[Patent Document 1] International Publication WO2009/125825
[Patent Document 2] International Publication WO2011/122011
[Non-patent Documents]
[Non-patent Document 1] Monoclonal antibody successes in the clinic, Janice M Reichert, Clark J Rosensweig, Laura B Faden & Matthew C Dewitz, Nat. Biotechnol. (2005) 23, 1073 – 1078
[Non-patent Document 2] Pavlou AK, Belsey MJ., The therapeutic antibodies market to 2008., Eur. J. Pharm. Biopharm. (2005) 59 (3), 389-396
[Non-patent Document 3] Kim SJ, Park Y, Hong HJ., Antibody engineering for the development of therapeutic antibodies, Mol. Cells. (2005) 20 (1), 17-29
[Non-patent Document 4] Hinton PR, Xiong JM, Johlfs MG, Tang MT, Keller S, Tsurushita N, J. Immunol. (2006) 176 (1), 346-356
[Non-patent Document 5] Ghetie V, Popov S, Borvak J, Radu C, Matesoi D, Medesan C, Ober RJ, Ward ES., Nat. Biotechnol. (1997) 15 (7), 637-640
[Non-patent Document 6] Rajpal A, Beyaz N, Haber L, Cappuccilli G, Yee H, Bhatt RR, Takeuchi T, Lerner RA, Crea R., Proc. Natl. Acad. Sci. USA. (2005) 102 (24), 8466-8471
[Non-patent Document 7] Wu H, Pfarr DS, Johnson S, Brewah YA, Woods RM, Patel NK, White WI, Young JF, Kiener PA., J. Mol. Biol. (2007) 368, 652-665
[Non-patent Document 8] Igawa T, et al., Nat. Biotechnol. (2010) 28, 1203-1207

Summary of the Disclosure

[Problems to be Solved by the Present Disclosure]

The present disclosure was achieved in view of the above circumstances. An objective of the present disclosure is to provide uses of antigen-binding molecules for eliminating antigens from plasma; methods for eliminating antigens from plasma, which comprise administering antigen-binding molecules; pharmaceutical compositions comprising antigen-binding molecules that are capable of eliminating antigens from plasma; methods of screening for antigen-binding molecules for eliminating antigens from plasma; and methods for producing antigen-binding molecules for eliminating antigens from plasma.

[Means for Solving the Problems]

The present inventors conducted dedicated studies to achieve the above-described objectives. As a result, the present inventors produced antigen-binding molecules comprising (i) an Fc region and (ii) two or more antigen-binding domains where at least one of the domains is an antigen-binding domain whose antigen binding activity varies depending on the ion concentration condition, which are antigen-binding molecules that can form an immune complex comprising (a) two or more of the antigen-binding molecules and (b) two or more antigen

molecules comprising two or more antigenic binding units. Furthermore, the present inventors discovered that the antigen-binding molecules can be used to eliminate antigens from plasma. Furthermore, the present inventors discovered that the antigen-binding molecules are useful as pharmaceutical compositions, and they produced methods for eliminating antigens from plasma, which comprise administering the antigen-binding molecules. Furthermore, the present inventors discovered methods of screening for antigen-binding molecules having the aforementioned properties, and created methods for producing the molecules, thereby completing the present disclosure.

More specifically, the present disclosure provides the following:

[1] use of an antigen-binding molecule comprising
(i) an Fc region and
(ii) two or more antigen-binding domains,
wherein at least one of the domains is an antigen-binding domain of which antigen-binding activity varies depending on an ion concentration condition, and
wherein the antigen-binding molecule can form an immune complex which comprises
(a) two or more of the antigen-binding molecules and
(b) two or more antigens, wherein the antigens comprise two or more antigenic binding units,
in the manufacture of a medicament for eliminating the antigens from plasma;

[2] the use of [1], wherein the ion concentration condition is a calcium ion concentration condition;

[3] the use of [2], wherein the antigen-binding domain has an antigen-binding activity under a low calcium-ion concentration condition that is lower than the antigen-binding activity under a high calcium-ion concentration condition;

[4] the use of any one of [1] to [3], wherein the ion concentration condition is a pH condition;

[5] the use of [4], wherein the antigen-binding domain has an antigen binding activity in an acidic pH range that is lower than the antigen-binding activity in a neutral pH range condition;

[6] the use of any one of [1] to [5], wherein the antigens comprising two or more antigenic binding units are multimers;

[7] the use of [6], wherein the antigen is any one of GDF, GDF-1, GDF-3 (Vgr-2), GDF-5 (BMP-14, CDMP-1), GDF-6 (BMP-13, CDMP-2), GDF-7 (BMP-12, CDMP-3), GDF-8 (myostatin), GDF-9, GDF-15 (MIC-1), TNF, TNF-alpha, TNF-alphabeta, TNF-beta2, TNFSF10 (TRAIL Apo-2 ligand, TL2), TNFSF11 (TRANCE/RANK ligand ODF, OPG ligand), TNFSF12 (TWEAK Apo-3 ligand, DR3 ligand), TNFSF13 (APRIL TALL2), TNFSF13B (BAFF BLYS, TALL1, THANK, TNFSF20), TNFSF14 (LIGHT HVEM ligand, LTg), TNFSF15 (TL1A/VEGI), TNFSF18 (GITR ligand AITR ligand, TL6), TNFSF1A (TNF-a Conectin, DIF, TNFSF2), TNFSF1B (TNF-b LTa, TNFSF1), TNFSF3 (LTb TNFC, p33), TNFSF4 (OX40 ligand gp34,

CLAIMS

1. Use of an antigen-binding molecule comprising
(i) an Fc region and
(ii) two or more antigen-binding domains,
wherein at least one of the domains is an antigen-binding domain of which antigen-binding activity varies depending on an ion concentration condition, and
wherein the antigen-binding molecule can form an immune complex which comprises
(a) two or more of the antigen-binding molecules and
(b) two or more antigens, wherein the antigens comprise two or more antigenic binding units,
in the manufacture of a medicament for eliminating the antigens from plasma.

2. The use of claim 1, wherein the ion concentration condition is a pH condition.

3. The use of claim 2, wherein the antigen-binding domain has an antigen binding activity in an acidic pH range that is lower than the antigen-binding activity in a neutral pH range condition.

4. The use of any one of claims 1 to 3, wherein the antigens comprising two or more antigenic binding units are multimers.

5. The use of claim 4, wherein the antigen is any one of GDF, GDF-1, GDF-3 (Vgr-2), GDF-5 (BMP-14, CDMP-1), GDF-6 (BMP-13, CDMP-2), GDF-7 (BMP-12, CDMP-3), GDF-8 (myostatin), GDF-9, GDF-15 (MIC-1), TNF, TNF-alpha, TNF-alphabeta, TNF-beta2, TNFSF10 (TRAIL Apo-2 ligand, TL2), TNFSF11 (TRANCE/RANK ligand ODF, OPG ligand), TNFSF12 (TWEAK Apo-3 ligand, DR3 ligand), TNFSF13 (APRIL TALL2), TNFSF13B (BAFF BLYS, TALL1, THANK, TNFSF20), TNFSF14 (LIGHT HVEM ligand, LTg), TNFSF15 (TL1A/VEGI), TNFSF18 (GITR ligand AITR ligand, TL6), TNFSF1A (TNF-a Conectin, DIF, TNFSF2), TNFSF1B (TNF-b LTa, TNFSF1), TNFSF3 (LTb TNFC, p33), TNFSF4 (OX40 ligand gp34, TXGP1), TNFSF5 (CD40 ligand CD154, gp39, HIGM1, IMD3, TRAP), TNFSF6 (Fas ligand Apo-1 ligand, APT1 ligand), TNFSF7 (CD27 ligand CD70), TNFSF8 (CD30 ligand CD153), TNFSF9 (4-1BB ligand CD137 ligand), VEGF, IgE, IgA, IgG, IgM, RANKL, TGF-alpha, TGF-beta, TGF-beta Pan Specific, and IL-8.

6. The use of any one of claims 1 to 3, wherein the antigens comprising two or more antigenic binding units are monomers.

7. The use of any one of claims 1 to 6, wherein the antigen-binding molecules are a multispecific or multiparatopic antigen-binding molecule, or a cocktail of antigen-binding molecules.

8. The use of any one of claims 1 to 7, wherein the Fc region is represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

9. The use of any one of claims 1 to 7, wherein the Fc region is an Fc region with an enhanced FcRn-binding activity under an acidic pH range condition compared to that of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

10. The use of claim 9, wherein the Fc region is an Fc region with a substitution of at least one or more amino acids selected from the group consisting of amino acids at positions 238, 244, 245, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 260, 262, 265, 270, 272, 279, 283, 285, 286, 288, 293, 303, 305, 307, 308, 309, 311, 312, 314, 316, 317, 318, 332, 339, 340, 341, 343, 356, 360, 362, 375, 376, 377, 378, 380, 382, 385, 386, 387, 388, 389, 400, 413, 415, 423, 424, 427, 428, 430, 431, 433, 434, 435, 436, 438, 439, 440, 442, and 447 (EU numbering) in the amino acid sequence of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

11. The use of claim 10, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
Leu for the amino acid of position 238;
Leu for the amino acid of position 244;
Arg for the amino acid of position 245;
Pro for the amino acid of position 249;
Gln or Glu for the amino acid of position 250;
Arg, Asp, Glu, or Leu for the amino acid of position 251;
Phe, Ser, Thr, or Tyr for the amino acid of position 252;
Ser or Thr for the amino acid of position 254;
Arg, Gly, Ile, or Leu for the amino acid of position 255;
Ala, Arg, Asn, Asp, Gln, Glu, Pro, or Thr for the amino acid of position 256;
Ala, Ile, Met, Asn, Ser, or Val for the amino acid of position 257;
Asp for the amino acid of position 258;
Ser for the amino acid of position 260;
Leu for the amino acid of position 262;
Lys for the amino acid of position 270;

Leu or Arg for the amino acid of position 272;
Ala, Asp, Gly, His, Met, Asn, Gln, Arg, Ser, Thr, Trp, or Tyr for the amino acid of position 279;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Arg, Ser, Thr, Trp, or Tyr for the amino acid of position 283;
Asn for the amino acid of position 285;
Phe for the amino acid of position 286;
Asn or Pro for the amino acid of position 288;
Val for the amino acid of position 293;
Ala, Glu, Gln, or Met for the amino acid of position 307;
Ala, Glu, Ile, Lys, Leu, Met, Ser, Val, or Trp for the amino acid of position 311;
Pro for the amino acid of position 309;
Ala, Asp, or Pro for the amino acid of position 312;
Ala or Leu for the amino acid of position 314;
Lys for the amino acid of position 316;
Pro for the amino acid of position 317;
Asn or Thr for the amino acid of position 318;
Phe, His, Lys, Leu, Met, Arg, Ser, or Trp for the amino acid of position 332;
Asn, Thr, or Trp for the amino acid of position 339;
Pro for the amino acid of position 341;
Glu, His, Lys, Gln, Arg, Thr, or Tyr for the amino acid of position 343;
Arg for the amino acid of position 375;
Gly, Ile, Met, Pro, Thr, or Val for the amino acid of position 376;
Lys for the amino acid of position 377;
Asp, Asn, or Val for the amino acid of position 378;
Ala, Asn, Ser, or Thr for the amino acid of position 380;
Phe, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 382;
Ala, Arg, Asp, Gly, His, Lys, Ser, or Thr for the amino acid of position 385;
Arg, Asp, Ile, Lys, Met, Pro, Ser, or Thr for the amino acid of position 386;
Ala, Arg, His, Pro, Ser, or Thr for the amino acid of position 387;
Asn, Pro, or Ser for the amino acid of position 389;
Asn for the amino acid of position 423;
Asn for the amino acid of position 427;
Leu, Met, Phe, Ser, or Thr for the amino acid of position 428;
Ala, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, or Tyr for the amino acid of position 430;

His or Asn for the amino acid of position 431;
Arg, Gln, His, Ile, Lys, Pro, or Ser for the amino acid of position 433;
Ala, Gly, His, Phe, Ser, Trp, or Tyr for the amino acid of position 434;
Arg, Asn, His, Ile, Leu, Lys, Met, or Thr for the amino acid of position 436;
Lys, Leu, Thr, or Trp for the amino acid of position 438;
Lys for the amino acid of position 440; and
Lys for the amino acid of position 442; Ile, Pro, or Thr for the amino acid of position 308;
as indicated by EU numbering in the amino acid sequence of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

12. The use of any one of claims 1 to 7, wherein the Fc region is an Fc region with an enhanced FcRn-binding activity under a neutral pH range condition compared to that of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

13. The use of claim 12, wherein the Fc region is an Fc region with a substitution of at least one or more amino acids selected from the group consisting 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 (EU numbering) in the amino acid sequence of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

14. The use of claim 13, wherein the Fc region comprises at least one or more amino acids selected from the group consisting of:
Met for the amino acid of position 237;
Ile for the amino acid of position 248;
Ala, Phe, Ile, Met, Gln, Ser, Val, Trp, or Tyr for the amino acid of position 250;
Phe, Trp, or Tyr for the amino acid of position 252;
Thr for the amino acid of position 254;
Glu for the amino acid of position 255;
Asp, Asn, Glu, or Gln for the amino acid of position 256;
Ala, Gly, Ile, Leu, Met, Asn, Ser, Thr, or Val for the amino acid of position 257;
His for the amino acid of position 258;
Ala for the amino acid of position 265;
Ala or Glu for the amino acid of position 286;
His for the amino acid of position 289;
Ala for the amino acid of position 297;

Ala for the amino acid of position 303;
Ala for the amino acid of position 305;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr for the amino acid of position 307;
Ala, Phe, Ile, Leu, Met, Pro, Gln, or Thr for the amino acid of position 308;
Ala, Asp, Glu, Pro, or Arg for the amino acid of position 309;
Ala, His, or Ile for the amino acid of position 311;
Ala or His for the amino acid of position 312;
Lys or Arg for the amino acid of position 314;
Ala, Asp, or His for the amino acid of position 315;
Ala for the amino acid of position 317;
Val for the amino acid of position 332;
Leu for the amino acid of position 334;
His for the amino acid of position 360;
Ala for the amino acid of position 376;
Ala for the amino acid of position 380;
Ala for the amino acid of position 382;
Ala for the amino acid of position 384;
Asp or His for the amino acid of position 385;
Pro for the amino acid of position 386;
Glu for the amino acid of position 387;
Ala or Ser for the amino acid of position 389;
Ala for the amino acid of position 424;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 428;
Lys for the amino acid of position 433;
Ala, Phe, His, Ser, Trp, or Tyr for the amino acid of position 434; and
His , Ile, Leu, Phe, Thr, or Val for the amino acid of position 436;
as indicated by EU numbering in the amino acid sequence of the Fc region represented by any one of SEQ ID NOs: 13, 14, 15, and 16.

15. The use of any one of claims 1 to 11, wherein the Fc region includes an Fc region that has a higher Fcγ receptor-binding activity than that of the Fc region of a native human IgG.

16. The use of claim 15, wherein the Fc region comprises in its amino acid sequence at least one or more amino acids that are different from amino acids of the native human IgG Fc region

selected from the group consisting of 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 (EU numbering).

17. The use of claim 16, wherein the Fc region comprises in its amino acid sequence at least one amino acid selected from the group consisting of:
Lys or Tyr for the amino acid of position 221;
Phe, Trp, Glu, or Tyr for the amino acid of position 222;
Phe, Trp, Glu, or Lys for the amino acid of position 223;
Phe, Trp, Glu, or Tyr for the amino acid of position 224;
Glu, Lys, or Trp for the amino acid of position 225;
Glu, Gly, Lys, or Tyr for the amino acid of position 227;
Glu, Gly, Lys, or Tyr for the amino acid of position 228;
Ala, Glu, Gly, or Tyr for the amino acid of position 230;
Glu, Gly, Lys, Pro, or Tyr for the amino acid of position 231;
Glu, Gly, Lys, or Tyr for the amino acid of position 232;
Ala, Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 233;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 234;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 235;
Ala, Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 236;
Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 237;
Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 238;
Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 239;
Ala, Ile, Met, or Thr for the amino acid of position 240;
Asp, Glu, Leu, Arg, Trp, or Tyr for the amino acid of position 241;

Leu, Glu, Leu, Gln, Arg, Trp, or Tyr for the amino acid of position 243;
His for the amino acid of position 244;
Ala for the amino acid of position 245;
Asp, Glu, His, or Tyr for the amino acid of position 246;
Ala, Phe, Gly, His, Ile, Leu, Met, Thr, Val, or Tyr for the amino acid of position 247;
Glu, His, Gln, or Tyr for the amino acid of position 249;
Glu or Gln for the amino acid of position 250;
Phe for the amino acid of position 251;
Phe, Met, or Tyr for the amino acid of position 254;
Glu, Leu, or Tyr for the amino acid of position 255;
Ala, Met, or Pro for the amino acid of position 256;
Asp, Glu, His, Ser, or Tyr for the amino acid of position 258;
Asp, Glu, His, or Tyr for the amino acid of position 260;
Ala, Glu, Phe, Ile, or Thr for the amino acid of position 262;
Ala, Ile, Met, or Thr for the amino acid of position 263;
Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Trp, or Tyr for the amino acid of position 264;
Ala, Leu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 265;
Ala, Ile, Met, or Thr for the amino acid of position 266;
Asp, Glu, Phe, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 267;
Asp, Glu, Phe, Gly, Ile, Lys, Leu, Met, Pro, Gln, Arg, Thr, Val, or Trp for the amino acid of position 268;
Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 269;
Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Gln, Arg, Ser, Thr, Trp, or Tyr for the amino acid of position 270;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 271;
Asp, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 272;
Phe or Ile for the amino acid of position 273;
Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 274;
Leu or Trp for the amino acid of position 275;

Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 276;

Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Trp for the amino acid of position 278;

Ala for the amino acid of position 279;

Ala, Gly, His, Lys, Leu, Pro, Gln, Trp, or Tyr for the amino acid of position 280;

Asp, Lys, Pro, or Tyr for the amino acid of position 281;

Glu, Gly, Lys, Pro, or Tyr for the amino acid of position 282;

Ala, Gly, His, Ile, Lys, Leu, Met, Pro, Arg, or Tyr for the amino acid of position 283;

Asp, Glu, Leu, Asn, Thr, or Tyr for the amino acid of position 284;

Asp, Glu, Lys, Gln, Trp, or Tyr for the amino acid of position 285;

Glu, Gly, Pro, or Tyr for the amino acid of position 286;

Asn, Asp, Glu, or Tyr for the amino acid of position 288;

Asp, Gly, His, Leu, Asn, Ser, Thr, Trp, or Tyr for the amino acid of position 290;

Asp, Glu, Gly, His, Ile, Gln, or Thr for the amino acid of position 291;

Ala, Asp, Glu, Pro, Thr, or Tyr for the amino acid of position 292;

Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 293;

Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 294;

Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 295;

Ala, Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, or Val for the amino acid of position 296;

Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 297;

Ala, Asp, Glu, Phe, His, Ile, Lys, Met, Asn, Gln, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 298;

Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Val, Trp, or Tyr for the amino acid of position 299;

Ala, Asp, Glu, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Trp for the amino acid of position 300;

Asp, Glu, His, or Tyr for the amino acid of position 301;

Ile for the amino acid of position 302;

Asp, Gly, or Tyr for the amino acid of position 303;

Asp, His, Leu, Asn, or Thr for the amino acid of position 304;

Glu, Ile, Thr, or Tyr for the amino acid of position 305;
Ala, Asp, Asn, Thr, Val, or Tyr for the amino acid of position 311;
Phe for the amino acid of position 313;
Leu for the amino acid of position 315;
Glu or Gln for the amino acid of position 317;
His, Leu, Asn, Pro, Gln, Arg, Thr, Val, or Tyr for the amino acid of position 318;
Asp, Phe, Gly, His, Ile, Leu, Asn, Pro, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 320;
Ala, Asp, Phe, Gly, His, Ile, Pro, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 322;
Ile for the amino acid of position 323;
Asp, Phe, Gly, His, Ile, Leu, Met, Pro, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 324;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 325;
Ala, Asp, Glu, Gly, Ile, Leu, Met, Asn, Pro, Gln, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 326;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 327;
Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 328;
Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 329;
Cys, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 330;
Asp, Phe, His, Ile, Leu, Met, Gln, Arg, Thr, Val, Trp, or Tyr for the amino acid of position 331;
Ala, Asp, Glu, Phe, Gly, His, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr for the amino acid of position 332;
Ala, Asp, Glu, Phe, Gly, His, Ile, Leu, Met, Pro, Ser, Thr, Val, or Tyr for the amino acid of position 333;
Ala, Glu, Phe, Ile, Leu, Pro, or Thr for the amino acid of position 334;
Asp, Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Arg, Ser, Val, Trp, or Tyr for the amino acid of position 335;
Glu, Lys, or Tyr for the amino acid of position 336;
Glu, His, or Asn for the amino acid of position 337;
Asp, Phe, Gly, Ile, Lys, Met, Asn, Gln, Arg, Ser, or Thr for the amino acid of position 339;
Ala or Val for the amino acid of position 376;

Gly or Lys for the amino acid of position 377;
Asp for the amino acid of position 378;
Asn for the amino acid of position 379;
Ala, Asn, or Ser for the amino acid of position 380;
Ala or Ile for the amino acid of position 382;
Glu for the amino acid of position 385;
Thr for the amino acid of position 392;
Leu for the amino acid of position 396;
Lys for the amino acid of position 421;
Asn for the amino acid of position 427;
Phe or Leu for the amino acid of position 428;
Met for the amino acid of position 429;
Trp for the amino acid of position 434;
Ile for the amino acid of position 436; and
Gly, His, Ile, Leu, or Tyr for the amino acid of position 440;
as indicated by EU numbering.

18. The use of any one of claims 1 to 14, wherein the Fc region has a higher binding activity toward an inhibitory Fcγ receptor than toward an activating Fcγ receptor.

19. The use of claim 18, wherein the inhibitory Fcγ receptor is human FcγRIIb.

20. The use of claim 18 or 19, wherein the activating Fcγ receptor is human FcγRIa, human FcγRIIa (R), human FcγRIIa (H), human FcγRIIIa (V), or human FcγRIIIa (F).

21. The use of any one of claims 18 to 20, wherein the amino acid at position 238 or 328 (EU numbering) in the Fc region is different from the amino acid in the native human IgG Fc region.

22. The use of claim 21, wherein the amino acid at position 238 of the Fc region is Asp or the amino acid of position 328 of the Fc region is Glu as indicated by EU numbering.

23. The use of claim 21 or 22, wherein the amino acid sequence of the Fc region comprises at least one or more amino acids selected from the group consisting of:
Asp for the amino acid of position 233;
Trp or Tyr for the amino acid of position 234;
Ala, Asp, Glu, Leu, Met, Phe, Trp, or Tyr for the amino acid of position 237;

Asp for the amino acid of position 239;
Ala, Gln, or Val for the amino acid of position 267;
Asn, Asp, or Glu for the amino acid of position 268;
Gly for the amino acid of position 271;
Ala, Asn, Asp, Gln, Glu, Leu, Met, Ser, or Thr for the amino acid of position 326;
Arg, Lys, or Met for the amino acid of position 330;
Ile, Leu, or Met for the amino acid of position 323; and
Asp for the amino acid of position 296;
as indicated by EU numbering.