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Summary ~~of the Invention~~

[Problems to be Solved by the ~~Invention~~disclosure]

The present ~~invention~~ disclosure was achieved in view of the above circumstances. An objective of the present ~~invention~~ disclosure is to provide pharmaceutical compositions comprising as an active ingredient an antigen-binding molecule that induces an immune response in subjects affected with cancer or infected with foreign biological species when administered to these subjects, or therapeutic methods that use the pharmaceutical compositions. Another objective is to provide pharmaceutical compositions comprising as an active ingredient an antigen-binding molecule that induces the above-mentioned immune response and also has cytotoxicity (cytotoxic activity) or antiproliferative action (cell proliferation inhibitory activity) against cancer cells or infecting foreign biological species, or therapeutic methods that use the pharmaceutical compositions.

[Means for Solving the Problems]

The present inventors have discovered that in living organisms that have received an antigen-binding molecule containing an antigen-binding domain whose binding activity against an antigen changes depending on ion concentration conditions and containing an FcRn-binding domain having FcRn-binding activity under a neutral pH range, immune responses to the antigen are induced. Furthermore, the present inventors have discovered that in living organisms that have received an antigen-binding molecule containing an antigen-binding domain whose antigen-binding activity changes depending on ion concentration conditions and an FcRn-binding domain having FcRn-binding activity under a neutral pH range, immune responses to the antigen are induced, and the antigen-binding molecule can also have cytotoxicity or antiproliferative effect against cancer cells, foreign biological species, or the like that express the antigen to which the antigen-binding molecule binds. Based on these findings, the present inventors have elucidated that the antigen-binding molecules of the present ~~invention~~disclosure are useful

as pharmaceutical compositions for inducing an immune response in a subject infected with a foreign biological species or affected with cancer when administered to the subject. The present inventors have also elucidated that the antigen-binding molecules of the present ~~invention~~disclosure are useful as pharmaceutical compositions that, when administered to a subject infected with a foreign biological species or affected with cancer, induce an immune response in the subject and also have cytotoxicity or antiproliferative effect against the cancer cells and foreign biological species. Methods for producing these pharmaceutical compositions have also been discovered.

In one apect, there is provided a pharmaceutical composition that induces an immune response to an antigen, which comprises as an active ingredient an antibody, wherein the antibody comprises an antigen-binding domain whose binding activity to the antigen changes depending on an ion concentration condition and comprises an FcRn-binding domain having binding activity to FcRn in a neutral pH range, wherein the antigen-binding domain comprises an antibody variable region in which at least one or more amino acids selected from the group consisting of amino acids at positions 95, 96, 100a and 101 according to Kabat numbering in the antibody heavy chain variable region and amino acids at positions 30, 31, 32, 50 and 92 according to Kabat numbering in the antibody light chain variable region are amino acids having a metal-chelating activity or antibody variable region in which at least one or more amino acids are His, and wherein the FcRn-binding domain comprises an antibody Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids.at corresponding positions in a naturally-occurring Fc region.

In one aspect, there is provided the use of the antibody as defined herein in the manufacture of a medicament for inducing an immune response in a living organism.

In one aspect, there is provided a method for producing an antibody that induces an immune response, which comprises imparting FcRn-binding activity in a neutral pH range to an FcRn-binding domain that is contained in an antibody containing an antigen-binding domain whose antigen-binding activity changes depending on an ion concentration condition, wherein the antigen-binding domain comprises an antibody variable region in which at least one or more amino acids selected from the group consisting of amino acids at positions 95, 96, 100a and 101 according to Kabat numbering in the antibody heavy chain variable region and amino acids at positions 30, 31, 32, 50 and 92 according to Kabat numbering in the antibody light chain variable region are amino acids having a metal-chelating activity or antibody variable region in which at least one or more amino acids are His, and wherein the FcRn-binding domain comprises an antibody Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and

434 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region.

More specifically, the present ~~invention~~disclosure provides [1] to [47] below:

[1] a pharmaceutical composition that induces an immune response to an antigen, which comprises as an active ingredient an antigen-binding molecule, wherein the antigen-binding molecule comprises an antigen-binding domain whose binding activity to the antigen changes depending on an ion concentration condition and comprises an FcRn-binding domain having binding activity to FcRn in a neutral pH range;

[2] the pharmaceutical composition of [1], wherein the ion concentration is a calcium ion concentration;

[3] the pharmaceutical composition of [2], wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher under a high calcium ion concentration condition than under a low calcium ion concentration condition;

[4] the pharmaceutical composition of [1], wherein the ion concentration condition is a pH condition;

[5] the pharmaceutical composition of [4], wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher in a neutral pH range than under an acidic pH range;

[6] the pharmaceutical composition of any one of [1] to [5], wherein the antigen-binding molecule has neutralizing activity against the antigen;

[7] the pharmaceutical composition of any one of [1] to [6], wherein the antigen-binding molecule has cytotoxic activity against a cell expressing the antigen;

[8] the pharmaceutical composition of any one of [1] to [7], wherein the FcRn-binding domain comprises an antibody Fc region;

[9] the pharmaceutical composition of [8], wherein the Fc region is an Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region;

[10] the pharmaceutical composition of [8] or [9], wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:

Glu at amino acid position 385;
Thr at amino acid position 392;
Leu at amino acid position 396;
Lys at amino acid position 421;
Asn at amino acid position 427;
either Phe or Leu at amino acid position 428;
Met at amino acid position 429;
Trp at amino acid position 434;
Ile at amino acid position 436; and
any one of Gly, His, Ile, Leu, and Tyr at amino acid position 440;
according to EU numbering in the Fc region;
[46] the method of any one of [43] to [45], wherein the naturally-occurring Fc region is an Fc region of any one of human IgG1, human IgG2, human IgG3, and human IgG4 in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain;
[47] the method of any one of [43] to [46], wherein the Fc region is modified so that the percentage of the Fc region to which a fucose-deficient sugar chain is attached, or bisecting *N*-acetylglucosamine is added, at position 297 according to EU numbering in the Fc region, will become higher.

[Effects of the ~~Invention~~Disclosure]

The present ~~invention~~ disclosure provides pharmaceutical compositions comprising an antigen-binding molecule that, when administered to a living organism, can not only exhibit pharmacological actions on a target antigen but also induce an immune response to the target antigen, which was not possible with conventional antibodies, and provides methods for manufacturing them. This enables effective treatment of cancer and infectious diseases by induction of immune response to a target antigen while having binding activity to the target antigen and having cytotoxicity and antiproliferative activity against target cells, which was not possible with conventional vaccines.

Brief Description of the Drawings

Fig. 1 shows changes in the concentration of soluble human IL-6 receptor in mice plasma for the anti-mouse CD4 antibody administration group and the non-administration group in a soluble human IL-6 receptor steady-state model. The horizontal axis shows the number of days from anti-mouse CD4 antibody administration, and the vertical axis shows the plasma concentration of soluble human IL-6 receptor.

CLAIMS

1. A pharmaceutical composition that induces an immune response to an antigen, which comprises as an active ingredient an antibody~~antigen-binding molecule~~, wherein the antibody~~antigen-binding molecule~~ comprises an antigen-binding domain whose binding activity to the antigen changes depending on an ion concentration condition and comprises an FcRn-binding domain having binding activity to FcRn in a neutral pH range, wherein the antigen-binding domain comprises an antibody variable region in which at least one or more amino acids selected from the group consisting of amino acids at positions 95, 96, 100a and 101 according to Kabat numbering in the antibody heavy chain variable region and amino acids at positions 30, 31, 32, 50 and 92 according to Kabat numbering in the antibody light chain variable region are amino acids having a metal-chelating activity or antibody variable region in which at least one or more amino acids are His, and wherein the FcRn-binding domain comprises an antibody Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids.at corresponding positions in a naturally-occurring Fc region.

2. The pharmaceutical composition of claim 1, wherein the ion concentration is a calcium ion concentration.

3. The pharmaceutical composition of claim 2, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher under a high calcium ion concentration condition than under a low calcium ion concentration condition.

4. The pharmaceutical composition of claim 1, wherein the ion concentration condition is a pH condition.

5. The pharmaceutical composition of claim 4, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher in a neutral pH range than under an acidic pH range.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the antibody~~antigen-binding molecule~~ has neutralizing activity against the antigen.

7. The pharmaceutical composition of any one of claims 1 to 6, wherein the

antibody~~antigen-binding molecule~~ has cytotoxic activity against a cell expressing the antigen.

~~8. The pharmaceutical composition of any one of claims 1 to 7, wherein the FcRn-binding domain comprises an antibody Fc region.~~

~~9. The pharmaceutical composition of claim 8, wherein the Fc region is an Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region.~~

~~10~~8. The pharmaceutical composition of ~~claim 8 or 9~~any one of claims 1 to 7, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
Ala at amino acid position 257;
Pro at amino acid position 308;
Leu at amino acid position 428; and
Tyr at amino acid position 434,
according to EU numbering in the Fc region.

~~11~~9. The pharmaceutical composition of any one of claims ~~8 to 10~~1 to 8, wherein the Fcγ receptor-binding activity of the Fc region is higher than that of a naturally-occurring human IgG Fc region in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

~~12~~10. The pharmaceutical composition of claim ~~11~~9, wherein the Fcγ receptor is FcγRIa, FcγRIIa(R), FcγRIIa(H), FcγRIIb, FcγRIIIa(V), or FcγRIIIa(F).

~~13~~11. The pharmaceutical composition of claim ~~11 or 12~~9 or 10, wherein the Fc region is an Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 221, 222, 223, 224, 225, 227, 228, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 243, 244, 245, 246, 247, 249, 250, 251, 254, 255, 256, 258, 260, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 278, 279, 280, 281, 282, 283, 284, 285, 286, 288, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 311, 313, 315, 317, 318, 320, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 339, 376, 377, 378, 379, 380, 382, 385, 392, 396, 421, 427, 428, 429, 434, 436, and 440 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region.

~~14~~12. The pharmaceutical composition of any one of claims ~~11 to 13~~9 to 11, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
either Lys or Tyr at amino acid position 221;
any one of Phe, Trp, Glu, and Tyr at amino acid position 222;
any one of Phe, Trp, Glu, and Lys at amino acid position 223;
any one of Phe, Trp, Glu, and Tyr at amino acid position 224;
any one of Glu, Lys, and Trp at amino acid position 225;
any one of Glu, Gly, Lys, and Tyr at amino acid position 227;
any one of Glu, Gly, Lys, and Tyr at amino acid position 228;

according to EU numbering in the Fc region.

~~15~~13. The pharmaceutical composition of any one of claims ~~11 to 14~~9 to 12, wherein the naturally-occurring Fc region is an Fc region of any one of human IgG1, human IgG2, human IgG3, and human IgG4 in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

~~16~~14. The pharmaceutical composition of any one of claims ~~11 to 15~~9 to 13, wherein the Fc region is modified so that the percentage of the Fc region to which a fucose-deficient sugar chain is attached, or bisecting *N*-acetylglucosamine is added, at position 297 according to EU numbering in the Fc region, will become higher.

~~17~~15. Use of the antibody~~antigen-binding molecule~~ of any one of claims 1 to ~~16~~14 in the manufacture of a medicament for inducing an immune response in a living organism.

~~18~~16. A method for producing an antibody~~antigen-binding molecule~~ that induces an immune response, which comprises imparting FcRn-binding activity in a neutral pH range to an FcRn-binding domain that is contained in an antibody~~antigen-binding molecule~~ containing an antigen-binding domain whose antigen-binding activity changes depending on an ion concentration condition, wherein the antigen-binding domain comprises an antibody variable region in which at least one or more amino acids selected from the group consisting of amino acids at positions 95, 96, 100a and 101 according to Kabat numbering in the antibody heavy chain variable region and amino acids at positions 30, 31, 32, 50 and 92 according to Kabat numbering in the antibody light chain variable region are amino acids having a metal-chelating activity or antibody variable region in which at least one or more amino acids are His, and wherein the FcRn-binding domain comprises an antibody Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region.

~~19~~17. The method of claim ~~18~~16, wherein the ion concentration is a calcium ion concentration.

~~20~~18. The method of claim ~~19~~17, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher under a high calcium ion concentration condition than under a low calcium ion concentration condition.

~~21~~19. The method of claim ~~18~~16, wherein the ion concentration condition is a pH condition.

~~22~~20. The method of claim ~~21~~19, wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity is higher in a neutral pH range than in an acidic pH range.

~~23~~21. The method of any one of claims ~~18 to 22~~16 to 20, wherein the antibody~~antigen-binding molecule~~ has neutralizing activity against the antigen.

~~24~~22. The method of any one of claims ~~18 to 23~~16 to 20, wherein the antibody~~antigen-binding molecule~~ has

cytotoxic activity against a cell expressing the antigen.

~~25. The method of any one of claims 18 to 24, wherein the FcRn-binding domain comprises an antibody Fc region.~~

~~26. The method of claim 25, comprising the step of substituting at least one or more amino acids selected from the group consisting of amino acids at positions 239, 252, 257, 286, 307, 308, 428, and 434 according to EU numbering in the Fc region.~~

~~27~~23. The method of ~~claim 25 or 26~~any one of claims 16 to 22, comprising the step of performing at least one or more amino acid substitutions selected from the group consisting of:
amino acid substitution with Ala at position 257;
amino acid substitution with Pro at position 308;
amino acid substitution with Leu at position 428; and
amino acid substitution with Tyr at position 434,
according to EU numbering in the Fc region.

~~28~~24. The method of any one of claims ~~25 to 27~~16 to 23, comprising the step of enhancing the Fcγ receptor-binding activity of the Fc region as compared to that of a naturally-occurring human IgG Fc region in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

~~29~~25. The method of claim ~~28~~24, wherein the Fcγ receptor is FcγRIa, FcγRIIa(R), FcγRIIa(H), FcγRIIb, FcγRIIIa(V), or FcγRIIIa(F).

~~30~~26. The method of claim ~~28 or 29~~24 or 25, comprising the step of substituting at least one or more amino acids selected from the group consisting of amino acids at positions 221, 222, 223, 224, 225, 227, 228, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 243, 244, 245, 246, 247, 249, 250, 251, 254, 255, 256, 258, 260, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 278, 279, 280, 281, 282, 283, 284, 285, 286, 288, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 311, 313, 315, 317, 318, 320, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 339, 376, 377, 378, 379, 380, 382, 385, 392, 396, 421, 427, 428, 429, 434, 436, and 440 according to EU numbering in the Fc region.

~~31~~27. The method of any one of claims ~~28 to 30~~24 to 26, comprising the step of performing at least one

amino acid substitution with Asp at position 378;
amino acid substitution with Asn at position 379;
amino acid substitution with any one of Ala, Asn, and Ser at position 380;
amino acid substitution with either Ala or Ile at position 382;
amino acid substitution with Glu at position 385;
amino acid substitution with Thr at position 392;
amino acid substitution with Leu at position 396;
amino acid substitution with Lys at position 421;
amino acid substitution with Asn at position 427;
amino acid substitution with either Phe or Leu at position 428;
amino acid substitution with Met at position 429;
amino acid substitution with Trp at position 434;
amino acid substitution with Ile at position 436; and
amino acid substitution with any one of Gly, His, Ile, Leu, and Tyr at position 440,
according to EU numbering in the Fc region.

~~32~~28. The method of any one of claims ~~28 to 31~~24 to 27, wherein the naturally-occurring Fc region is an Fc region of any one of human IgG1, human IgG2, human IgG3, and human IgG4 in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

~~33~~29. The method of any one of claims ~~28 to 32~~24 to 28, comprising the step of modifying the Fc region so that the percentage of the Fc region to which a fucose-deficient sugar chain is attached, or bisecting *N*-acetylglucosamine is added, at position 297 according to EU numbering in the Fc region, will become higher.

~~34. A method for producing a pharmaceutical composition which induces an immune response, which comprises the steps of:~~
~~(a) determining the antigen-binding activity of an antigen-binding domain under a high calcium ion concentration condition;~~
~~(b) determining the antigen-binding activity of the antigen-binding domain under a low calcium ion concentration condition;~~
~~(c) selecting the antigen-binding domain whose antigen-binding activity determined in (a) is higher than that determined in (b);~~
~~(d) linking a polynucleotide encoding the antigen-binding domain selected in (c) to a polynucleotide encoding an FcRn-binding domain having FcRn-binding activity in a neutral pH~~

range;

(e) culturing a cell into which a vector to which the polynucleotide obtained in (d) is operably linked has been introduced; and

(f) collecting an antigen-binding molecule from culture fluid of the cell cultured in (e).

35. A method for producing a pharmaceutical composition which induces an immune response, which comprises the steps of:

(a) determining the antigen-binding activity of an antibody under a high calcium ion concentration condition;

(b) determining the antigen-binding activity of the antibody under a low calcium ion concentration condition;

(c) selecting the antibody whose antigen-binding activity determined in (a) is higher than that determined in (b);

(d) linking a polynucleotide encoding the antigen-binding domain of the antibody selected in (c) to a polynucleotide encoding an FcRn-binding domain having FcRn-binding activity in a neutral pH range;

(e) culturing a cell into which a vector to which the polynucleotide obtained in (d) is operably linked has been introduced; and

(f) collecting an antigen-binding molecule from culture fluid of the cell cultured in (e).

36. A method for producing an antigen-binding molecule, which comprises the steps of:

(a) determining the antigen-binding activity of an antigen-binding domain in a neutral pH range;

(b) determining the antigen-binding activity of the antigen-binding domain in an acidic pH range;

(c) selecting the antigen-binding domain whose antigen-binding activity determined in (a) is higher than that determined in (b);

(d) linking a polynucleotide encoding the antigen-binding domain selected in (c) to a polynucleotide encoding an FcRn-binding domain having FcRn-binding activity in a neutral pH range;

(e) culturing a cell into which a vector to which the polynucleotide obtained in (d) is operably linked has been introduced; and

(f) collecting an antigen-binding molecule from culture fluid of the cell cultured in (e).

37. A method for producing an antigen-binding molecule, which comprises the steps of:

(a) determining the antigen-binding activity of an antibody in a neutral pH range;

(b) determining the antigen-binding activity of the antibody in an acidic pH range;
(c) selecting the antibody whose antigen-binding activity determined in (a) is higher than that determined in (b);
(d) linking a polynucleotide encoding the antigen-binding domain of the antibody selected in (c) to a polynucleotide encoding an FcRn-binding domain having FcRn-binding activity in a neutral pH range;
(e) culturing a cell into which a vector to which the polynucleotide obtained in (d) is operably linked has been introduced; and
(f) collecting an antigen-binding molecule from culture fluid of the cell cultured in (e).

38. The method of any one of claims 34 to 37, wherein the antigen-binding molecule has neutralizing activity against the antigen.

39. The method of any one of claims 34 to 38, wherein the antigen-binding molecule has cytotoxic activity against a cell expressing the antigen.

40. The method of any one of claims 34 to 39, wherein the FcRn-binding domain comprises an antibody Fc region.

41. The method of claim 40, wherein the Fc region is an Fc region in which at least one or more amino acids selected from the group consisting of amino acids at positions 257, 308, 428, and 434 according to EU numbering in the Fc region are different from amino acids at corresponding positions in a naturally-occurring Fc region.

42. The method of claim 40 or 41, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
Ala at amino acid position 257;
Pro at amino acid position 308;
Leu at amino acid position 428; and
Tyr at amino acid position 434,
according to EU numbering in the Fc region.

43. The method of any one of claims 40 to 42, wherein the Fcγ receptor-binding activity of the Fc region is higher than that of a naturally-occurring human IgG Fc region in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

44. The method of claim 43, wherein the Fcγ receptor is FcγRIa, FcγRIIa(R), FcγRIIa(H), FcγRIIb, FcγRIIIa(V), or FcγRIIIa(F).

45. The method of claim 43 or 44, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
either Lys or Tyr at amino acid position 221;
any one of Phe, Trp, Glu, and Tyr at amino acid position 222;
any one of Phe, Trp, Glu, and Lys at amino acid position 223;
any one of Phe, Trp, Glu, and Tyr at amino acid position 224;
any one of Glu, Lys, and Trp at amino acid position 225;
any one of Glu, Gly, Lys, and Tyr at amino acid position 227;
any one of Glu, Gly, Lys, and Tyr at amino acid position 228;
any one of Ala, Glu, Gly, and Tyr at amino acid position 230;
any one of Glu, Gly, Lys, Pro, and Tyr at amino acid position 231;
any one of Glu, Gly, Lys, and Tyr at amino acid position 232;
any one of Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 233;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 234;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 235;
any one of Ala, Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 236;
any one of Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 237;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 238;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Thr, Val, Trp, and Tyr at amino acid position 239;
any one of Ala, Ile, Met, and Thr at amino acid position 240;
any one of Asp, Glu, Leu, Arg, Trp, and Tyr at amino acid position 241;
any one of Leu, Glu, Leu, Gln, Arg, Trp, and Tyr at amino acid position 243;
His at amino acid position 244;
Ala at amino acid position 245;
any one of Asp, Glu, His, and Tyr at amino acid position 246;
any one of Ala, Phe, Gly, His, Ile, Leu, Met, Thr, Val, and Tyr at amino acid position 247;

any one of Glu, His, Gln, and Tyr at amino acid position 249;
either Glu or Gln at amino acid position 250;
Phe at amino acid position 251;
any one of Phe, Met, and Tyr at amino acid position 254;
any one of Glu, Leu, and Tyr at amino acid position 255;
any one of Ala, Met, and Pro at amino acid position 256;
any one of Asp, Glu, His, Ser, and Tyr at amino acid position 258;
any one of Asp, Glu, His, and Tyr at amino acid position 260;
any one of Ala, Glu, Phe, Ile, and Thr at amino acid position 262;
any one of Ala, Ile, Met, and Thr at amino acid position 263;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Trp, and Tyr at amino acid position 264;
any one of Ala, Leu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Val, Trp, and Tyr at amino acid position 265;
any one of Ala, Ile, Met, and Thr at amino acid position 266;
any one of Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Thr, Val, Trp, and Tyr at amino acid position 267;
any one of Asp, Glu, Phe, Gly, Ile, Lys, Leu, Met, Pro, Gln, Arg, Thr, Val, and Trp at amino acid position 268;
any one of Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 269;
any one of Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Arg, Ser, Thr, Trp, and Tyr at amino acid position 270;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 271;
any one of Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 272;
either Phe or Ile at amino acid position 273;
any one of Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 274;
either Leu or Trp at amino acid position 275;
any one of Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 276;
any one of Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, and Trp at amino acid position 278;
Ala at amino acid position 279;

any one of Ala, Gly, His, Lys, Leu, Pro, Gln, Trp, and Tyr at amino acid position 280;
any one of Asp, Lys, Pro, and Tyr at amino acid position 281;
any one of Glu, Gly, Lys, Pro, and Tyr at amino acid position 282;
any one of Ala, Gly, His, Ile, Lys, Leu, Met, Pro, Arg, and Tyr at amino acid position 283;
any one of Asp, Glu, Leu, Asn, Thr, and Tyr at amino acid position 284;
any one of Asp, Glu, Lys, Gln, Trp, and Tyr at amino acid position 285;
any one of Glu, Gly, Pro, and Tyr at amino acid position 286;
any one of Asn, Asp, Glu, and Tyr at amino acid position 288;
any one of Asp, Gly, His, Leu, Asn, Ser, Thr, Trp, and Tyr at amino acid position 290;
any one of Asp, Glu, Gly, His, Ile, Gln, and Thr at amino acid position 291;
any one of Ala, Asp, Glu, Pro, Thr, and Tyr at amino acid position 292;
any one of Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 293;
any one of Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 294;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 295;
any one of Ala, Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, and Val at amino acid position 296;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 297;
any one of Ala, Asp, Glu, Phe, His, Ile, Lys, Met, Asn, Gln, Arg, Thr, Val, Trp, and Tyr at amino acid position 298;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, and Tyr at amino acid position 299;
any one of Ala, Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, and Trp at amino acid position 300;
any one of Asp, Glu, His, and Tyr at amino acid position 301;
Ile at amino acid position 302;
any one of Asp, Gly, and Tyr at amino acid position 303;
any one of Asp, His, Leu, Asn, and Thr at amino acid position 304;
any one of Glu, Ile, Thr, and Tyr at amino acid position 305;
any one of Ala, Asp, Asn, Thr, Val, and Tyr at amino acid position 311;
Phe at amino acid position 313;
Leu at amino acid position 315;
either Glu or Gln at amino acid position 317;

any one of His, Leu, Asn, Pro, Gln, Arg, Thr, Val, and Tyr at amino acid position 318;
any one of Asp, Phe, Gly, His, Ile, Leu, Asn, Pro, Ser, Thr, Val, Trp, and Tyr at amino acid position 320;
any one of Ala, Asp, Phe, Gly, His, Ile, Pro, Ser, Thr, Val, Trp, and Tyr at amino acid position 322;
Ile at amino acid position 323;
any one of Asp, Phe, Gly, His, Ile, Leu, Met, Pro, Arg, Thr, Val, Trp, and Tyr at amino acid position 324;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 325;
any one of Ala, Asp, Glu, Gly, Ile, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, and Tyr at amino acid position 326;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Thr, Val, Trp, and Tyr at amino acid position 327;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 328;
any one of Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 329;
any one of Cys, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 330;
any one of Asp, Phe, His, Ile, Leu, Met, Gln, Arg, Thr, Val, Trp, and Tyr at amino acid position 331;
any one of Ala, Asp, Glu, Phe, Gly, His, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, and Tyr at amino acid position 332;
any one of Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Ser, Thr, Val, and Tyr at amino acid position 333;
any one of Ala, Glu, Phe, Ile, Leu, Pro, and Thr at amino acid position 334;
any one of Asp, Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Val, Trp, and Tyr at amino acid position 335;
any one of Glu, Lys, and Tyr at amino acid position 336;
any one of Glu, His, and Asn at amino acid position 337;
any one of Asp, Phe, Gly, Ile, Lys, Met, Asn, Gln, Arg, Ser, and Thr at amino acid position 339;
either Ala or Val at amino acid position 376;
either Gly or Lys at amino acid position 377;
Asp at amino acid position 378;
Asn at amino acid position 379;

any one of Ala, Asn, and Ser at amino acid position 380;
either Ala or Ile at amino acid position 382;
Glu at amino acid position 385;
Thr at amino acid position 392;
Leu at amino acid position 396;
Lys at amino acid position 421;
Asn at amino acid position 427;
either Phe or Leu at amino acid position 428;
Met at amino acid position 429;
Trp at amino acid position 434;
Ile at amino acid position 436; and
any one of Gly, His, Ile, Leu, and Tyr at amino acid position 440;
according to EU numbering in the Fc region.

46. The method of any one of claims 43 to 45, wherein the naturally-occurring Fc region is an Fc region of any one of human IgG1, human IgG2, human IgG3, and human IgG4 in which the sugar chain attached at position 297 according to EU numbering is a fucose-containing sugar chain.

47. The method of any one of claims 43 to 46, wherein the Fc region is modified so that the percentage of the Fc region to which a fucose-deficient sugar chain is attached, or bisecting *N*-acetylglucosamine is added, at position 297 according to EU numbering in the Fc region, will become higher.