg, a substitution of the amino acid at position 235 with Ala, a substitution of the amino acid at

position 236 with Gln, a substitution of the amino acid at position 237 with Arg or Lys, a substitution of the amino acid at position 239 with Lys, a substitution of the amino acid at position 265 with Lys, Asn, Arg, Ser, or Val, a substitution of the amino acid at position 267 with Lys, Arg, or Tyr, and a substitution of the amino acid at position 297 with Ala according to EU numbering.

43. The method of any one of claims 35, 36, and 39 to 42, wherein the FcγRIIb-binding activity is maintained with at least 80% of the binding amount of a native IgG Fc region, and an FcγRIIaR-binding activity is reduced to 30% or less of the binding amount of the native IgG Fc region.

44. The method of any one of claims 35, 36, and 39 to 43, wherein a ratio of the FcγRIIb-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is maintained at 0.75 at least, and the ratios of the binding activities to all activating FcγRs are reduced to 0.2 or less.

45. The method of claim 44, wherein additionally a ratio of an FcγRIIaR-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is reduced to 0.05 or less.

46. A method of producing a polypeptide comprising an Fc region variant, wherein binding activities to all activating FcγRs are decreased while an FcγRIIb-binding activity is maintained at a similar level in comparison to those of a native IgG, wherein the method comprises combining and introducing an amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of a native IgG Fc region, and an amino acid alteration(s) that decreases the binding activities to all FcγRs.

47. The method of claim 46, wherein the amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of the native IgG Fc region is an amino acid alteration of Table 11.

48. The method of claim 46 or 47, wherein the amino acid alteration(s) that decreases the binding activities to all FcγRs is an alteration of at least one amino acid selected from the amino acids at positions 234, 235, 236, 237, 239, 265, 267, and 297 of an Fc region according to EU numbering to another amino acid.

49. The method of any one of claims 46 to 48, wherein the amino acid alteration(s) of the Fc region is a substitution of the amino acid at position 234 with Ala, His, Asn, Lys, or Arg, a substitution of the amino acid at position 235 with Ala, a substitution of the amino acid at position 236 with Gln, a substitution of the amino acid at position 237 with Arg or Lys, a substitution of the amino acid at position 239 with Lys, a substitution of the amino acid at position 265 with Lys, Asn, Arg, Ser, or Val, a substitution of the amino acid at position 267 with Lys, Arg, or Tyr, and a substitution of the amino acid at position 297 with Ala according to EU numbering.

50. The method of any one of claims 37, 38, and 46 to 49, wherein the FcγRIIb-binding activity is maintained with at least 80% of the binding amount of a native IgG Fc region, and the binding activities to all activating FcγRs are reduced to 30% or less of the binding amount of the native IgG Fc region.

51. The method of any one of claims 37, 38, and 46 to 50, wherein a ratio of the FcγRIIb-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is maintained at 0.75 at least, and the ratios of binding activities to all activating FcγRs are decreased to 0.2 or less.

52. The method of claim 51, wherein additionally a ratio of the FcγRIIaR-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is reduced to 0.1 or less.

53. The method of any one of claims 37, 38, and 46 to 52, wherein the method further comprises combining and introducing an alteration(s) that decreases complement-binding.

54. The method of claim 53, wherein the alteration(s) that decreases complement-binding is an amino acid alteration at position 322 of the Fc region according to EU numbering, or amino acid alterations at positions 327, 330, and 331 of the Fc region according to EU numbering.

55. The method of claim 53, wherein the alteration(s) that decreases complement-binding is a substitution of the amino acid at position 322 with Ala or Glu in the Fc region according to EU numbering, or alternatively, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, and a substitution of the amino acid at position 331 with Ser in the Fc region according to EU numbering.

56. A method of reducing bindings of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity of the polypeptide, which comprises altering the amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering to other amino acids, or further comprises altering at least one amino acid selected from the amino acids at positions 233, 237, 264, 267, and 268 of the Fc region according to EU numbering to another amino acid.

57. The method of claim 56, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 271 with Gly, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, a substitution of the amino acid at position 331 with Ser, a substitution of the amino acid at position 233 with Asp, a substitution of the amino acid at position 237 with Asp, a substitution of the amino acid at position 264 with Ile, a substitution of the amino acid at position 267 with Ala, and a substitution of the amino acid at position 268 with Asp or Glu in the Fc region according to EU numbering.

58. A method of producing a polypeptide comprising an Fc region variant, wherein the method comprises altering the amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering to other amino acids, or further comprising altering at least one amino acid selected from the amino acids at positions 233, 237, 264, 267, and 268 of the Fc region according to EU numbering to another amino acid, wherein bindings to all activating FcγRs are decreased and complement-binding is decreased while an FcγRIIb-binding activity is maintained as compared to those of the polypeptide before the altering.

59. The method of claim 58, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 271 with Gly, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, a substitution of the amino acid at position 331 with Ser, a substitution of the amino acid at position 233 with Asp, a substitution of the amino acid at position 237 with Asp, a substitution of the amino acid at position 264 with Ile, a substitution of the amino acid at position 267 with Ala, and a substitution of the amino acid at position 268 with Asp or Glu in the Fc region according to EU numbering.

CLAIMS

1. An Fc region variant, wherein the variant comprises alteration of amino acid at position 238 of the Fc region according to EU numbering and any one of the amino acids of (a) to (g) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:

(a) amino acid at position 235 of the Fc region according to EU numbering;

(b) amino acid at position 237 of the Fc region according to EU numbering;

(c) amino acid at position 241 of the Fc region according to EU numbering;

(d) amino acid at position 295 of the Fc region according to EU numbering;

(e) amino acid at position 298 of the Fc region according to EU numbering;

(f) amino acid at position 324 of the Fc region according to EU numbering; and

(g) at least two amino acids selected from (a) to (f).

2. The variant of claim 1, wherein at least two amino acids selected in (k) of claim 1 are any one of the following amino acid combinations (1) to (3):

(1) amino acids at positions 241, 268, 296, and 324 of the Fc region according to EU numbering;

(2) amino acids at positions 237, 241, 296, and 330 of the Fc region according to EU numbering; and

(3) amino acids at positions 235, 237, 241, and 296 of the Fc region according to EU numbering.

3. An Fc region variant, wherein the amino acid at position 238 of the Fc region according to EU numbering is Asp, and wherein the variant comprises any one of the amino acids of (a) to (j) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:

(a) Phe at amino acid position 235 of the Fc region according to EU numbering;

(b) Gln or Asp at amino acid position 237 of the Fc region according to EU numbering;

(c) Met or Leu at amino acid position 241 of the Fc region according to EU numbering;

(d) Pro at amino acid position 268 of the Fc region according to EU numbering;

(e) Met or Val at amino acid position 295 of the Fc region according to EU numbering;

(f) Glu, His, or Asn at amino acid position 296 of the Fc region according to EU numbering;

(g) Ala or Met at amino acid position 298 of the Fc region according to EU numbering;

(h) Asn or His at amino acid position 324 of the Fc region according to EU numbering;

(i) His or Tyr at amino acid position 330 of the Fc region according to EU numbering; and
(j) at least two amino acids selected from (a) to (i).

4. An Fc region variant, wherein the amino acid at position 238 of the Fc region according to EU numbering is Asp, and wherein the variant comprises the amino acids of any one of (1) to (3) below:
(1) Met at amino acid position 241, Pro at amino acid position 268, Glu at amino acid position 296, and His at amino acid position 324 of the Fc region according to EU numbering;
(2) Gln or Asp at amino acid position 237, Met at amino acid position 241, Glu at amino acid position 296, and His at amino acid position 330 of the Fc region according to EU numbering; and
(3) Phe at amino acid position 235, Gln or Asp at amino acid position 237, Met at amino acid position 241, and Glu at amino acid position 296 of the Fc region according to EU numbering.

5. An Fc region variant, wherein the variant comprises alterations of amino acids at positions 238 and 271 of the Fc region according to EU numbering and any one of the amino acids of (a) to (f) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:
(a) amino acid at position 235 of the Fc region according to EU numbering;
(b) amino acid at position 236 of the Fc region according to EU numbering;
(c) amino acid at position 239 of the Fc region according to EU numbering;
(d) amino acid at position 265 of the Fc region according to EU numbering;
(e) amino acid at position 267 of the Fc region according to EU numbering; and
(f) amino acid at position 297 of the Fc region according to EU numbering.

6. The variant of claim 5, wherein the amino acid alteration is a combination of amino acid alterations of any one of (1) to (3) below:
(1) amino acids at positions 233, 238, 264, 267, 268, and 271 of the Fc region according to EU numbering;
(2) amino acids at positions 233, 237, 238, 264, 267, 268, 271, 296, 297, 330, and 396 of the Fc region according to EU numbering; and
(3) amino acids at positions 233, 238, 264, 267, 268, 271 and 296 of the Fc region according to EU numbering.

7. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at

position 271 is Gly in the Fc region according to EU numbering, and wherein the variant comprises any one of the amino acids of (a) to (h) below, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region:

(a) Ala, His, Asn, Lys, or Arg at amino acid position 234 of the Fc region according to EU numbering;

(b) Ala at amino acid position 235 of the Fc region according to EU numbering;

(c) Gln at amino acid position 236 of the Fc region according to EU numbering;

(d) Arg or Lys at amino acid position 237 of the Fc region according to EU numbering;

(e) Lys at amino acid position 239 of the Fc region according to EU numbering;

(f) Lys, Asn, Arg, Ser, or Val at amino acid position 265 of the Fc region according to EU numbering;

(g) Lys, Arg, or Tyr at amino acid position 267 of the Fc region according to EU numbering; and

(h) Ala at amino acid position 297 of the Fc region according to EU numbering.

8. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, and wherein the variant comprises the amino acids of any one of (1) to (3) below:

(1) Asp at amino acid position 233, Asp at amino acid position 238, Ile at amino acid position 264, Arg at amino acid position 267, Glu at amino acid position 268, and Gly at amino acid position 271 of the Fc region according to EU numbering;

(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Ile at amino acid position 264, Ala at amino acid position 267, Glu at amino acid position 268, Gly at amino acid position 271, Asp at amino acid position 296, Ala at amino acid position 297, Arg at amino acid position 330, and Met at amino acid position 396 of the Fc region according to EU numbering; and

(3) Asp at amino acid position 233, Asp at amino acid position 238, Ile at amino acid position 264, Arg at amino acid position 267, Pro at amino acid position 268, Gly at amino acid position 271, and Glu at amino acid position 296 of the Fc region according to EU numbering.

9. The Fc region variant of any one of claims 1 to 8, wherein its complement-binding is also decreased.

10. The Fc region variant of claim 9, wherein the Fc region variant with decreased complement-binding comprises an amino acid alteration at position 322 of the Fc region according to EU

numbering, or amino acid alterations at positions 327, 330, and 331 of the Fc region according to EU numbering.

11. The Fc region variant of claim 9, wherein the amino acid at position 322 is Ala or Glu in the Fc region according to EU numbering; or the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering.

12. An Fc region variant, wherein the variant comprises alterations of amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region.

13. The variant of claim 12, wherein the variant further comprises an amino acid alteration of any one of (a) to (e) below:

(a) the amino acid at position 233 of the Fc region according to EU numbering;

(b) the amino acid at position 237 of the Fc region according to EU numbering;

(c) the amino acid at position 264 of the Fc region according to EU numbering;

(d) the amino acid at position 267 of the Fc region according to EU numbering; and

(e) the amino acid at position 268 of the Fc region according to EU numbering.

14. The variant of claim 13, wherein the amino acid alteration is a combination of amino acid alterations of any one of (1) to (4) below:

(1) amino acids at positions 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;

(2) amino acids at positions 233, 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;

(3) amino acids at positions 238, 267, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering; and

(4) amino acids at positions 238, 264, 267, 271, 327, 330, and 331 of the Fc region according to EU numbering.

15. An Fc region variant, wherein the amino acid at position 238 is Asp, the amino acid at position 271 is Gly, the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to

all activating FcγRs are decreased when compared to those of a native IgG Fc region.

16. The variant of claim 15, wherein the variant further comprises any one of the amino acids of (a) to (e) below:

(a) Asp at amino acid position 233 of the Fc region according to EU numbering;

(b) Asp at amino acid position 237 of the Fc region according to EU numbering;

(c) Ile at amino acid position 264 of the Fc region according to EU numbering;

(d) Ala at amino acid position 267 of the Fc region according to EU numbering; and

(e) Asp or Glu at amino acid position 268 of the Fc region according to EU numbering.

17. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, wherein the variant also comprises the amino acids of any one of (1) to (4) below:

(1) Asp at amino acid position 237, Asp at amino acid position 238, Asp or Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering;

(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Asp at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and, Ser at amino acid position 331 of the Fc region according to EU numbering;

(3) Asp at amino acid position 238, Ala at amino acid position 267, Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering; and

(4) Asp at amino acid position 238, Ile at amino acid position 264, Ala at amino acid position 267, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering.

18. The Fc region variant of any one of claims 1 to 17, wherein the variant has an FcγRIIb-binding activity that is at least 80% of the binding amount of a native IgG Fc region, and has an FcγRIIaR-binding activity that is 30% or less of the binding amount of the native IgG Fc region.

19. The Fc region variant of any one of claims 1 to 18, wherein a ratio of the FcγRIIb-binding activity of the variant relative to the binding activity of a polypeptide comprising the native IgG Fc region is at least 0.75, and the ratios of the binding activities to all activating FcγRs are 0.2 or less.

20. The Fc region variant of claim 19, wherein additionally a ratio of an FcγRIIaR-binding activity of the variant relative to the binding activity of a polypeptide comprising the native IgG Fc region is 0.1 or less.

21. A polypeptide comprising the Fc region variant of any one of claims 1 to 20.

22. The polypeptide of claim 21, wherein the polypeptide comprising the Fc region variant is an IgG antibody.

23. The polypeptide of claim 21, wherein the polypeptide comprising the Fc region variant is an Fc fusion protein molecule.

24. A pharmaceutical composition comprising the polypeptide of any one of claims 21 to 23, and a medically acceptable carrier.

25. The polypeptide of claim 21, which further comprises an antigen-binding domain whose antigen-binding activity changes depending on an ion concentration condition.

26. The polypeptide of claim 25, wherein the ion concentration condition is a calcium ion concentration condition.

27. The polypeptide of claim 26, wherein the aforementioned antigen-binding domain has a lower antigen-binding activity under a low calcium ion concentration condition than under a high calcium ion concentration condition.

28. The polypeptide of any one of claims 25 to 27, wherein the ion concentration condition is a pH condition.

29. The polypeptide of claim 28, wherein the antigen-binding domain has a lower antigen-binding activity in an acidic pH range condition than under a neutral pH range condition.

30. The polypeptide of any one of claims 25 to 29, wherein the polypeptide comprising the Fc region variant is an IgG antibody.

31. The polypeptide of any one of claims 25 to 29, wherein the polypeptide comprising the Fc region variant is an Fc fusion protein molecule.

32. A pharmaceutical composition comprising the polypeptide of any one of claims 25 to 31 and a medically acceptable carrier.

33. The pharmaceutical composition of claim 32 for promoting elimination of an antigen from plasma, wherein the antigen binds to the antigen-binding domain of the polypeptide of any one of claims 25 to 31, and is in the plasma.

34. Use of the polypeptide of any one of claims 25 to 31 for promoting elimination of an antigen from plasma, wherein the antigen binds to the antigen-binding domain of the polypeptide, and is in the plasma.

35. A method of reducing bindings of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity of the polypeptide, which comprises altering the amino acid at position 238 of the Fc region according to EU numbering and at least one amino acid selected from the amino acids at positions 235, 237, 241, 295, 298, and 324 of the Fc region according to EU numbering to other amino acids.

36. The method of claim 35, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 235 with Phe, a substitution of the amino acid at position 237 with Gln, a substitution of the amino acid at position 241 with Met or Leu, a substitution of the amino acid at position 295 with Met or Val, His, Asn, or Asp, a substitution of the amino acid at position 298 with Ala or Met, and a substitution of the amino acid at position 324 with Asn or His with His or Tyr according to EU numbering.

37. A method of producing a polypeptide comprising an Fc region variant, wherein the method comprises altering the amino acid at position 238 of the Fc region according to EU numbering and at least one amino acid selected from the amino acids at positions 235, 237, 241, 295, 298, and 324 of the Fc region according to EU numbering to other amino acids, wherein bindings to all activating FcγRs are decreased while an FcγRIIb-binding activity is maintained as compared to those of the polypeptide before the altering.

38. The method of claim 37, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, substitution of the amino acid at position 235 with Phe, substitution of the amino acid at position 237 with Gln, substitution of the amino acid at

position 241 with Met or Leu, substitution of the amino acid at position 295 with Met or Val, His, Asn, or Asp, substitution of the amino acid at position 298 with Ala or Met, and substitution of the amino acid at position 324 with Asn or His with His or Tyr according to EU numbering.

39. A method of reducing binding activities of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity at a similar level in comparison to those of a native IgG, wherein the method comprises combining and introducing an amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of a native IgG Fc region, and an amino acid alteration(s) that decreases the binding activities to all FcγRs.

40. The method of claim 39, wherein the amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of the native IgG Fc region is an amino acid alteration(s) of Table 11.

41. The method of claim 39 or 40, wherein the amino acid alteration(s) that decreases the binding activities to all FcγRs is an alteration(s) of at least one amino acid selected from the amino acids at positions 234, 235, 236, 237, 239, 265, 267, and 297 of the Fc region according to EU numbering to another amino acid.

42. The method of any one of claims 39 to 41, wherein the amino acid alteration(s) of the Fc region is a substitution of the amino acid at position 234 with Ala, His, Asn, Lys, or Arg, a substitution of the amino acid at position 235 with Ala, a substitution of the amino acid at position 236 with Gln, a substitution of the amino acid at position 237 with Arg or Lys, a substitution of the amino acid at position 239 with Lys, a substitution of the amino acid at position 265 with Lys, Asn, Arg, Ser, or Val, a substitution of the amino acid at position 267 with Lys, Arg, or Tyr, and a substitution of the amino acid at position 297 with Ala according to EU numbering.

43. The method of any one of claims 35, 36, and 39 to 42, wherein the FcγRIIb-binding activity is maintained with at least 80% of the binding amount of a native IgG Fc region, and an FcγRIIaR-binding activity is reduced to 30% or less of the binding amount of the native IgG Fc region.

44. The method of any one of claims 35, 36, and 39 to 43, wherein a ratio of the FcγRIIb-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc

region is maintained at 0.75 at least, and the ratios of the binding activities to all activating FcγRs are reduced to 0.2 or less.

45. The method of claim 44, wherein additionally a ratio of an FcγRIIaR-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is reduced to 0.05 or less.

46. A method of producing a polypeptide comprising an Fc region variant, wherein binding activities to all activating FcγRs are decreased while an FcγRIIb-binding activity is maintained at a similar level in comparison to those of a native IgG, wherein the method comprises combining and introducing an amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of a native IgG Fc region, and an amino acid alteration(s) that decreases the binding activities to all FcγRs.

47. The method of claim 46, wherein the amino acid alteration(s) that increases the FcγRIIb-binding activity by two-fold or more as compared to that of the native IgG Fc region is an amino acid alteration of Table 11.

48. The method of claim 46 or 47, wherein the amino acid alteration(s) that decreases the binding activities to all FcγRs is an alteration of at least one amino acid selected from the amino acids at positions 234, 235, 236, 237, 239, 265, 267, and 297 of an Fc region according to EU numbering to another amino acid.

49. The method of any one of claims 46 to 48, wherein the amino acid alteration(s) of the Fc region is a substitution of the amino acid at position 234 with Ala, His, Asn, Lys, or Arg, a substitution of the amino acid at position 235 with Ala, a substitution of the amino acid at position 236 with Gln, a substitution of the amino acid at position 237 with Arg or Lys, a substitution of the amino acid at position 239 with Lys, a substitution of the amino acid at position 265 with Lys, Asn, Arg, Ser, or Val, a substitution of the amino acid at position 267 with Lys, Arg, or Tyr, and a substitution of the amino acid at position 297 with Ala according to EU numbering.

50. The method of any one of claims 37, 38, and 46 to 49, wherein the FcγRIIb-binding activity is maintained with at least 80% of the binding amount of a native IgG Fc region, and the binding activities to all activating FcγRs are reduced to 30% or less of the binding amount of the native IgG Fc region.

51. The method of any one of claims 37, 38, and 46 to 50, wherein a ratio of the FcγRIIb-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is maintained at 0.75 at least, and the ratios of binding activities to all activating FcγRs are decreased to 0.2 or less.

52. The method of claim 51, wherein additionally a ratio of the FcγRIIaR-binding activity relative to the binding activity of a polypeptide comprising the native IgG Fc region is reduced to 0.1 or less.

53. The method of any one of claims 37, 38, and 46 to 52, wherein the method further comprises combining and introducing an alteration(s) that decreases complement-binding.

54. The method of claim 53, wherein the alteration(s) that decreases complement-binding is an amino acid alteration at position 322 of the Fc region according to EU numbering, or amino acid alterations at positions 327, 330, and 331 of the Fc region according to EU numbering.

55. The method of claim 53, wherein the alteration(s) that decreases complement-binding is a substitution of the amino acid at position 322 with Ala or Glu in the Fc region according to EU numbering, or alternatively, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, and a substitution of the amino acid at position 331 with Ser in the Fc region according to EU numbering.

56. A method of reducing bindings of a polypeptide comprising an Fc region to all activating FcγRs while maintaining an FcγRIIb-binding activity of the polypeptide, which comprises altering the amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering to other amino acids, or further comprises altering at least one amino acid selected from the amino acids at positions 233, 237, 264, 267, and 268 of the Fc region according to EU numbering to another amino acid.

57. The method of claim 56, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 271 with Gly, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, a substitution of the amino acid at position 331 with Ser, a substitution of the amino acid at position 233 with Asp, a substitution of the amino acid at position 237 with Asp, a substitution of the amino acid at position 264 with Ile, a substitution of the amino acid at

position 267 with Ala, and a substitution of the amino acid at position 268 with Asp or Glu in the Fc region according to EU numbering.

58. A method of producing a polypeptide comprising an Fc region variant, wherein the method comprises altering the amino acids at positions 238, 271, 327, 330, and 331 of the Fc region according to EU numbering to other amino acids, or further comprising altering at least one amino acid selected from the amino acids at positions 233, 237, 264, 267, and 268 of the Fc region according to EU numbering to another amino acid, wherein bindings to all activating FcγRs are decreased and complement-binding is decreased while an FcγRIIb-binding activity is maintained as compared to those of the polypeptide before the altering.

59. The method of claim 58, wherein the amino acid alteration of the Fc region is a substitution of the amino acid at position 238 with Asp, a substitution of the amino acid at position 271 with Gly, a substitution of the amino acid at position 327 with Gly, a substitution of the amino acid at position 330 with Ser, a substitution of the amino acid at position 331 with Ser, a substitution of the amino acid at position 233 with Asp, a substitution of the amino acid at position 237 with Asp, a substitution of the amino acid at position 264 with Ile, a substitution of the amino acid at position 267 with Ala, and a substitution of the amino acid at position 268 with Asp or Glu in the Fc region according to EU numbering.