Claims

1. A polypeptide complex which comprises:
(1) a cancer antigen-binding domain, wherein said antigen is not CD3;
(2) any one of the Fc domains of SEQ ID NOs: 23, 24, 25, and 26 in which an amino acid(s) forming the Fc domain is mutated, wherein the Fc domain mutant has reduced Fcγ receptor-binding activity by said mutation as compared with control polypeptide complex comprising the Fc domain of the same isotype selected from SEQ ID NO: 23, 24, 25, and 26, and wherein the Fc domain mutant has reduced binding activity to human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and/or FcγRIIIB; and
(3) a CD3-binding domain, wherein the polypeptide complex is any one selected from the group consisting of:
(i) the polypeptide complex which comprises two cancer antigen-binding domains having an F(ab')2 structure, one CD3-binding domain which is a monovalent Fab, Fv, or scFv, and two polypeptides forming the Fc domain, wherein the cancer antigen-binding domains are individually linked to either of the two polypeptides, and wherein the CD3-binding domain is linked to either or both of two CH3 domains of the two polypeptides via either or both of heavy-chain and light-chain Fv fragments forming the CD3 binding domain;
(ii) the polypeptide complex which comprises two cancer antigen-binding domains having an F(ab')2 structure, one CD3-binding domain which is a monovalent Fab, Fv, or scFv, and two polypeptides forming the Fc domain, wherein the cancer antigen-binding domains are individually linked to either of the two polypeptides, and wherein the CD3-binding domain is linked to either or both of the two cancer antigen-binding domains via a heavy-chain or light-chain Fv fragment forming the CD3 binding domain; and
(iii) the polypeptide complex which comprises one cancer antigen-binding domain which is a monovalent Fab, one CD3-binding domain which is a monovalent Fab, and two polypeptides forming the Fc domain, wherein a heavy chain Fv fragment forming the cancer antigen-binding domain is linked to one of the polypeptides via a CH1 domain forming the antigen-binding domain and a light chain Fv fragment forming the cancer antigen-binding domain is linked to a CL domain; and a heavy chain Fv fragment forming the CD3 binding domain is linked to the other polypeptide via a CH1 domain forming the CD3-binding domain and a light chain Fv fragment forming the CD3-binding domain is linked to a CL domain.

2. The polypeptide complex of claim 1 (iii),
wherein electric charges of the CH1 and CL domains are controlled so that the heavy chain Fv fragment of the cancer antigen-binding domain assembles with the light chain Fv fragment of the cancer antigen-binding domain, or the heavy chain Fv fragment of the CD3-binding domain assembles with the light chain Fv fragment of the CD3-binding domain.

3. The polypeptide complex of claim 2, wherein the amino acid residues in the CH1 and CL domains are one, two, or more combinations of amino acid residues selected from the group consisting of the combinations of:
(a) the amino acid residue at position 147 (EU numbering) in the CH1 domain, and the amino acid residue at position 180 (EU numbering) in the CL domain;
(b) the amino acid residue at position 147 (EU numbering) in the CH1 domain, and the amino acid residue at position 131 (EU numbering) in the CL domain;
(c) the amino acid residue at position 147 (EU numbering) in the CH1 domain, and the amino acid residue at position 164 (EU numbering) in the CL domain;
(d) the amino acid residue at position 147 (EU numbering) in the CH1 domain, and the amino acid residue at position 138 (EU numbering) in the CL domain;
(e) the amino acid residue at position 147 (EU numbering) in the CH1 domain, and the amino acid residue at position 123 (EU numbering) in the CL domain; and
(f) the amino acid residue at position 175 (EU numbering) in the CH1 domain, and the amino acid residue at position 160 (EU numbering) in the CL domain; or
(g) optionally comprising the amino acid residue at position 213 (EU numbering) in the CH1 domain, and the amino acid residue at position 123 (EU numbering) in the CL domain of any one, two or more combinations of (a) to (f),
and in which the amino acid residue in the CH1 domain has an electric charge opposite to that of the amino acid residue in the CL domain,
and wherein the amino acid residue having an opposite electric charge is selected from an amino acid residue in either group:
(X) glutamic acid (E) and aspartic acid (D); or
(Y) lysine (K), arginine (R), and histidine (H);
particularly
i) wherein the amino acid residues having an opposite electric charge are:
Lys at position 175 (EU numbering) in the CH1 domain, and Glu at positions 131, 160, and

180 (EU numbering) in the CL domain;
or,
ii) wherein the amino acid residues having an opposite electric charge are:
Glu at positions 147 and 175 (EU numbering) in the CH1 domain, and Lys at positions 131, 160, and 180 (EU numbering) in the CL domain, especially
wherein the amino acid residue at position 213 (EU numbering) in the CH1 domain is Glu, and the amino acid residue of position 123 (EU numbering) in the CL domain is Lys.

4. The polypeptide complex of any one of claims 1 to 3, wherein the Fc domain comprises any one of the amino acids below:
the amino acid sequence of positions 118 to 260 (EU numbering) is the sequence described in SEQ ID NO: 24; or
the amino acid sequence at positions 261 to 447 (EU numbering) is the sequence described in SEQ ID NO: 26.

5. The polypeptide complex of any one of claims 1 to 4, wherein the Fc domain comprises a mutation in the amino acids of the Fc domain of SEQ ID NO: 23 at any one of the following positions:
220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

6. The polypeptide complex of claim 5,
i) wherein the Fc domain is an Fc domain comprising a substitution of the amino acid at position 233, 234, 235, 236, 237, 327, 330, or 331 (EU numbering) by the amino acid at a corresponding position (EU numbering) in the corresponding IgG2 or IgG4;
or
ii) wherein the Fc domain comprises an amino acid mutation at position 234, 235, or 297 (EU numbering) and the amino acid(s) at position(s) 234, 235, and/or 297 is substituted with alanine.

7. The polypeptide complex of any one of claims 4 to 6,
i) wherein the sequences of the two polypeptides are different from each other and
wherein the amino acid at position 349 is substituted with cysteine and the amino acid at position 366 (EU numbering) is substituted with tryptophan among the amino acid

residues of one of the two polypeptides; and wherein the amino acid at position 356 is substituted with cysteine, the amino acid at position 366 is substituted with serine, the amino acid at position 368 is substituted with alanine, and the amino acid at position 407 (EU numbering) is substituted with valine among the amino acid residues of the other polypeptide;

or

ii) wherein the sequences of the two polypeptides are different from each other and wherein the amino acid at position 356 (EU numbering) is substituted with lysine among the amino acid residues of one of the two polypeptides; the amino acid at position 439 (EU numbering) is substituted with glutamic acid in the other polypeptide; and the amino acid at position 435 (EU numbering) is substituted with arginine among the amino acid residues of either of the two polypeptides.

8. The polypeptide complex of claim 7, wherein the amino acids G and K are deleted from the carboxyl termini of the two polypeptides.

9. The polypeptide complex of any one of claims 1 to 8, wherein the Fc domain mutant has reduced binding activity to human FcγRs of FcγRI, FcγRIIIA, and FcγRIIIB.

10. The polypeptide complex of any one of claims 1 to 8, wherein the Fc domain mutant has reduced binding activity to all human FcγRs of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and FcγRIIIB.

11. The polypeptide complex of any one of claims 1 to 10, wherein the Fc domain mutant has any one of the Fc domains of SEQ ID NOs: 23, 24, 25, and 26 in which an amino acid(s) forming the Fc domain is substituted.

12. The polypeptide complex of claim 1, wherein said mutation of the Fc domain comprises a mutation in the amino acids of the Fc domain of any one of SEQ ID NO: 23, 24, 25 or 26 at any one of the following positions:
220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

13. The polypeptide complex of claim 12, wherein said mutation of the Fc domain comprises a mutation in the amino acids of the Fc domain of SEQ ID NO: 23 at any one of the following positions:
220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

14. The polypeptide complex of claim 13, wherein the Fc domain is an Fc domain comprising a substitution of the amino acid at position 233, 234, 235, 236, 237, 327, 330, or 331 (EU numbering) by the amino acid at a corresponding position (EU numbering) in the corresponding IgG2 or IgG4.

15. The polypeptide complex of claim 13, wherein the Fc domain comprises an amino acid mutation at position 234, 235, or 297 (EU numbering) and the amino acid(s) at position(s) 234, 235, and/or 297 is substituted with alanine.

16. The polypeptide complex of claim 1, wherein the Fc domain mutant has reduced binding activity to all human FcγRs of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and FcγRIIIB.

17. The polypeptide complex of claim 1 or 15, wherein the sequences of two polypeptides forming the Fc region mutant are different from each other.

18. The polypeptide complex of any of claims 1, 12 and 16, wherein said mutation of the Fc domain of any one of SEQ ID NO: 23, 24, 25 or 26 is selected from the following:
substitution at any one of the following positions:
220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

19. The polypeptide complex of claim 18, wherein said mutation of the Fc domain is selected from the following:
substitution at any one of the following positions: 220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

20. The polypeptide complex of claim 18, wherein said mutation of the Fc domain is selected from the following:

substitution at any one of the following positions:
220, 226, 229, 231, 232, 233,235, 237, 238, 240, 264, 266, 267, 269, 270, 295, 300, 325, 327, 329, 330, and 331 (EU numbering).

21. The polypeptide complex of claim 18, wherein said mutation is present at the two polypeptides forming the Fc domain.

22. The polypeptide complex of claim 18, wherein the substitution is D265A.

23. A polypeptide complex which comprises:

(1) a cancer antigen-binding domain, wherein said antigen is not CD3;

(2) the Fc domain of SEQ ID NO: 24 in which an amino acid(s) forming the Fc domain is mutated, wherein the Fc domain mutant has reduced Fcγ receptor-binding activity by said mutation as compared with control polypeptide complex comprising the Fc domain of the same isotype of SEQ ID NO: 24, and wherein the Fc domain mutant has reduced binding activity to human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and/or FcγRIIIB; and

(3) a CD3-binding domain, wherein the polypeptide complex is the polypeptide complex which comprises one cancer antigen-binding domain which is a monovalent Fab, one CD3-binding domain which is a monovalent Fab, and two polypeptides forming the Fc domain, wherein a heavy chain Fv fragment forming the cancer antigen-binding domain is linked to one of the polypeptides via a CH1 domain forming the antigen-binding domain and a light chain Fv fragment forming the cancer antigen-binding domain is linked to a CL domain; and a heavy chain Fv fragment forming the CD3 binding domain is linked to the other polypeptide via a CH1 domain forming the CD3-binding domain and a light chain Fv fragment forming the CD3-binding domain is linked to a CL domain, and

wherein said mutation reducing the Fcγ receptor-binding activity by the Fc domain is selected from the following:

substitution at any one of the following positions:

220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

24. The polypeptide complex of claim 23, wherein the Fc domain mutant has reduced binding activity to all human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and FcγRIIIB.

25. The polypeptide complex of claim 23 or 24, wherein said mutation reducing the Fcγ receptor-

binding activity by the Fc domain is selected from any one of the following:

A330S, P331S, or D265A.

26. The polypeptide complex of claim 23 or 24, wherein the substitution is D265A.

27. The polypeptide complex of claim 23, wherein said mutation is present at the two polypeptides forming the Fc domain.

28. A polypeptide complex which comprises:

(1) a cancer antigen-binding domain, wherein said antigen is not CD3;

(2) the Fc domain of SEQ ID NO: 23 in which an amino acid(s) forming the Fc domain is mutated, wherein the Fc domain mutant has reduced Fcγ receptor-binding activity by said mutation as compared with control polypeptide complex comprising the Fc domain of the same isotype of SEQ ID NO: 23, and wherein the Fc domain mutant has reduced binding activity to human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and/or FcγRIIIB; and

(3) a CD3-binding domain, wherein the polypeptide complex is the polypeptide complex which comprises one cancer antigen-binding domain which is a monovalent Fab, one CD3-binding domain which is a monovalent Fab, and two polypeptides forming the Fc domain, wherein a heavy chain Fv fragment forming the cancer antigen-binding domain is linked to one of the polypeptides via a CH1 domain forming the antigen-binding domain and a light chain Fv fragment forming the cancer antigen-binding domain is linked to a CL domain; and a heavy chain Fv fragment forming the CD3 binding domain is linked to the other polypeptide via a CH1 domain forming the CD3-binding domain and a light chain Fv fragment forming the CD3-binding domain is linked to a CL domain, and

wherein said mutation reducing the Fcγ receptor-binding activity by the Fc domain is selected from the following:

substitution at any one of the following positions:

220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

29. The polypeptide complex of claim 28, wherein the Fc domain mutant has reduced binding activity to all human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and FcγRIIIB.

30. The polypeptide complex of claim 28 or 29, wherein said mutation reducing the Fcγ receptor-binding activity by the Fc domain is selected from any one of the following:

L234F, L235E, P331S, or D265A.

31. The polypeptide complex of claim 28 or 29, wherein the substitution is D265A.

32. The polypeptide complex of claim 28, wherein said mutation is present at the two polypeptides forming the Fc domain.

33. A polypeptide complex which comprises:

(1) a cancer antigen-binding domain, wherein said antigen is not CD3;

(2) the Fc domain of SEQ ID NO: 26 in which an amino acid(s) forming the Fc domain is mutated, wherein the Fc domain mutant has reduced Fcγ receptor-binding activity by said mutation as compared with control polypeptide complex comprising the Fc domain of the same isotype of SEQ ID NO: 26, and wherein the Fc domain mutant has reduced binding activity to human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and/or FcγRIIIB; and

(3) a CD3-binding domain, wherein the polypeptide complex is the polypeptide complex which comprises one cancer antigen-binding domain which is a monovalent Fab, one CD3-binding domain which is a monovalent Fab, and two polypeptides forming the Fc domain, wherein a heavy chain Fv fragment forming the cancer antigen-binding domain is linked to one of the polypeptides via a CH1 domain forming the antigen-binding domain and a light chain Fv fragment forming the cancer antigen-binding domain is linked to a CL domain; and a heavy chain Fv fragment forming the CD3 binding domain is linked to the other polypeptide via a CH1 domain forming the CD3-binding domain and a light chain Fv fragment forming the CD3-binding domain is linked to a CL domain, and

wherein said mutation reducing the Fcγ receptor-binding activity by the Fc domain is selected from the following:

mutation at any one of the following positions:

220, 226, 229, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 264, 265, 266, 267, 269, 270, 295, 296, 297, 298, 299, 300, 325, 327, 328, 329, 330, 331, and 332 (EU numbering).

34. The polypeptide complex of claim 33, wherein the Fc domain mutant has reduced binding activity to all human FcγR(s) of FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, and FcγRIIIB.

35. The polypeptide complex of claim 33 or 34, wherein said mutation reducing the Fcγ receptor-

binding activity by the Fc domain is a substitution of any one of the following:

L235A, G237A, L235E, or F234A.

36. The polypeptide complex of claims 33 or 34, wherein said mutation reducing the Fcγ receptor-binding activity by the Fc domain are the following substitutions:

F234A and L235A.

37. The polypeptide complex of claim 33, wherein said mutation is present at the two polypeptides forming the Fc domain.

38~~12~~. A polynucleotide encoding the polypeptide complex of any one of claims 1 to 37~~11~~.

39~~13~~. A vector comprising the polynucleotide of claim 38~~12~~.

40~~14~~. A cell comprising the vector of claim 39~~13~~.

41~~15~~. A method for producing a polypeptide complex, which comprises culturing the cell of claim 40~~14~~ and isolating the polypeptide complex from the culture supernatant.

42~~16~~. A therapeutic agent for cancer, which comprises as an active ingredient the polypeptide complex of any one of claims 1 to 37~~11~~.