CLAIMS

1. An antibody comprising an antigen-binding domain and a human FcRn-binding domain, whose antigen-binding activity is different between two different calcium concentration conditions and is lower under a low calcium concentration condition than under a high calcium concentration condition, wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM and the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM, and wherein a light chain or heavy chain of the antigen-binding domain comprises a calcium-binding motif derived from a human antibody, wherein in the calcium-binding motif in the light chain any four or more of the amino acids at positions 30, 31, 32, 50, and 92 according to Kabat's numbering have a metal-chelating activity.

2. The antibody of claim 1, wherein the calcium-binding motif is comprised at positions 30, 31, and/or 32 according to Kabat’s numbering in the light chain.

3. The antibody of claim 1 or 2, wherein the calcium-binding motif is comprised at position 50 according to Kabat’s numbering in the light chain.

4. The antibody of any one of claims 1 to 3, wherein the calcium-binding motif is comprised at position 92 according to Kabat’s numbering in the light chain.

5. The antibody of any one of claims 1 to 4, wherein the antigen bound by the antibody is either IgA or glypican 3.

6. The antibody of claim 1, wherein the calcium-binding motif is comprised in the heavy chain CDR1, CDR2, and/or CDR3 of the antigen-binding domain.

7. The antibody of claim 6, wherein the calcium-binding motif is comprised at positions 95, 96, 100a, and/or 101 according to Kabat’s numbering in the heavy chain CDR3.

8. The antibody of claim 6 or 7, wherein the antigen bound by the antibody is either IL-6R or IL-6.

9. The antibody of any one of claims 1 to 8, which comprises an FcRn-binding domain that has FcRn-binding activity in the neutral pH range.

10. The antibody of claim 9, wherein the FcRn-binding domain is an Fc region.

11. The antibody of claim 9 or 10, wherein one or more amino acids at positions 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 (EU numbering) in the amino acid sequence of the Fc region are different from those of the natural Fc region.

12. The antibody of claim 11, which comprises any one or combination 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;
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; or
His, Ile, Leu, or Val at amino acid position 436;
according to EU numbering in the Fc region.

13. A method of producing an antibody having at least one function selected from:
(i) function of promoting uptake of an antigen into cells,
(ii) function of binding to an antigen two or more times,
(iii) function of promoting the reduction of plasma antigen concentration, and
(iv) function of excellence in plasma retention,
wherein the method comprises the steps of (a) to (e) below:
(a) determining the antigen-binding activity of an antibody under a low calcium concentration condition;
(b) determining the antigen-binding activity of the antibody under a high calcium concentration condition;
(c) selecting an antibody that has a lower antigen-binding activity under the low calcium concentration condition than under the high calcium concentration condition;
(d) obtaining a gene encoding the antibody selected in step (c); and
(e) producing the antibody using the gene obtained in step (d),
wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM and the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

14. A method of producing an antibody having at least one function selected from:
(i) function of promoting uptake of an antigen into cells,
(ii) function of binding to an antigen two or more times,
(iii) function of promoting the reduction of plasma antigen concentration, and
(iv) function of excellence in plasma retention,
wherein the method comprises the steps of (a) to (e) below:
(a) contacting an antigen with an antibody or a library of antibodies under a high calcium concentration condition;
(b) placing an antibody that binds to the antigen in step (a) under a low calcium concentration condition;
(c) obtaining an antibody that dissociates in step (b);
(d) obtaining a gene encoding the antibody obtained in step (c); and
(e) producing the antibody using the gene obtained in step (d),
wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM and the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

15. A method of producing an antibody having at least one function selected from:
(i) function of promoting uptake of an antigen into cells,
(ii) function of binding to an antigen two or more times,
(iii) function of promoting the reduction of plasma antigen concentration, and
(iv) function of excellence in plasma retention,
wherein the method comprises the steps of (a) to (f) below:
(a) contacting an antigen with an antibody or a library of antibodies under a low calcium concentration condition;
(b) selecting an antibody that does not bind to the antigen in step (a);
(c) allowing the antibody selected in step (b) to bind to the antigen under a high calcium concentration condition;
(d) obtaining an antibody that bound to the antigen in step (c);
(e) obtaining a gene encoding the antibody obtained in step (d); and
(f) producing the antibody using the gene obtained in step (e),
wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM and the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

16. The production method of any one of claims 13 to 15, which additionally comprises

the step of conferring or increasing the human FcRn-binding activity under a neutral pH condition by modifying an amino acid in the antibody.

17. The production method of any one of claims 13 to 15, which additionally comprises the step of reducing the antigen-binding activity under an acidic pH condition to be lower than that under a neutral pH condition by modifying an amino acid in the antibody.

18. The production method of any one of claims 13 to 15, wherein the low calcium concentration is an intraendosomal concentration of ionized calcium.

19. The production method of any one of claims 13 to 15, wherein the high calcium concentration is a plasma concentration of ionized calcium.

20. The production method of claim 17, wherein the amino acid modification in the antibody is modification by substituting at least one amino acid with histidine, or inserting at least one histidine into the antibody.

21. The production method of any one of claims 13 to 20, wherein the antigen bound by the antibody is an antigen selected from the group consisting of IL-6R, IL-6, IgA, human glypican 3, and IgE.

22. A pharmaceutical composition comprising:
the antibody of any one of claims 1 to 12 or an antibody produced by the production method of any one of claims 13 to 21, and
a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22 for use in promoting internalization of the antigen into cells.

24. The pharmaceutical composition of claim 22 for use in promoting reduction of the antigen concentration in plasma.