CLAIMS

1. An antibody, which has a human FcRn-binding activity at an acidic and neutral pH, and a lower antigen-binding activity at the acidic pH than at the neutral pH, wherein the acidic pH is 5.8 and the neutral pH is 7.4, wherein the human FcRn-binding activity at the neutral pH is stronger than that of a human IgG1 comprising an unmodified Fc region, wherein the ratio of antigen-binding activity at the acidic pH and neutral pH is at least 2 in the value of KD (at the acidic pH)/KD (at the neutral pH), wherein the antibody comprises an amino acid mutation of the antigen-binding domain, which comprises a substitution of histidine for at least one amino acid of the antigen-binding domain or the insertion of at least one histidine, wherein the antibody comprises as the human FcRn-binding domain an Fc domain resulting from substituting a different amino acid for at least one amino acid in the Fc domain of a human IgG1, IgG2, IgG3, or IgG4, wherein the human FcRn-binding domain is a human FcRn-binding domain comprising an amino acid sequence with a substitution of a different amino acid for at least one amino acid selected from those of positions 237, 238, 239, 248, 250, 252, 254, 255, 256, 257, 258, 265, 270, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 325, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 (EU numbering) in the Fc domain of a human IgG1, IgG2, IgG3, or IgG4, wherein the antibody has the augmented ability of an antibody to eliminate an antigen from plasma.

2. The antibody of claim 1, which comprises a human FcRn-binding domain comprising amino acid substitution in the Fc domain of the human IgG1, IgG2, IgG3, or IgG4 which comprises at least one amino acid substitution selected from:
an amino acid substitution of Met for Gly at position 237;
an amino acid substitution of Ala for Pro at position 238;
an amino acid substitution of Lys for Ser at position 239;
an amino acid substitution of Ile for Lys at position 248;
an amino acid substitution of Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr for Thr at position 250;
an amino acid substitution of Phe, Trp, or Tyr for Met at position 252;
an amino acid substitution of Thr for Ser at position 254;
an amino acid substitution of Glu for Arg at position 255;
an amino acid substitution of Asp, Glu, or Gln for Thr at position 256;
an amino acid substitution of Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val for Pro at position 257;
an amino acid substitution of His for Glu at position 258;

an amino acid substitution of Ala for Asp at position 265;
an amino acid substitution of Phe for Asp at position 270;
an amino acid substitution of Ala, or Glu for Asn at position 286;
an amino acid substitution of His for Thr at position 289;
an amino acid substitution of Ala for Asn at position 297;
an amino acid substitution of Gly for Ser at position 298;
an amino acid substitution of Ala for Val at position 303;
an amino acid substitution of Ala for Val at position 305;
an amino acid substitution of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr for Thr at position 307;
an amino acid substitution of Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr for Val at position 308;
an amino acid substitution of Ala, Asp, Glu, Pro, or Arg for Leu or Val at position 309;
an amino acid substitution of Ala, His, or Ile for Gln at position 311;
an amino acid substitution of Ala, or His for Asp at position 312;
an amino acid substitution of Lys, or Arg for Leu at position 314;
an amino acid substitution of Ala, or His for Asn at position 315;
an amino acid substitution of Ala for Lys at position 317;
an amino acid substitution of Gly for Asn at position 325;
an amino acid substitution of Val for Ile at position 332;
an amino acid substitution of Leu for Lys at position 334;
an amino acid substitution of His for Lys at position 360;
an amino acid substitution of Ala for Asp at position 376;
an amino acid substitution of Ala for Glu at position 380;
an amino acid substitution of Ala for Glu at position 382;
an amino acid substitution of Ala for Asn or Ser at position 384;
an amino acid substitution of Asp, or His for Gly at position 385;
an amino acid substitution of Pro for Gln at position 386;
an amino acid substitution of Glu for Pro at position 387;
an amino acid substitution of Ala, or Ser for Asn at position 389;
an amino acid substitution of Ala for Ser at position 424;
an amino acid substitution of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr for Met at position 428;
an amino acid substitution of Lys for His at position 433;
an amino acid substitution of Ala, Phe, His, Ser, Trp, or Tyr for Asn at position 434;
and an amino acid substitution of His or Phe for Tyr at position 436 in EU numbering.

3. The antibody of claim 1, whose human FcRn-binding domain comprises at least one

amino acid selected from:
Met at amino acid position 237;
Ala at amino acid position 238;
Lys at amino acid position 239;
Ile at amino acid position 248;
Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr at amino acid at position 250;
Phe, Trp, or Tyr as an amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
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;
Phe at amino acid position 270;
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;
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 or His at amino acid position 315;
Ala at amino acid position 317;
Gly at amino acid position 325;
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 or Phe as an amino acid at position 436 (EU numbering) in the Fc domain of a parent IgG.

4. The antibody of any one of claims 1 to 3, which has an antagonistic activity.

5. The antibody of any one of claims 1 to 4, which binds to a membrane antigen or soluble antigen.

6. The antibody of any of claims 1 to 5, wherein the antibody is selected from a chimeric antibody, a humanized antibody or a human antibody.

7. A pharmaceutical composition comprising an antibody according to any one of claims 1 to 6.

8. A method for producing the antibody of any one of claim 1 to 6, which comprises the steps of:
   (a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;
   (b) altering at least one amino acid in the antigen-binding domain of an antibody and selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;
   (c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and
   (d) producing an antibody using the gene prepared in (c).

9. A method for producing the antibody of any one of claim 1 to 6, which comprises the steps of:
   (a) selecting an antibody that has stronger human FcRn-binding activity in the

neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;

(b) selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;

(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and

(d) producing an antibody using the gene prepared in (c).

10. A method for screening an antibody of any one of claim 1 to 6, which comprises the steps of:

(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;

(b) altering at least one amino acid in the antigen-binding domain of an antibody and selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;

(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and

(d) producing an antibody using the gene prepared in (c).

11. A method for screening an antibody of any one of claim 1 to 6, which comprises the steps of:

(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;

(b) selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;

(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and

(d) producing an antibody using the gene prepared in (c).

12. A method for augmenting the ability of an antibody to eliminate an antigen from plasma by increasing its human FcRn-binding activity in the neutral pH range and reducing its antigen-binding activity in the acidic pH range to less than that in the neutral pH range, wherein the antibody comprises an antigen-binding domain and a human FcRn-binding

domain, and has a human FcRn-binding activity in the acidic pH range.

CLAIMS

[Claim 1] An antibody, which has a human FcRn-binding activity in the acidic and neutral pH ranges, and a lower antigen-binding activity in the acidic pH range than in the neutral pH range, wherein the human FcRn-binding activity in the neutral pH range is stronger than that of an unmodified human IgG , wherein the ratio of antigen-binding activity in the acidic pH range and neutral pH range is at least 2 in the value of KD (in the acidic pH range)/KD (in the neutral pH range), wherein the antibody comprises an amino acid mutation of the antigen-binding domain, which comprises a substitution of histidine for at least one amino acid of the antigen-binding domain or the insertion of at least one histidine, wherein the antibody comprises as the human FcRn-binding domain an Fc domain resulting from substituting a different amino acid for at least one amino acid in the Fc domain of parent human IgG, wherein the human FcRn-binding domain is a human FcRn-binding domain comprising an amino acid sequence with a substitution of a different amino acid for at least one amino acid selected from those of positions 237, 238, 239, 248, 250, 252, 254, 255, 256, 257, 258, 265, 270, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 325, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, and 436 (EU numbering) in the Fc domain of parent IgG, wherein the antibody has the augmented ability of an antibody to eliminate an antigen from plasma.

[Claim2] The antibody of claim 1 , wherein the antigen-binding domain is obtained from antigen-binding domain library.

[Claim 3] The antibody of any one of claims 1 to 2, which comprises a human FcRn-binding domain comprising amino acid substitution in the Fc domain of parent IgG which comprises at least one amino acid substitution selected from:
an amino acid substitution of Met for Gly at position 237;
an amino acid substitution of Ala for Pro at position 238;
an amino acid substitution of Lys for Ser at position 239;
an amino acid substitution of Ile for Lys at position 248;
an amino acid substitution of Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr for Thr at position 250;
an amino acid substitution of Phe, Trp, or Tyr for Met at position 252;
an amino acid substitution of Thr for Ser at position 254;
an amino acid substitution of Glu for Arg at position 255;
an amino acid substitution of Asp, Glu, or Gln for Thr at position 256;

an amino acid substitution of Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val for Pro at position 257;
an amino acid substitution of His for Glu at position 258;
an amino acid substitution of Ala for Asp at position 265;
an amino acid substitution of Phe for Asp at position 270;
an amino acid substitution of Ala, or Glu for Asn at position 286;
an amino acid substitution of His for Thr at position 289;
an amino acid substitution of Ala for Asn at position 297;
an amino acid substitution of Gly for Ser at position 298;
an amino acid substitution of Ala for Val at position 303;
an amino acid substitution of Ala for Val at position 305;
an amino acid substitution of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr for Thr at position 307;
an amino acid substitution of Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr for Val at position 308;
an amino acid substitution of Ala, Asp, Glu, Pro, or Arg for Leu or Val at position 309;
an amino acid substitution of Ala, His, or Ile for Gln at position 311;
an amino acid substitution of Ala, or His for Asp at position 312;
an amino acid substitution of Lys, or Arg for Leu at position 314;
an amino acid substitution of Ala, or His for Asn at position 315;
an amino acid substitution of Ala for Lys at position 317;
an amino acid substitution of Gly for Asn at position 325;
an amino acid substitution of Val for Ile at position 332;
an amino acid substitution of Leu for Lys at position 334;
an amino acid substitution of His for Lys at position 360;
an amino acid substitution of Ala for Asp at position 376;
an amino acid substitution of Ala for Glu at position 380;
an amino acid substitution of Ala for Glu at position 382;
an amino acid substitution of Ala for Asn or Ser at position 384;
an amino acid substitution of Asp, or His for Gly at position 385;
an amino acid substitution of Pro for Gln at position 386;
an amino acid substitution of Glu for Pro at position 387;
an amino acid substitution of Ala, or Ser for Asn at position 389;
an amino acid substitution of Ala for Ser at position 424;
an amino acid substitution of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr for Met at position 428;
an amino acid substitution of Lys for His at position 433;
an amino acid substitution of Ala, Phe, His, Ser, Trp, or Tyr for Asn at position 434;

and an amino acid substitution of His or Phe for Tyr at position 436in EU numbering.

[Claim 4] The antibody of any one of claims 1 to 2, whose human FcRn-binding domain comprises at least one amino acid selected from:
Met at amino acid position 237;
Ala at amino acid position 238;
Lys at amino acid position 239;
Ile at amino acid position 248;
Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr at amino acid at position 250;
Phe, Trp, or Tyr as an amino acid position 252;
Thr at amino acid position 254;
Glu at amino acid position 255;
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;
Phe at amino acid position 270;
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;
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 or His at amino acid position 315;
Ala at amino acid position 317;
Gly at amino acid position 325;
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 or Phe as an amino acid at position 436 (EU numbering) in the Fc domain of a parent IgG.

[Claim 5] The antibody of any one of claims 1 to 4, which has an antagonistic activity.

[Claim 6] The antibody of any one of claims 1 to 5, which binds to a membrane antigen or soluble antigen.

[Claim 7] The antibody of any one of claims 1 to 6, wherein the antibody is selected from a chimeric antibody, a humanized antibody or a human antibody.

[Claim 8] A pharmaceutical composition comprising any one of the antibody of claims 1 to 7.

[Claim 9] A method for producing the antibody of any one of claim 1 to 7, which comprises the steps of:
(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;
(b) altering at least one amino acid in the antigen-binding domain of an antibody and selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;
(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and
(d) producing an antibody using the gene prepared in (c).

[Claim 10] A method for producing the antibody of any one of claim 1 to 7, which comprises the steps of:

(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;
(b) selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;
(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and
(d) producing an antibody using the gene prepared in (c).

[Claim 11] A method for screening an antibody of any one of claim 1 to 7, which comprises the steps of:
(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;
(b) altering at least one amino acid in the antigen-binding domain of an antibody and selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;
(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and
(d) producing an antibody using the gene prepared in (c).

[Claim 12] A method for screening an antibody of any one of claim 1 to 7, which comprises the steps of:
(a) selecting an antibody that has stronger human FcRn-binding activity in the neutral pH range than before alteration of at least one amino acid in the human FcRn-binding domain of an antibody having a human FcRn-binding activity in the acidic pH range;
(b) selecting an antibody that has stronger antigen-binding activity in the neutral pH range than in the acidic pH range;
(c) obtaining a gene encoding an antibody in which a human FcRn-binding domain and an antigen-binding domain prepared in (a) and (b) are linked; and
(d) producing an antibody using the gene prepared in (c).

[Claim 13] A method for augmenting the ability of an antibody to eliminate an antigen from plasma by increasing its human FcRn-binding activity in the

neutral pH range and reducing its antigen-binding activity in the acidic pH range to less than that in the neutral pH range, wherein the antibody comprises an antigen-binding domain and a human FcRn-binding domain, and has a human FcRn-binding activity in the acidic pH range.