CLAIMS

1. An antigen-binding molecule comprising an antigen-binding domain and a human FcRn-binding domain, whose antigen-binding activity is different under two different calcium concentration conditions and is lower under a low calcium concentration condition than under a high calcium concentration condition, and which has binding activity to human FcRn under a neutral pH condition.

2. The antigen-binding molecule of claim 1, wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM.

3. The antigen-binding molecule of claim 1, wherein the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

4. The antigen-binding molecule of claim 1 or 2, wherein the low calcium concentration is an intraendosomal concentration of ionized calcium.

5. The antigen-binding molecule of claim 1 or 3, wherein the high calcium concentration is a plasma concentration of ionized calcium.

6. The antigen-binding molecule of any one of claims 1 to 5, wherein the FcRn-binding domain is an Fc region.

7. The antigen-binding molecule of any one of claims 1 to 6, further wherein the antigen-binding activity is lower under an acidic pH condition than under a neutral pH condition.

8. The antigen-binding molecule of claim 7, wherein at least one amino acid is substituted with histidine, or at least one histidine is inserted into the antigen-binding molecule.

9. The antigen-binding molecule of any one of claims 1 to 8, which binds to a membrane antigen or soluble antigen.

10. The antigen-binding molecule of any one of claims 1 to 9, wherein the antigen is an antigen selected from the group consisting of IL-6R, IL-6, IgA, human glypican 3, and IgE.

11. An antigen-binding molecule 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, and wherein a light chain or heavy chain of the antigen-binding domain comprises a calcium-binding motif derived from a human antibody.

12. The antigen-binding molecule of claim 11, wherein the calcium-binding motif is comprised in the light chain CDR1, CDR2, and/or CDR3 of the antigen-binding domain.

13. The antigen-binding molecule of claim 12, wherein the calcium-binding motif is comprised at positions 30, 31, and/or 32 according to Kabat's numbering in the light chain CDR1.

14. The antigen-binding molecule of claim 12 or 13, wherein the calcium-binding motif is comprised at position 50 according to Kabat's numbering in the light chain CDR2.

15. The antigen-binding molecule of any one of claims 12 to 14, wherein the calcium-binding motif is comprised at position 92 according to Kabat's numbering in the light chain CDR3.

16. The antigen-binding molecule of any one of claims 12 to 15, wherein the antigen of the antigen-binding molecule is either IgA or glypican 3.

17. The antigen-binding molecule of claim 11, wherein the calcium-binding motif is comprised in the heavy chain CDR1, CDR2, and/or CDR3 of the antigen-binding domain.

18. The antigen-binding molecule of claim 16, 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.

19. The antigen-binding molecule of claim 17 or 18, wherein the antigen of the antigen-binding molecule is either IL-6R or IL-6.

20. The antigen-binding molecule of any one of claims 11 to 19, which comprises an FcRn-binding domain that has FcRn-binding activity in the neutral pH range.

21. The antigen-binding molecule of claim 20, wherein the FcRn-binding domain is an Fc region.

22. The antigen-binding molecule of any one of claims 1 to 10, 20, or 21, 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.

23. The antigen-binding molecule of claim 22, 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.

24. The antigen-binding molecule of any one of claims 1 to 23, wherein the antigen-binding molecule is an antibody.

25. A method of producing an antigen-binding molecule 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 antigen-binding molecule under a low calcium concentration condition;
(b) determining the antigen-binding activity of the antigen-binding molecule under a high calcium concentration condition;
(c) selecting an antigen-binding molecule 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 antigen-binding molecule selected in step (c); and
(e) producing the antigen-binding molecule using the gene obtained in step (d).

26. A method of producing an antigen-binding molecule 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 antigen-binding molecule or a library of antigen-binding molecules under a high calcium concentration condition;
(b) placing an antigen-binding molecule that binds to the antigen in step (a) under a low calcium concentration condition;
(c) obtaining an antigen-binding molecule that dissociates in step (b);
(d) obtaining a gene encoding the antigen-binding molecule obtained in step (c); and
(e) producing the antigen-binding molecule using the gene obtained in step (d).

27. A method of producing an antigen-binding molecule 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 antigen-binding molecule or a library of antigen-binding molecules under a low calcium concentration condition;
(b) selecting an antigen-binding molecule that does not bind to the antigen in step (a);
(c) allowing the antigen-binding molecule selected in step (b) to bind to the antigen under a high calcium concentration condition;
(d) obtaining an antigen-binding molecule that bound to the antigen in step (c);
(e) obtaining a gene encoding the antigen-binding molecule obtained in step (d); and
(f) producing the antigen-binding molecule using the gene obtained in step (e).

28. The production method of any one of claims 25 to 27, 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 antigen-binding molecule.

29. The production method of any one of claims 25 to 27, 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 antigen-binding molecule.

30. The production method of any one of claims 25 to 27, wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM.

31. The production method of any one of claims 25 to 27, wherein the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

32. The production method of any one of claims 25 to 27, wherein the low calcium concentration is an intraendosomal concentration of ionized calcium.

33. The production method of any one of claims 25 to 27, wherein the high calcium concentration is a plasma concentration of ionized calcium.

34. The production method of claim 29, wherein the amino acid modification in the antigen-binding molecule is modification by substituting at least one amino acid with histidine, or inserting at least one histidine into the antigen-binding molecule.

35. The production method of any one of claims 25 to 34, wherein an antigen bound by the antigen-binding molecule is an antigen selected from the group consisting of IL-6R, IL-6, IgA, human glypican 3, and IgE.

36. The production method of any one of claims 25 to 35, wherein the antigen-binding molecule is an antibody.

37. A pharmaceutical composition comprising:
the antigen-binding molecule of any one of claims 1 to 24 or an antigen-binding molecule produced by the production method of any one of claims 25 to 36, and
a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37 for use in promoting internalization of the antigen into cells.

39. The pharmaceutical composition of claim 37 for use in promoting reduction of the antigen concentration in plasma.

40. A pharmaceutical composition for use in promoting antigen uptake into cells or reduction of plasma antigen concentration, which comprises an antigen-binding molecule comprising an

antigen-binding domain and a human FcRn-binding domain, whose antigen-binding activity is different between two different calcium concentrations and is lower under a low calcium concentration condition than under a high calcium concentration condition.

41. The pharmaceutical composition of claim 40, wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM.

42. The pharmaceutical composition of claim 40, wherein the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

43. The pharmaceutical composition of claim 40 or 41, wherein the low calcium concentration is an intraendosomal concentration of ionized calcium.

44. The pharmaceutical composition of claim 40 or 42, wherein the high calcium concentration is a plasma concentration of ionized calcium.

45. The pharmaceutical composition of any one of claims 40 to 44, wherein the FcRn-binding domain comprised in the antigen-binding molecule is an Fc region.

46. The pharmaceutical composition of any one of claims 40 to 45, wherein the antigen-binding activity of the antigen-binding molecule is lower under an acidic pH condition than under a neutral pH condition.

47. The pharmaceutical composition of claim 46, wherein the amino acid modification in the antigen-binding molecule is modification by substituting at least one amino acid with histidine, or inserting at least one histidine into the antigen-binding molecule .

48. The pharmaceutical composition of any one of claims 40 to 47, wherein the antigen to which the antigen-binding molecule binds is an antigen selected from the group consisting of IL-6R, IL-6, IgA, human glypican 3, and IgE.

49. A method of screening for an antigen-binding molecule that has 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 (c) below:

(a) determining the antigen-binding activity of an antigen-binding molecule under a low calcium concentration condition;

(b) determining the antigen-binding activity of an antigen-binding molecule under a high calcium concentration condition; and

(c) selecting an antigen-binding molecule whose antigen-binding activity is lower under the low calcium concentration condition than under the high calcium concentration condition.

50. A method of screening for an antigen-binding molecule that comprises 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 (c) below:

(a) contacting an antigen with an antigen-binding molecule or a library of antigen-binding molecules under a high calcium concentration condition;

(b) placing an antigen-binding molecule that binds to the antigen in step (a) under a low calcium concentration condition; and

(c) obtaining an antigen-binding molecule that dissociates in step (b).

51. A method of screening for an antigen-binding molecule that comprises 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 (d) below:

(a) contacting an antigen with an antigen-binding molecule or a library of antigen-binding molecules under a low calcium concentration condition;

(b) selecting an antigen-binding molecule that does not bind to the antigen in step (a);

(c) allowing the antigen-binding molecule selected in step (b) to bind to the antigen under a high calcium concentration condition; and

(d) obtaining an antigen-binding molecule bound to the antigen in step (c).

52. The screening method of any one of claims 49 to 51, wherein the low calcium concentration is an ionized calcium concentration of 0.1 to 30 μM.

53. The screening method of any one of claims 49 to 51, wherein the high calcium concentration is an ionized calcium concentration of 100 μM to 10 mM.

54. The screening method of any one of claims 49 to 52, wherein the low calcium concentration is an intraendosomal concentration of ionized calcium.

55. The screening method of any one of claims 49 to 51, or 53, wherein the high calcium concentration is a plasma concentration of ionized calcium.

56. The screening method of any one of claims 49 to 55, wherein the antigen to which the antigen-binding molecule binds is an antigen selected from the group consisting of IL-6R, IL-6, IgA, human glypican 3, and IgE.

57. The screening method of any one of claims 49 to 56, wherein the antigen-binding molecule is an antibody.