CLAIMS

1. A method of either (a) or (b) below, wherein the method comprises modifying the Fc region of an IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range into an Fc region that does not form a hetero complex comprising two molecules of FcRn and one molecule of activating Fcγ receptor in a neutral pH range,
wherein the ion concentration
(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more; or
(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more;

(a) a method for improving pharmacokinetics of an IgG-type antibody; and

(b) a method for reducing immunogenicity of an IgG-type antibody.

2. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modifying the Fc region into an Fc region whose binding activity to an activating Fcγ receptor is lower than the binding activity of an Fc region of native human IgG to the activating Fcγ receptor.

3 The method of claim 1 or 2, wherein the activating Fcγ receptor is human FcγRIa, human FcγRIIa(R), human FcγRIIa(H), human FcγRIIIa(V), or human FcγRIIIa(F).

4. The method of any one of claims 1 to 3, which comprises substituting an amino acid of said Fc region at any one or more amino acids of positions 235, 237, 238, 239, 270, 298, 325, and 329 as indicated by EU numbering.

5. The method of any one of claims 1 to 3, which comprises substituting an amino acid of said Fc region as indicated by EU numbering at any one or more of:
the amino acid of position 234 with any one of Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Lys, Met,

Phe, Pro, Ser, Thr, and Trp;
the amino acid of position 235 with any one of Ala, Asn, Asp, Gln, Glu, Gly, His, Ile, Lys, Met, Pro, Ser, Thr, Val, and Arg;
the amino acid of position 236 with any one of Arg, Asn, Gln, His, Leu, Lys, Met, Phe, Pro, and Tyr;
the amino acid of position 237 with any one of Ala, Asn, Asp, Gln, Glu, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Val, Tyr, and Arg;
the amino acid of position 238 with any one of Ala, Asn, Gln, Glu, Gly, His, Ile, Lys, Thr, Trp, and Arg;
the amino acid of position 239 with any one of Gln, His, Lys, Phe, Pro, Trp, Tyr, and Arg;
the amino acid of position 265 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 266 with any one of Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Lys, Phe, Pro, Ser, Thr, Trp, and Tyr;
the amino acid of position 267 with any one of Arg, His, Lys, Phe, Pro, Trp, and Tyr;
the amino acid of position 269 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 270 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 271 with any one of Arg, His, Phe, Ser, Thr, Trp, and Tyr;
the amino acid of position 295 with any one of Arg, Asn, Asp, Gly, His, Phe, Ser, Trp, and Tyr;
the amino acid of position 296 with any one of Arg, Gly, Lys, and Pro;
the amino acid of position 297 with Ala;
the amino acid of position 298 with any one of Arg, Gly, Lys, Pro, Trp, and Tyr;
the amino acid of position 300 with any one of Arg, Lys, and Pro;
the amino acid of position 324 with Lys or Pro;
the amino acid of position 325 with any one of Ala, Arg, Gly, His, Ile, Lys, Phe, Pro, Thr, Trp, Tyr, and Val;
the amino acid of position 327 with any one of Arg, Gln, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 328 with any one of Arg, Asn, Gly, His, Lys, and Pro;
the amino acid of position 329 with any one of Asn, Asp, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, Val, and Arg;
the amino acid of position 330 with Pro or Ser;
the amino acid of position 331 with any one of Arg, Gly, and Lys; or
the amino acid of position 332 with any one of Arg, Lys, and Pro.

6. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modifying the Fc region into an Fc region that has a higher binding activity to an inhibitory Fcγ receptor than to an activating Fcγ receptor.

7. The method of claim 6, wherein the inhibitory Fcγ receptor is human FcγRIIb.

8. The method of claim 6 or 7, wherein the activating Fcγ receptor is human FcγRIa, human FcγRIIa(R), human FcγRIIa(H), human FcγRIIIa(V), or human FcγRIIIa(F).

9. The method of any one of claims 6 to 8, which comprises substituting the amino acid of position 238 or 328 indicated by EU numbering.

10. The method of any one of claims 6 to 8, which comprises substituting Asp for the amino acid of position 238 or Glu for the amino acid of position 328 indicated by EU numbering.

11. The method of any one of claims 6 to 8, which comprises substituting any one or more amino acids of:
the amino acid of position 233 with Asp;
the amino acid of position 234 with Trp or Tyr;
the amino acid of position 237 with any one of Ala, Asp, Glu, Leu, Met, Phe, Trp, and Tyr;
the amino acid of position 239 with Asp;
the amino acid of position 267 with any one of Ala, Gln, and Val;
the amino acid of position 268 with any one of Asn, Asp, and Glu;
the amino acid of position 271 with Gly;
the amino acid of position 326 with any one of Ala, Asn, Asp, Gln, Glu, Leu, Met, Ser, and Thr;
the amino acid of position 330 with any one of Arg, Lys, and Met;
the amino acid of position 323 with any one of Ile, Leu, and Met; and
the amino acid of position 296 with Asp; wherein the amino acids are indicated by EU numbering.

12. The method of any one of claims 1 to 8, wherein the Fc region comprises one or more amino acids that are different from amino acids of the native Fc region at any of amino acid positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 of said Fc region as indicated by EU numbering.

13. The method of any one of claims 1 to 8, wherein the amino acids of said Fc region indicated by EU numbering are a combination of one or more of:
Met at amino acid position 237;
Ile at amino acid position 248;
any one of Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, and Tyr at amino acid position 250;
any one of Phe, Trp, and Tyr at amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
any one of Asn, Asp, Glu, and Gln at amino acid position 256;
any one of Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, and Val at amino acid position 257;
His at amino acid position 258;
Ala at amino acid position 265;
Ala or Glu at amino acid position 286;
His at amino acid position 289;
Ala at amino acid position 297;
Gly at amino acid position 298;
Ala at amino acid position 303;
Ala at amino acid position 305;
any one of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, and Tyr at amino acid position 307;
any one of Ala, Phe, Ile, Leu, Met, Pro, Gln, and Thr at amino acid position 308;
any one of Ala, Asp, Glu, Pro, and Arg at amino acid position 309;
any one of Ala, His, and Ile at amino acid position 311;
Ala or His at amino acid position 312;
Lys or Arg at amino acid position 314;
any one of Ala, Asp, and His at amino acid position 315;
Ala at amino acid position 317;
Val at amino acid position 332;
Leu at amino acid position 334;
His at amino acid position 360;
Ala at amino acid position 376;
Ala at amino acid position 380;
Ala at amino acid position 382;
Ala at amino acid position 384;
Asp or His at amino acid position 385;

Pro at amino acid position 386;
Glu at amino acid position 387;
Ala or Ser at amino acid position 389;
Ala at amino acid position 424;
any one of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, and Tyr at amino acid position 428;
Lys at amino acid position 433;
any one of Ala, Phe, His, Ser, Trp, and Tyr at amino acid position 434; and
any one of His, Ile, Leu, Phe, Thr, and Val at amino acid position 436.

14. The method of any one of claims 1 to 13, wherein the antigen-binding domain is an antibody variable region.

15. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modification into an Fc region in which one of the two polypeptides constituting the Fc region has FcRn-binding activity in a neutral pH range and the other does not have FcRn-binding activity in a neutral pH range.

16. The method of claim 15, which comprises substituting an amino acid at any one or more of positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 as indicated by EU numbering in the amino acid sequence of one of the two polypeptides constituting said Fc region.

17. The method of claim 16, which comprises substituting an amino acid of said Fc region at any one or more of:
the amino acid of position 237 with Met;
the amino acid of position 248 with Ile;
the amino acid of position 250 with Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr;
the amino acid of position 252 with Phe, Trp, or Tyr;
the amino acid of position 254 with Thr;
the amino acid of position 255 with Glu;
the amino acid of position 256 with Asn, Asp, Glu, or Gln;
the amino acid of position 257 with Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val;
the amino acid of position 258 with His;
the amino acid of position 265 with Ala;

the amino acid of position 286 with Ala or Glu;
the amino acid of position 289 with His;
the amino acid of position 297 with Ala;
the amino acid of position 298 with Gly;
the amino acid of position 303 with Ala;
the amino acid of position 305 with Ala;
the amino acid of position 307 with Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr;
the amino acid of position 308 with Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr;
the amino acid of position 309 with Ala, Asp, Glu, Pro, or Arg;
the amino acid of position 311 with Ala, His, or Ile;
the amino acid of position 312 with Ala or His;
the amino acid of position 314 with Lys or Arg;
the amino acid of position 315 with Ala, Asp, or His;
the amino acid of position 317 with Ala;
the amino acid of position 332 with Val;
the amino acid of position 334 with Leu;
the amino acid of position 360 with His;
the amino acid of position 376 with Ala;
the amino acid of position 380 with Ala;
the amino acid of position 382 with Ala;
the amino acid of position 384 with Ala;
the amino acid of position 385 with Asp or His;
the amino acid of position 386 with Pro;
the amino acid of position 387 with Glu;
the amino acid of position 389 with Ala or Ser;
the amino acid of position 424 with Ala;
the amino acid of position 428 with Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr;
the amino acid of position 433 with Lys;
the amino acid of position 434 with Ala, Phe, His, Ser, Trp, or Tyr; and
the amino acid of position 436 with His, Ile, Leu, Phe, Thr, or Val; wherein the amino acids are indicated by EU numbering.

18. The method of any one of claims 15 to 17, wherein the antigen-binding domain is an antibody variable region.

19. An IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range, wherein the Fc region comprises one or more amino acids selected from:
Ala at amino acid position 234;
Ala, Lys, or Arg at amino acid position 235;
Arg at amino acid position 236;
Arg at amino acid position 238;
Lys at amino acid position 239;
Phe at amino acid position 270;
Ala at amino acid position 297;
Gly at amino acid position 298;
Gly at amino acid position 325;
Arg at amino acid position 328; and
Lys or Arg at amino acid position 329; wherein the amino acids are indicated by EU numbering, wherein the ion concentration
(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more, wherein the antigen-binding domain comprises at least one His residue ; or
(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more.

20. The IgG-type antibody of claim 19, which comprises one or more amino acids selected from:
Lys or Arg at amino acid position 237;
Lys at amino acid position 238;
Arg at amino acid position 239; and
Lys or Arg at amino acid position 329; wherein the amino acids are indicated by EU numbering.

21. An IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region in which one of the two polypeptides constituting the Fc region has FcRn-binding activity in a neutral pH range and the other does not

have FcRn-binding activity in a neutral pH range, wherein the ion concentration
(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more, wherein the antigen-binding domain comprises at least one His residue ; or
(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more.

22. The IgG-type antibody of any one of claims 19 to 21, wherein the Fc region comprises one or more amino acids that are different from amino acids of a native Fc region at any of amino acid positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 indicated by EU numbering in the amino acid sequence of one of the two polypeptides constituting the Fc region.

23. The IgG-type antibody of claim 22, which comprises a combination of one or more amino acids of said Fc region of:
Met at amino acid position 237;
Ile at amino acid position 248;
Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr at amino acid position 250;
Phe, Trp, or Tyr at amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
Asn, Asp, Glu, or Gln at amino acid position 256;
Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val at amino acid position 257;
His at amino acid position 258;
Ala at amino acid position 265;
Ala or Glu at amino acid position 286;
His at amino acid position 289;
Ala at amino acid position 297;
Ala at amino acid position 303;
Ala at amino acid position 305;

Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr at amino acid position 307;
Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr at amino acid position 308;
Ala, Asp, Glu, Pro, or Arg at amino acid position 309;
Ala, His, or Ile at amino acid position 311;
Ala or His at amino acid position 312;
Lys or Arg at amino acid position 314;
Ala, Asp, or His at amino acid position 315;
Ala at amino acid position 317;
Val at amino acid position 332;
Leu at amino acid position 334;
His at amino acid position 360;
Ala at amino acid position 376;
Ala at amino acid position 380;
Ala at amino acid position 382;
Ala at amino acid position 384;
Asp or His at amino acid position 385;
Pro at amino acid position 386;
Glu at amino acid position 387;
Ala or Ser at amino acid position 389;
Ala at amino acid position 424;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr at amino acid position 428;
Lys at amino acid position 433;
Ala, Phe, His, Ser, Trp, or Tyr at amino acid position 434; and
His, Ile, Leu, Phe, Thr, or Val at amino acid position 436; wherein the amino acids are indicated by EU numbering.

24. The IgG-type antibody of any one of claims 19 to 23, wherein the antigen-binding domain is an antibody variable region.

25. A polynucleotide encoding the IgG-type antibody of any one of claims 19 to 24.

26. A vector which is operably linked to the polynucleotide of claim 25.

27. A cell introduced with the vector of claim 26.

28. A method for producing the IgG-type antibody of any one of claims 19 to 24, which comprises the step of collecting the IgG-type antibody from a culture of the cell of claim 27.

29. A pharmaceutical composition which comprises as an active ingredient the IgG-type antibody of any one of claims 19 to 24 or an IgG-type antibody obtained by the production method of claim 28.

CLAIMS

1. A method of either (a) or (b) below, wherein the method comprises modifying the Fc region of an antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range into an Fc region that does not form a hetero complex comprising two molecules of FcRn and one molecule of activating Fcγ receptor in a neutral pH range:

(a) a method for improving pharmacokinetics of an antigen-binding molecule; and

(b) a method for reducing immunogenicity of an antigen-binding molecule.

2. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modifying the Fc region into an Fc region whose binding activity to an activating Fcγ receptor is lower than the binding activity of an Fc region of native human IgG to the activating Fcγ receptor.

3 The method of claim 1 or 2, wherein the activating Fcγ receptor is human FcγRIa, human FcγRIIa(R), human FcγRIIa(H), human FcγRIIIa(V), or human FcγRIIIa(F).

4. The method of any one of claims 1 to 3, which comprises substituting an amino acid of said Fc region at any one or more amino acids of positions 235, 237, 238, 239, 270, 298, 325, and 329 as indicated by EU numbering.

5. The method of claim 4, which comprises substituting an amino acid of said Fc region as indicated by EU numbering at any one or more of:

the amino acid of position 234 with any one of Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Lys, Met, Phe, Pro, Ser, Thr, and Trp;

the amino acid of position 235 with any one of Ala, Asn, Asp, Gln, Glu, Gly, His, Ile, Lys, Met, Pro, Ser, Thr, Val, and Arg;

the amino acid of position 236 with any one of Arg, Asn, Gln, His, Leu, Lys, Met, Phe, Pro, and Tyr;

the amino acid of position 237 with any one of Ala, Asn, Asp, Gln, Glu, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Val, Tyr, and Arg;

the amino acid of position 238 with any one of Ala, Asn, Gln, Glu, Gly, His, Ile, Lys, Thr, Trp, and Arg;

the amino acid of position 239 with any one of Gln, His, Lys, Phe, Pro, Trp, Tyr, and Arg;

the amino acid of position 265 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met,

Phe, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 266 with any one of Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Lys, Phe, Pro, Ser, Thr, Trp, and Tyr;
the amino acid of position 267 with any one of Arg, His, Lys, Phe, Pro, Trp, and Tyr;
the amino acid of position 269 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 270 with any one of Ala, Arg, Asn, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 271 with any one of Arg, His, Phe, Ser, Thr, Trp, and Tyr;
the amino acid of position 295 with any one of Arg, Asn, Asp, Gly, His, Phe, Ser, Trp, and Tyr;
the amino acid of position 296 with any one of Arg, Gly, Lys, and Pro;
the amino acid of position 297 with Ala;
the amino acid of position 298 with any one of Arg, Gly, Lys, Pro, Trp, and Tyr;
the amino acid of position 300 with any one of Arg, Lys, and Pro;
the amino acid of position 324 with Lys or Pro;
the amino acid of position 325 with any one of Ala, Arg, Gly, His, Ile, Lys, Phe, Pro, Thr, Trp, Tyr, and Val;
the amino acid of position 327 with any one of Arg, Gln, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val;
the amino acid of position 328 with any one of Arg, Asn, Gly, His, Lys, and Pro;
the amino acid of position 329 with any one of Asn, Asp, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, Val, and Arg;
the amino acid of position 330 with Pro or Ser;
the amino acid of position 331 with any one of Arg, Gly, and Lys; or
the amino acid of position 332 with any one of Arg, Lys, and Pro.

6. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modifying the Fc region into an Fc region that has a higher binding activity to an inhibitory Fcγ receptor than to an activating Fcγ receptor.

7. The method of claim 6, wherein the inhibitory Fcγ receptor is human FcγRIIb.

8. The method of claim 6 or 7, wherein the activating Fcγ receptor is human FcγRIa, human FcγRIIa(R), human FcγRIIa(H), human FcγRIIIa(V), or human FcγRIIIa(F).

9. The method of any one of claims 6 to 8, which comprises substituting the amino acid of

position 238 or 328 indicated by EU numbering.

10. The method of claim 9, which comprises substituting Asp for the amino acid of position 238 or Glu for the amino acid of position 328 indicated by EU numbering.

11. The method of claim 9 or 10, which comprises substituting any one or more amino acids of:
the amino acid of position 233 with Asp;
the amino acid of position 234 with Trp or Tyr;
the amino acid of position 237 with any one of Ala, Asp, Glu, Leu, Met, Phe, Trp, and Tyr;
the amino acid of position 239 with Asp;
the amino acid of position 267 with any one of Ala, Gln, and Val;
the amino acid of position 268 with any one of Asn, Asp, and Glu;
the amino acid of position 271 with Gly;
the amino acid of position 326 with any one of Ala, Asn, Asp, Gln, Glu, Leu, Met, Ser, and Thr;
the amino acid of position 330 with any one of Arg, Lys, and Met;
the amino acid of position 323 with any one of Ile, Leu, and Met; and
the amino acid of position 296 with Asp; wherein the amino acids are indicated by EU numbering.

12. The method of any one of claims 1 to 11, wherein the Fc region comprises one or more amino acids that are different from amino acids of the native Fc region at any of amino acid positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 of said Fc region as indicated by EU numbering.

13. The method of claim 12, wherein the amino acids of said Fc region indicated by EU numbering are a combination of one or more of:
Met at amino acid position 237;
Ile at amino acid position 248;
any one of Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, and Tyr at amino acid position 250;
any one of Phe, Trp, and Tyr at amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
any one of Asn, Asp, Glu, and Gln at amino acid position 256;
any one of Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, and Val at amino acid position 257;
His at amino acid position 258;

Ala at amino acid position 265;
Ala or Glu at amino acid position 286;
His at amino acid position 289;
Ala at amino acid position 297;
Gly at amino acid position 298;
Ala at amino acid position 303;
Ala at amino acid position 305;
any one of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, and Tyr at amino acid position 307;
any one of Ala, Phe, Ile, Leu, Met, Pro, Gln, and Thr at amino acid position 308;
any one of Ala, Asp, Glu, Pro, and Arg at amino acid position 309;
any one of Ala, His, and Ile at amino acid position 311;
Ala or His at amino acid position 312;
Lys or Arg at amino acid position 314;
any one of Ala, Asp, and His at amino acid position 315;
Ala at amino acid position 317;
Val at amino acid position 332;
Leu at amino acid position 334;
His at amino acid position 360;
Ala at amino acid position 376;
Ala at amino acid position 380;
Ala at amino acid position 382;
Ala at amino acid position 384;
Asp or His at amino acid position 385;
Pro at amino acid position 386;
Glu at amino acid position 387;
Ala or Ser at amino acid position 389;
Ala at amino acid position 424;
any one of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, and Tyr at amino acid position 428;
Lys at amino acid position 433;
any one of Ala, Phe, His, Ser, Trp, and Tyr at amino acid position 434; and
any one of His, Ile, Leu, Phe, Thr, and Val at amino acid position 436.

14. The method of any one of claims 1 to 13, wherein said antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on calcium ion

concentration.

15. The method of claim 14, wherein said antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity at a low calcium ion concentration is lower than the antigen-binding activity at a high calcium ion concentration.

16. The method of any one of claims 1 to 13, wherein said antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on pH.

17. The method of claim 16, wherein said antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity in an acidic pH range is lower than the antigen-binding activity in a neutral pH range.

18. The method of any one of claims 1 to 17, wherein the antigen-binding domain is an antibody variable region.

19. The method of any one of claims 1 to 18, wherein the antigen-binding molecule is an antibody.

20. The method of claim 1, wherein the modification into an Fc region that does not form said hetero complex comprises modification into an Fc region in which one of the two polypeptides constituting the Fc region has FcRn-binding activity in a neutral pH range and the other does not have FcRn-binding activity in a neutral pH range.

21. The method of claim 20, which comprises substituting an amino acid at any one or more of positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 as indicated by EU numbering in the amino acid sequence of one of the two polypeptides constituting said Fc region.

22. The method of claim 21, which comprises substituting an amino acid of said Fc region at any one or more of:
the amino acid of position 237 with Met;
the amino acid of position 248 with Ile;
the amino acid of position 250 with Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr;
the amino acid of position 252 with Phe, Trp, or Tyr;

the amino acid of position 254 with Thr;
the amino acid of position 255 with Glu;
the amino acid of position 256 with Asn, Asp, Glu, or Gln;
the amino acid of position 257 with Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val;
the amino acid of position 258 with His;
the amino acid of position 265 with Ala;
the amino acid of position 286 with Ala or Glu;
the amino acid of position 289 with His;
the amino acid of position 297 with Ala;
the amino acid of position 298 with Gly;
the amino acid of position 303 with Ala;
the amino acid of position 305 with Ala;
the amino acid of position 307 with Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr;
the amino acid of position 308 with Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr;
the amino acid of position 309 with Ala, Asp, Glu, Pro, or Arg;
the amino acid of position 311 with Ala, His, or Ile;
the amino acid of position 312 with Ala or His;
the amino acid of position 314 with Lys or Arg;
the amino acid of position 315 with Ala, Asp, or His;
the amino acid of position 317 with Ala;
the amino acid of position 332 with Val;
the amino acid of position 334 with Leu;
the amino acid of position 360 with His;
the amino acid of position 376 with Ala;
the amino acid of position 380 with Ala;
the amino acid of position 382 with Ala;
the amino acid of position 384 with Ala;
the amino acid of position 385 with Asp or His;
the amino acid of position 386 with Pro;
the amino acid of position 387 with Glu;
the amino acid of position 389 with Ala or Ser;
the amino acid of position 424 with Ala;
the amino acid of position 428 with Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr;
the amino acid of position 433 with Lys;

the amino acid of position 434 with Ala, Phe, His, Ser, Trp, or Tyr; and
the amino acid of position 436 with His, Ile, Leu, Phe, Thr, or Val; wherein the amino acids are indicated by EU numbering.

23. The method of any one of claims 20 to 22, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on calcium concentration.

24. The method of claim 23, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity at a low calcium concentration is lower than the antigen-binding activity at a high calcium concentration.

25. The method of any one of claims 20 to 22, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on pH.

26. The method of claim 25, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity in an acidic pH range is lower than the antigen-binding activity in a neutral pH range.

27. The method of any one of claims 20 to 26, wherein the antigen-binding domain is an antibody variable region.

28. The method of any one of claims 20 to 27, wherein the antigen-binding molecule is an antibody.

29. An antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range, wherein the Fc region comprises one or more amino acids selected from:
Ala at amino acid position 234;
Ala, Lys, or Arg at amino acid position 235;
Arg at amino acid position 236;
Arg at amino acid position 238;
Lys at amino acid position 239;
Phe at amino acid position 270;
Ala at amino acid position 297;
Gly at amino acid position 298;

Gly at amino acid position 325;
Arg at amino acid position 328; and
Lys or Arg at amino acid position 329; wherein the amino acids are indicated by EU numbering.

30. The antigen-binding molecule of claim 29, which comprises one or more amino acids selected from:
Lys or Arg at amino acid position 237;
Lys at amino acid position 238;
Arg at amino acid position 239; and
Lys or Arg at amino acid position 329; wherein the amino acids are indicated by EU numbering.

31. An antigen-binding molecule comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region in which one of the two polypeptides constituting the Fc region has FcRn-binding activity in a neutral pH range and the other does not have FcRn-binding activity in a neutral pH range.

32. The antigen-binding molecule of any one of claims 29 to 31, wherein the Fc region comprises one or more amino acids that are different from amino acids of a native Fc region at any of amino acid positions 237, 248, 250, 252, 254, 255, 256, 257, 258, 265, 286, 289, 297, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 indicated by EU numbering in the amino acid sequence of one of the two polypeptides constituting the Fc region.

33. The antigen-binding molecule of claim 32, which comprises a combination of one or more amino acids of said Fc region of:
Met at amino acid position 237;
Ile at amino acid position 248;
Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr at amino acid position 250;
Phe, Trp, or Tyr at amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
Asn, Asp, Glu, or Gln at amino acid position 256;
Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val at amino acid position 257;
His at amino acid position 258;
Ala at amino acid position 265;
Ala or Glu at amino acid position 286;

His at amino acid position 289;
Ala at amino acid position 297;
Ala at amino acid position 303;
Ala at amino acid position 305;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr at amino acid position 307;
Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr at amino acid position 308;
Ala, Asp, Glu, Pro, or Arg at amino acid position 309;
Ala, His, or Ile at amino acid position 311;
Ala or His at amino acid position 312;
Lys or Arg at amino acid position 314;
Ala, Asp, or His at amino acid position 315;
Ala at amino acid position 317;
Val at amino acid position 332;
Leu at amino acid position 334;
His at amino acid position 360;
Ala at amino acid position 376;
Ala at amino acid position 380;
Ala at amino acid position 382;
Ala at amino acid position 384;
Asp or His at amino acid position 385;
Pro at amino acid position 386;
Glu at amino acid position 387;
Ala or Ser at amino acid position 389;
Ala at amino acid position 424;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr at amino acid position 428;
Lys at amino acid position 433;
Ala, Phe, His, Ser, Trp, or Tyr at amino acid position 434; and
His, Ile, Leu, Phe, Thr, or Val at amino acid position 436; wherein the amino acids are indicated by EU numbering.

34. The antigen-binding molecule of any one of claims 29 to 33, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on calcium ion concentration.

35. The antigen-binding molecule of claim 34, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity at a low calcium concentration is lower than the antigen-binding activity at a high calcium concentration.

36. The antigen-binding molecule of any one of claims 29 to 33, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on pH.

37. The antigen-binding molecule of claim 36, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity in an acidic pH range is lower than the antigen-binding activity in a neutral pH range.

38. The antigen-binding molecule of any one of claims 29 to 37, wherein the antigen-binding domain is an antibody variable region.

39. The antigen-binding molecule of any one of claims 29 to 38, wherein the antigen-binding molecule is an antibody.

40. A polynucleotide encoding the antigen-binding molecule of any one of claims 29 to 39.

41. A vector which is operably linked to the polynucleotide of claim 40.

42. A cell introduced with the vector of claim 41.

43. A method for producing the antigen-binding molecule of any one of claims 29 to 39, which comprises the step of collecting the antigen-binding molecule from a culture of the cell of claim 42.

44. A pharmaceutical composition which comprises as an active ingredient the antigen-binding molecule of any one of claims 29 to 39 or an antigen-binding molecule obtained by the production method of claim 43.