cancer.

[69] A polypeptide complex which comprises:

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

(2) a domain comprising an Fc region that has reduced Fcγ receptor-binding activity; and

(3) a CD3-binding domain.

[70] A polynucleotide encoding the polypeptide complex as described herein, a vector comprising the said polynucleotide, or a cell comprising the said vector.

[71] A method for producing a polypeptide complex, which comprises culturing the cell as described herein and isolating the polypeptide complex from the culture supernatant.

[72] A therapeutic agent for cancer, which comprises as an active ingredient the polypeptide complex as described herein.

The present invention also relates to kits for use in a method of the present invention, which contain a polypeptide complex of the present invention or a polypeptide complex produced by a method of the present invention. The present invention also relates to use of a polypeptide complex of the present invention or a polypeptide complex produced by a method of the present invention in producing a therapeutic agent for inducing cellular cytotoxicity. The present invention also relates to polypeptide complexes of the present invention or polypeptide complexes produced by methods of the present invention for use in a method of the present invention.

[Effects of the Invention]

The present invention provides novel polypeptide complexes that retain the strong anti-tumor activity of BiTE and have a long half-life in blood, as well as excellent safety properties that result in no induction of cancer antigen-independent cytokine storm or such. When the antigen-binding domain of a polypeptide complex of the present invention is substituted, therapeutic agents that comprise the polypeptide complex as an active ingredient for inducing cellular cytotoxicity can target and damage various cells including cancer cells. Thus, various cancers can be treated or prevented. This allows desirable treatments that are highly safe and convenient, and reduce the physical burden for patients.

Brief Description of the Drawings

Fig. 1 is a graph showing comparison of the cytotoxic activities of GPC3 ERY1 (GPC3 BiTE), GPC3 ERY2, and an IgG-type anti-GPC3 antibody. Closed square (■), closed triangle (▲), and open square (□) represent the cytotoxic activities of GPC3 ERY1 (GPC3 BiTE), GPC3 ERY2, the IgG-type anti-GPC3 antibody, respectively.

Fig. 2 is a graph showing comparison of the cytotoxic activities of GPC3 BiTE and GPC3 ERY5. Closed square (■) and open circle (○) represent the cytotoxic activities of GPC3 BiTE and GPC3 ERY5, respectively.

Fig. 3 is a graph showing comparison of the cytotoxic activities of GPC3 BiTE and GPC3 ERY6. Closed square (■) and closed triangle (▲) represent the cytotoxic activities of GPC3 BiTE and GPC3 ERY6, respectively.

Fig. 4 is a graph showing comparison of the cytotoxic activities of GPC3 BiTE and GPC3 ERY7. Closed square (■) and closed diamond (♦) represent the cytotoxic activities of GPC3 BiTE and

CLAIMS

1. A polypeptide complex which comprises:
(1) an antigen-binding domain, wherein said antigen is not CD3;
(2) a domain comprising an Fc region that has reduced Fcγ receptor-binding activity; and
(3) a CD3-binding domain.

2. The polypeptide complex of claim 1, wherein the antigen-binding domain and CD3-binding domain are each a monovalent Fab.

3. The polypeptide complex of claim 2, in which the heavy chain Fv fragment of a monovalent Fab forming the antigen-binding domain is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the heavy chain Fv fragment of Fab forming the CD3-binding domain is linked to the other polypeptide forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain.

4. The polypeptide complex of claim 2 comprising:
(1) an antigen-binding domain in which the heavy chain Fv fragment of a monovalent Fab structure that binds to an antigen is linked *via* a CH1 domain to one of the polypeptides forming the Fc domain, and the light chain Fv fragment of the Fab structure is linked to a CL domain; and
(2) a CD3-binding domain in which the heavy chain Fv fragment of a monovalent Fab structure that binds to a CD3 is linked *via* a CH1 domain to the other polypeptide forming the Fc domain, and the light chain Fv fragment of the Fab structure is linked to a CL domain;
wherein electric charges of the CH1 and CL domains are controlled so that the heavy chain Fv fragment of the antigen-binding domain assembles with the light chain Fv fragment of the 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.

5. The polypeptide complex of claim 4, wherein
(i) an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the CD3-binding domain has the same type of electric charge as an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain; and wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the CD3-binding domain has an electric charge opposite to that of an amino acid residue in the

CL domain linked to the light chain Fv fragment of the CD3-binding domain;
(ii) an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has the same type of electric charge as an amino acid residue in the CL domain linked to the light chain Fv fragment of the CD3-binding domain; and wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has an electric charge opposite to that of an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain; or
(iii) an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the CD3-binding domain has the same type of electric charge as an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain, and an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has the same type of electric charge as an amino acid in the CL domain linked to the light chain Fv fragment of the CD3-binding domain; and wherein the amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the CD3-binding domain has an electric charge opposite to that of an amino acid residue in the CL domain linked to the light chain Fv fragment of the CD3-binding domain; and wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has an electric charge opposite to that of an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain.

6. The polypeptide complex of claim 5, 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.

7. The polypeptide complex of any one of claims 1 to 6, wherein the Fc domain is 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 and exhibits impaired Fcγ receptor-binding activity to FcγI, FcγIIA, FcγIIB, FcγIIIA, and/or FcγIIIB.

8. The polypeptide complex of claim 7, 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 of SEQ ID NO: 24; or

the amino acid sequence at positions 261 to 447 (EU numbering) is the sequence of SEQ ID NO: 26.

9. The polypeptide complex of claim 7, wherein the Fc domain comprises a mutation in the amino acids of SEQ ID NO: 23 forming the Fc domain and wherein the amino acids forming the Fc domain comprises a 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).

10. The polypeptide complex of claim 9,
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.

11. The polypeptide complex of any one of claims 8 to 10,
i) wherein the sequences of two polypeptides forming the Fc domain 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 forming the Fc domain; 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 two polypeptides forming the Fc domain 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 forming the Fc domain; 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.

12. The polypeptide complex of claim 11, wherein the sequence GK is deleted from the carboxyl termini of two polypeptides forming the Fc domain.

13. A polynucleotide encoding the polypeptide complex of any one of claims 1 to 12, a vector comprising the said polynucleotide, or a cell comprising the said vector.

14. A method for producing a polypeptide complex, which comprises culturing the cell of claim 13 and isolating the polypeptide complex from the culture supernatant.

15. A therapeutic agent for cancer, which comprises as an active ingredient the polypeptide complex of any one of claims 1 to 12.

CLAIMS

1. A polypeptide complex which comprises:
(1) an antigen-binding domain;
(2) a domain comprising an Fc region that has reduced Fcγ receptor-binding activity; and
(3) a T cell receptor complex-binding domain.

2. The polypeptide complex of claim 1, wherein the T cell receptor complex-binding domain is a T cell receptor-binding domain.

3. The polypeptide complex of claim 1, wherein the T cell receptor complex-binding domain is a CD3-binding domain.

4. The polypeptide complex of any one of claims 1 to 3, wherein the antigen-binding domain is a bivalent antigen-binding domain.

5. The polypeptide complex of claim 4, wherein the bivalent antigen-binding domain is a domain having an F(ab')2 structure.

6. The polypeptide complex of claim 5, in which two polypeptides forming a heavy chain constant region of the domain having the F(ab')2 structure are individually linked to either of the two polypeptides forming an Fc domain.

7. The polypeptide complex of claim 6, in which a CD3-binding domain is linked to either or both of the two CH3s forming the Fc domain.

8. The polypeptide complex of claim 7, in which a heavy chain Fv fragment forming the CD3-binding domain is linked to one of the CH3s forming the Fc domain and a light chain Fv fragment forming the CD3-binding domain is linked to the other CH3 forming the Fc domain.

9. The polypeptide complex of claim 8, in which an antibody CH1 domain is linked to the heavy chain Fv fragment forming the CD3-binding domain and an antibody CL domain is linked to the light chain Fv fragment.

10. The polypeptide complex of claim 6, in which the CD3-binding domain is linked to either or both of the two CLs forming the F(ab')2.

11. The polypeptide complex of claim 6, in which the CD3-binding domain is linked to either or both of the two VHs forming the F(ab')2.

12. The polypeptide complex of claim 6, in which the CD3-binding domain is linked to either or both of the two VLs forming the F(ab')2.

13. The polypeptide complex of any one of claims 1 to 12, wherein the CD3-binding domain is Fv.

14. The polypeptide complex of any one of claims 1 to 7 and 10 to 12, wherein the CD3-binding domain is Fab.

15. The polypeptide complex of any one of claims 1 to 7 and 10 to 12, wherein the CD3-binding domain is scFv.

16. The polypeptide complex of any one of claims 1 to 15, wherein the CD3-binding domain is monovalent.

17. The polypeptide complex of any one of claims 1 to 3, wherein the antigen-binding domain is a monovalent scFv and a monovalent Fab.

18. The polypeptide complex of claim 17, in which the monovalent scFv is linked to one of the polypeptides forming the Fc domain *via* the scFv that forms the CD3-binding domain; the heavy chain Fv fragment of the monovalent Fab is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain; and the light chain Fv fragment of the Fab is linked to the CL domain.

19. The polypeptide complex of any one of claims 1 to 3, wherein the antigen-binding domain is a bivalent scFv.

20. The polypeptide complex of claim 19, in which one monovalent scFv is linked to one of the polypeptides forming the Fc domain *via* the heavy chain Fv fragment forming the CD3-binding domain, and the other monovalent scFv is linked to the other polypeptide forming the Fc domain *via* the light chain Fv fragment forming the CD3-binding domain.

21. The polypeptide complex of claim 19, wherein one monovalent scFv is linked to one of the

polypeptides forming the Fc domain *via* the scFv forming the CD3-binding domain, and the other monovalent scFv is linked to the other polypeptide forming the Fc domain.

22. The polypeptide complex of any one of claims 1 to 3, wherein the antigen-binding domain and T cell receptor complex-binding domain are each a monovalent Fab.

23. The polypeptide complex of claim 22, in which the heavy chain Fv fragment of a monovalent Fab forming the antigen-binding domain is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the heavy chain Fv fragment of Fab forming the T cell receptor-binding domain is linked to the other polypeptide forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain.

24. The polypeptide complex of claim 22, in which the heavy chain Fv fragment of a monovalent Fab forming the antigen-binding domain is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the light chain Fv fragment of Fab forming the T cell receptor-binding domain is linked to the other polypeptide forming the Fc domain *via* a CH1 domain and the heavy chain Fv fragment of the Fab is linked to a CL domain.

25. The polypeptide complex of claim 22, in which the heavy chain Fv fragment of a monovalent Fab forming the antigen-binding domain is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the heavy chain Fv fragment of the Fab forming the T cell receptor-binding domain is linked to the other polypeptide forming the Fc domain *via* a CL domain and the light chain Fv fragment of the Fab is linked to a CH1 domain.

26. The polypeptide complex of claim 22, in which the heavy chain Fv fragment of a monovalent Fab forming the T cell receptor-binding domain is linked to one of the polypeptides forming the Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the light chain Fv fragment of Fab forming the antigen-binding domain is linked to the other polypeptide forming the Fc domain *via* a CH1 domain and the heavy chain Fv fragment of the Fab is linked to a CL domain.

27. The polypeptide complex of claim 22, in which the heavy chain Fv fragment of a monovalent Fab forming the T cell receptor-binding domain is linked to one of the polypeptide forming the

Fc domain *via* a CH1 domain and the light chain Fv fragment of the Fab is linked to a CL domain; and the heavy chain Fv fragment of the Fab forming the antigen-binding domain to the other polypeptide forming the Fc domain *via* a CL domain and the light chain Fv fragment of the Fab is linked to a CH1 domain.

28. The polypeptide complex of claim 22 comprising:
(1) an antigen-binding domain in which the heavy chain Fv fragment of a monovalent Fab structure that binds to an antigen is linked *via* a CH1 domain to one of the polypeptides forming the Fc domain, and the light chain Fv fragment of the Fab structure is linked to a CL domain; and
(2) a T cell receptor complex-binding domain in which the heavy chain Fv fragment of a monovalent Fab structure that binds to a T cell receptor complex is linked *via* a CH1 domain to the other polypeptide forming the Fc domain, and the light chain Fv fragment of the Fab structure is linked to a CL domain;
wherein electric charges of the CH1 and CL domains are controlled so that the heavy chain Fv fragment of the antigen-binding domain assembles with the light chain Fv fragment of the antigen-binding domain, or the heavy chain Fv fragment of the T cell receptor-binding domain assembles with the light chain Fv fragment of the T cell receptor-binding domain.

29. The polypeptide complex of claim 28, wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the T cell receptor complex-binding domain has the same type of electric charge as an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain.

30. The polypeptide complex of claim 28, wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has the same type of electric charge as an amino acid residue in the CL domain linked to the light chain Fv fragment of the T cell receptor complex-binding domain.

31. The polypeptide complex of claim 28, wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the T cell receptor complex-binding domain has the same type of electric charge as an amino acid in the CL domain linked to the light chain Fv fragment of the antigen-binding domain, and an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has the same type of electric charge as an amino acid in the CL domain linked to the light chain Fv fragment of the T cell receptor complex-binding domain.

32. The polypeptide complex of claim 29 or 31, wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the T cell receptor complex-binding domain has an electric charge opposite to that of an amino acid residue in the CL domain linked to the light chain Fv fragment of the T cell receptor-binding domain.

33. The polypeptide complex of claim 30 or 31, wherein an amino acid residue in the CH1 domain linked to the heavy chain Fv fragment of the antigen-binding domain has an electric charge opposite to that of an amino acid residue in the CL domain linked to the light chain Fv fragment of the antigen-binding domain.

34. The polypeptide complex of any one of claims 22 to 33, wherein the T cell receptor complex-binding domain is a T cell receptor-binding domain.

35. The polypeptide complex of claim 34, wherein the T cell receptor-binding domain is a CD3-binding domain.

36. The polypeptide complex of claim 32 or 33, 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;
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.

37. The polypeptide complex of claim 36, wherein the amino acid residues are selected from the

group additionally comprising the combination of amino acid residues:
(g) 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.

38. The polypeptide complex of claim 36 or 37, 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).

39. The polypeptide complex of any one of claims 36 to 38, 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.

40. The polypeptide complex of any one of claims 36 to 38, 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.

41. The polypeptide complex of claim 40, 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.

42. The polypeptide complex of any one of claims 1 to 41, wherein the Fc domain exhibits impaired Fcγ receptor-binding activity to FcγI, FcγIIA, FcγIIB, FcγIIIA, and/or FcγIIIB.

43. The polypeptide complex of any one of claims 1 to 42, wherein the Fc domain is 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.

44. The polypeptide complex of claim 43, 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 of SEQ ID NO: 24; or
the amino acid sequence at positions 261 to 447 (EU numbering) is the sequence of SEQ ID NO: 26.

45. The polypeptide complex of claim 43, wherein the amino acids forming the Fc domain comprises a 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).

46. The polypeptide complex of claim 45, wherein the Fc domain comprises a mutation in the amino acids of SEQ ID NO: 23 forming the Fc domain.

47. The polypeptide complex of claim 46, 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.

48. The polypeptide complex of claim 46, wherein the Fc domain comprises an amino acid mutation at position 234, 235, or 297 (EU numbering).

49. The polypeptide complex of claim 48, in which the amino acid(s) at position 234, 235, and/or 297 is substituted with alanine.

50. The polypeptide complex of any one of claims 43 to 49, wherein the sequences of two polypeptides forming the Fc domain are different from each other.

51. The polypeptide complex of any one of claims 1 to 50, 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 forming the Fc domain; 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.

52. The polypeptide complex of any one of claims 1 to 50, wherein the amino acid at position 356 (EU numbering) is substituted with lysine among the amino acid residues of one of the two polypeptides forming the Fc domain; 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.

53. The polypeptide complex of claim 51 or 52, wherein the sequence GK is deleted from the carboxyl termini of two polypeptides forming the Fc domain.

54. The polypeptide complex of any one of claims 1 to 53, wherein the antigen-binding domains bind to the same epitope.

55. The polypeptide complex of claim 54, wherein the same epitope is present in a protein comprising the amino acid sequence of SEQ ID NO: 2.

56. The polypeptide complex of claim 54, wherein the same epitope is present in a protein comprising the amino acid sequence of SEQ ID NO: 4.

57. The polypeptide complex of any one of claims 1 to 53, wherein the antigen-binding domains each bind to a different epitope.

58. The polypeptide complex of claim 57, wherein the different epitope is present in a protein comprising the amino acid sequence of SEQ ID NO: 2.

59. The polypeptide complex of claim 57, wherein the different epitope is present in a protein comprising the amino acid sequence of SEQ ID NO: 4.

60. A polynucleotide encoding the polypeptide complex of any one of claims 1 to 59.

61. A vector comprising the polynucleotide of claim 60.

62. A cell comprising the vector of claim 61.

63. A method for producing a polypeptide complex, which comprises culturing the cell of claim 62 and isolating the polypeptide complex from the culture supernatant.

64. A therapeutic agent for inducing cellular cytotoxicity, which comprises as an active ingredient the polypeptide complex of any one of claims 1 to 59.

65. The therapeutic agent of claim 64, wherein the therapeutic agent for inducing cellular

cytotoxicity is a therapeutic agent for cancer.

66. The therapeutic agent of claim 65, wherein the cancer is liver cancer or lung cancer.

67. A method for treating or preventing cancer, in which the polypeptide complex of any one of claims 1 to 59 is administered to a patient in need thereof.

68. The therapeutic or preventive method of claim 67, wherein the cancer is liver cancer or lung cancer.