

members. DLL3 is necessary for normal somite formation and patterning. Mutations in DLL3 cause rib defects or spondylolysis in autosomal recessive spondylocostal dysostosis patients (NPLs 11 and 12). There exist previous studies reporting the amplification of the DLL3 gene on chromosome and increased expression of this gene in cancer cell lines (NPL 13) and increased DLL3 expression in some glioma cases (NPL 14). In addition, DLL3 has been proposed previously in methods to diagnose and treat glioma, in addition to SCLC, using an ADCC enhanced antibody, antibody-drug conjugate (ADC), and T cell-engaging bispecific molecule using BiTE-Fc format (PTLs 1, 2, and 3).

Citation List

Patent Literature

[0008]

[PTL 1] WO 2011/093097

[PTL 2] WO 2013/126746

[PTL 3] WO 2017/021349

Non Patent Literature

[0009]

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[NPL 2] Nature. 1985 Apr 18-24;314(6012):628-31.

[NPL 3] Int J Cancer. 1988 Apr 15;41(4):609-15.

[NPL 4] Proc Natl Acad Sci U S A. 1986 Mar;83(5):1453-7.

[NPL 5] Proc Natl Acad Sci U S A. 1995 Jul 18;92(15):7021-5.

[NPL 6] Drug Discov Today. 2005 Sep 15;10(18):1237-44.

[NPL 7] Int J Cancer. 2002 Aug 20;100(6):690-7.

[NPL 8] Cancer Immunol Immunother (2007) 56 (10), 1637-44

[NPL 9] Cancer Immunol Immunother. (2006) 55 (5), 503-14

[NPL 10] Cancer Immunol Immunother. (2009) 58 (1), 95-109

[NPL 11] Bulman, M. P. et al. (2000) Nat Genet 24, 438-441.

[NPL 12] Turnpenny, P. D. et al. (2003) J Med Genet 40, 333-339.

[NPL 13] Phillips, H. S. (2006) Cancer Cell 9, 157-173.

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Summary of Invention

The present disclosure provides aspects as disclosed in the claims.

Technical Problem

[0010]

An objective of the present ~~disclosure~~~~invention~~ is to provide multispecific antigen-binding molecules that enable cancer treatment by recruiting T cells close to DLL3-expressing cells and using the cytotoxicity of T cells against DLL3-expressing cancer cells, methods for producing the multispecific antigen-binding molecules, and therapeutic agents comprising such a multispecific antigen-binding molecule as an active ingredient for inducing cellular cytotoxicity. Another objective of the present ~~invention~~~~disclosure~~

is to provide pharmaceutical compositions for use in treating or preventing various cancers, which comprise one of the above-mentioned antigen-binding molecules as an active ingredient, and therapeutic methods using the pharmaceutical compositions.

Solution to Problem

[0011]

The present ~~disclosure~~invention relates to multispecific antigen-binding molecules that comprise a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time (i.e. capable of binding to CD3 and CD137 but not simultaneously); and a third antigen-binding moiety that is capable of binding to DLL3, preferably human DLL3, which induce T-cell dependent cytotoxicity more efficiently whilst circumventing adverse toxicity concerns or side effects that other multispecific antigen-binding molecules may have. The present ~~disclosure~~invention provides multispecific antigen-binding molecules and pharmaceutical compositions that can treat various cancers, especially those associated with DLL3 such as DLL3-positive tumors, by comprising the antigen-binding molecule as an active ingredient.

[0012]

In one ~~aspect~~example, the multispecific antigen-binding molecule of the present ~~disclosure~~invention have very unique structure format(s), which improve or enhance the efficacy of the multispecific antigen-binding molecules. The new antigen-binding molecules with unique structure formats provide the increased number of antigen-binding domains to give the increased valency and/or specificities to respective antigens on effector cells and target cells with the reduced unwanted adverse effects.

[0013]

In one particular ~~aspect~~example, the present ~~disclosure~~invention relates to multispecific antigen-binding molecules that comprise a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time (i.e. capable of binding to CD3 and CD137 but not simultaneously); and a third antigen-binding moiety that is capable of binding to DLL3, preferably human DLL3, which induce T-cell dependent cytotoxicity efficiently whilst circumventing adverse toxicity concerns or side effects which other multispecific antigen-binding molecules may have. In one such ~~aspect~~example, each of the first and second antigen-binding moieties comprises at least one amino acid mutation(s) e.g. cysteine insertion/substitution/mutation which create a disulfide linkage between the first and second antigen-binding moieties to hold them close to each other, and, for example, promote cis-antigen binding to antigen (CD3 and/or CD137) on the same single effector cell as a result of steric hindrance or shorter distance between the two Dual-Fabs, thereby improving the safety profile of the trispecific Ab by preventing undesirable crosslinking of two CD3/CD137-expressing immune cells mediated by the two Dual-Fabs in an DLL3-independent manner. In one specific ~~aspect~~example, said each of

the first antigen-binding moiety and the second antigen-binding moiety is a Fab and comprises at least one cysteine residue (via mutation, substitution, or insertion) in the CH1 region, said at least one cysteine residue is capable of forming at least one disulfide bond between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety. In another specific example aspect, said each of the first antigen-binding moiety and the second antigen-binding moiety comprises one cysteine residue (via mutation, substitution, or insertion) at position 191 according to EU numbering in the CH1 region which is capable of forming one disulfide bond between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety.

[0014]

The antigen-binding molecules having such unique structure formats were surprisingly found to show superior efficacy compared to other multispecific antibody formats (e.g. BiTE) while exhibiting reduced or minimal off-target side-effects attributed by undesired cross-linking among different cells (e.g., effector cells such as T cells).

[0015]

More specifically, the present disclosure provides the following:

[1] A multispecific antigen-binding molecule comprising:

a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time; and

a third antigen-binding moiety that is capable of binding to a third antigen, preferably an antigen expressed on a cancer cell/tissue.

[1A] A multispecific antigen-binding molecule comprising:

a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time; and

a third antigen-binding moiety that is capable of binding to DLL3, preferably human DLL3.

[2] The multispecific antigen-binding molecule of any one of [1] to [1A], wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising any one of (a1) to (a17) below:

(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 17, the heavy chain CDR 2 of SEQ ID NO: 31, the heavy chain CDR 3 of SEQ ID NO: 45, the light chain CDR 1 of SEQ ID NO: 64, the light chain CDR 2 of SEQ ID NO: 69 and the light chain CDR 3 of SEQ ID NO: 74;

(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 18, the heavy chain CDR 2 of SEQ ID NO: 32, the heavy chain CDR 3 of SEQ ID NO: 46, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO:

position of [18].

[25] The use of [23] or the method of [24], wherein said disease is cancer, preferably DLL3-positive cancer or DLL3-expressing cancer.

[25A] The use of or the method of [25], wherein the cancer is DLL3-expressing cancer or DLL3-positive cancer.

[25B] The use of or the method of [25A], wherein the cancer is lung cancer (including small cell lung cancer) or melanoma.

[26] A method for inducing lysis of a target cell, comprising contacting a target cell with the multispecific antigen binding molecule of any one of [1] to [13] or the pharmaceutical composition of [18] in the presence of a T cell.

[27] A kit comprising the composition of [18]; and a package insert comprising instructions for administering to a subject to treat or delay progression of cancer, preferably DLL3-positive cancer or DLL3-expressing cancer.

[27A] The kit of [27], wherein the cancer is lung cancer (including small cell lung cancer) and melanoma.

[0016]

Another aspect-example of the present invention-disclosure relates to:

[28] A multispecific antigen-binding molecule comprising:

an antigen-binding moiety which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time; and

an antigen-binding moiety that is capable of binding to DLL3, preferably human DLL3.

[29] The multispecific antigen-binding molecule of [28], wherein the antigen-binding moiety which is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time, comprises an antibody variable region comprising any one of (a1) to (a17) below:

(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 17, the heavy chain CDR 2 of SEQ ID NO: 31, the heavy chain CDR 3 of SEQ ID NO: 45, the light chain CDR 1 of SEQ ID NO: 64, the light chain CDR 2 of SEQ ID NO: 69 and the light chain CDR 3 of SEQ ID NO: 74;

(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 18, the heavy chain CDR 2 of SEQ ID NO: 32, the heavy chain CDR 3 of SEQ ID NO: 46, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;

(a3) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 19, the heavy chain CDR 2 of SEQ ID NO: 33, the heavy chain CDR 3 of SEQ ID NO: 47, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;

(a4) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO:

- (a8) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 9, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;
- (a9) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 10, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;
- (a10) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 11, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;
- (a11) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 12, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;
- (a12) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 12, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;
- (a13) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 13, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;
- (a14) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 14, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;
- (a15) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 81, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 60;
- (a16) an antibody variable region that binds to the same epitope of any of the antibody variable region selected from (a1) to (a15); and
- (a17) an antibody variable fragment that competes with the binding of any of the antibody variable fragment selected from (a1) to (a15).

[0017]

In yet another aspect-example of the present invention-disclosure relates to:

[31] A multispecific antigen-binding molecule comprising five polypeptide chains in any one of the combinations selected from (a1) to (a15) below:

- (a1) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 201 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 208 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 214 (chain 4 & chain 5);
- (a2) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 203 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206

(a10) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 222 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 230 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 214 (chain 4 & chain 5);

(a11) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 223 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 212 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 215 (chain 4 & chain 5);

(a12) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 225 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 213 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 215 (chain 4 & chain 5);

(a13) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 226 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 213 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 215 (chain 4 & chain 5);

(a14) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 227 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 213 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 215 (chain 4 & chain 5); and

(a15) a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 228 (chain 1), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising the amino acid sequence of SEQ ID NO: 231 (chain 3) and two polypeptide chains each comprising the amino acid sequence of SEQ ID NO: 215 (chain 4 & chain 5);

and wherein, preferably the five polypeptide chains (chain 1 to chain 5) connect and/or associate with each other according to the orientation shown in Figure 1(a).

[0018]

Yet another aspect-example of the present invention-disclosure relates to:

[32] An antigen binding molecule capable of binding to DLL3, which comprises an antibody variable region comprising any one of (a1) to (a5) below:

(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 233, the heavy chain CDR 2 of SEQ ID NO: 234, the heavy chain CDR 3 of SEQ ID NO: 235, the light chain CDR 1 of SEQ ID NO: 237, the light chain CDR 2 of SEQ ID

NO: 238 and the light chain CDR 3 of SEQ ID NO: 239;

(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 276, the heavy chain CDR 2 of SEQ ID NO: 277, the heavy chain CDR 3 of SEQ ID NO: 278, the light chain CDR 1 of SEQ ID NO: 279, the light chain CDR 2 of SEQ ID NO: 280 and the light chain CDR 3 of SEQ ID NO: 281;

(a3) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 285, the heavy chain CDR 2 of SEQ ID NO: 286, the heavy chain CDR 3 of SEQ ID NO: 287, the light chain CDR 1 of SEQ ID NO: 288, the light chain CDR 2 of SEQ ID NO: 289 and the light chain CDR 3 of SEQ ID NO: 290;

(a4) an antibody variable region that binds to the same epitope of any of the antibody variable region selected from (a1) to (a3); and

(a5) an antibody variable fragment that competes with the binding of any of the antibody variable fragment selected from (a1) to (a3).

[33] An antigen binding molecule capable of binding to DLL3, which comprises an antibody variable region comprising any one of (a1) to (a6) below:

(a1) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 232, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 236;

(a2) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 264, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 265;

(a3) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 266, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 267;

(a4) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 268, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 269;

(a5) an antibody variable region that binds to the same epitope of any of the antibody variable region selected from (a1) to (a4); and

(a6) an antibody variable fragment that competes with the binding of any of the antibody variable fragment selected from (a1) to (a4).

Yet another aspect-example of the present invention-disclosure relates to:

[2-1] A multispecific antigen-binding molecule that comprises:

(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which binds to human CD3 and comprises an antibody variable region that can be the same or different and is independently selected from the group consisting of:

(a1) an antibody variable region comprising heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 17, heavy chain CDR 2 of SEQ ID NO: 31, heavy

comprises a first and a second Fc region subunit, the first Fc-region subunit is selected from the group comprising:

a Fc region polypeptide comprising alanine at each of positions 234 and 235;
 a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297; and
 a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297,
 cysteine at position 354, and tryptophan at position 366; and

the second Fc-region subunit is selected from the group comprising:

a Fc region polypeptide comprising alanine at each of positions 234 and 235;
 a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297; and
 a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297,
 cysteine at position 349, serine at position 366, alanine at position 368, and valine at
 position 407,

wherein all positions are by EU numbering.

Yet another ~~aspect-example~~ of the present ~~invention-disclosure~~ relates to:

[3-1] A multispecific antigen-binding molecule that comprises:

(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which binds to human CD137 and comprises an antibody variable region that can be the same or different and is independently selected from the group consisting of:

(a1) an antibody variable region comprising heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 17, heavy chain CDR 2 of SEQ ID NO: 31, heavy chain CDR 3 of SEQ ID NO: 45, light chain CDR 1 of SEQ ID NO: 64, light chain CDR 2 of SEQ ID NO: 69 and light chain CDR 3 of SEQ ID NO: 74;

(a2) an antibody variable region comprising heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 18, heavy chain CDR 2 of SEQ ID NO: 32, heavy chain CDR 3 of SEQ ID NO: 46, light chain CDR 1 of SEQ ID NO: 63, light chain CDR 2 of SEQ ID NO: 68 and light chain CDR 3 of SEQ ID NO: 73;

(a3) an antibody variable region comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 19, the heavy chain CDR 2 of SEQ ID NO: 33, the heavy chain CDR 3 of SEQ ID NO: 47, light chain CDR 1 of SEQ ID NO: 63, light chain CDR 2 of SEQ ID NO: 68 and light chain CDR 3 of SEQ ID NO: 73;

(a4) an antibody variable region comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 19, the heavy chain CDR 2 of SEQ ID NO: 33, the heavy chain CDR 3 of SEQ ID NO: 47, light chain CDR 1 of SEQ ID NO: 65, light chain CDR 2 of SEQ ID NO: 70 and light chain CDR 3 of SEQ ID NO: 75;

(a5) an antibody variable region comprising the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 20, the heavy chain CDR 2 of SEQ ID NO: 34, the heavy chain CDR 3 of SEQ ID NO: 48, light chain CDR 1 of SEQ ID NO: 63, light chain CDR 2 of SEQ ID NO: 68 and light chain CDR 3 of SEQ ID NO: 73;

second and third antigen binding moieties is a Fab comprising a heavy chain comprising a VH and a CH1 domain and a light chain comprising a VL and a light chain constant (CL) domain, and wherein the C-terminus of the heavy chain of the third antigen binding moiety is fused, directly or via a peptide linker, to the N-terminus of the Fab heavy chain of either the first antigen binding moiety or the second antigen binding moiety.

[3-5] The multispecific antigen-binding molecule of [3-4], wherein the C-terminus of the heavy chain of the third antigen binding moiety is fused, via a peptide linker, to the N-terminus of the Fab heavy chain of either the first antigen binding moiety or the second antigen binding moiety, and wherein the peptide linker has an amino acid sequence selected from the group consisting of SEQ ID NO: 248, SEQ ID NO: 249, and SEQ ID NO: 259.

[3-6] The multispecific antigen-binding molecule of [3-5], wherein, in the CL domain of each of the first and second antigen binding moieties, the amino acids at positions 123 and 124 (Kabat numbering) are arginine and lysine, respectively; and wherein, in the CH1 domain of each of the first and second antigen binding moieties, the amino acid at each of positions 147 and 213 (EU numbering) is glutamic acid.

[3-7] The multispecific antigen-binding molecule of [3-6], further comprising an Fc domain.

[3-8] The multispecific antigen-binding molecule of [3-7], wherein the Fc domain comprises a first and a second Fc region subunit, the first Fc-region subunit is selected from the group comprising:

a Fc region polypeptide comprising alanine at each of positions 234 and 235;

a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297; and

a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297, cysteine at position 354, and tryptophan at position 366; and

the second Fc-region subunit is selected from the group comprising:

a Fc region polypeptide comprising alanine at each of positions 234 and 235;

a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297; and

a Fc region polypeptide comprising alanine at each of positions 234, 235, and 297, cysteine at position 349, serine at position 366, alanine at position 368, and valine at position 407,

wherein all positions are by EU numbering.

Yet another aspect-example of the present invention-disclosure relates to:

[4-1] A multispecific antigen-binding molecule that comprises:

(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which binds to human CD3 and comprises an antibody variable region that can be the same or different and is independently selected from the group consisting of (a1) to (a15):

Claims

[Claim 1] A multispecific antigen-binding molecule ~~that comprises~~comprising:
~~(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to human CD3 and human CD137, but does not bind to human CD3 and human CD137 at the same time~~ is a Fab molecule that binds to human CD3 and comprises an antibody variable region comprising any one of (a1) to (a2) below:

(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 20, the heavy chain CDR 2 of SEQ ID NO: 34, the heavy chain CDR 3 of SEQ ID NO: 48, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73; and

(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 28, the heavy chain CDR 2 of SEQ ID NO: 42, the heavy chain CDR 3 of SEQ ID NO: 56, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;

and

(b) a third antigen-binding moiety which binds to human DLL3 that binds to human Delta-like 3 (DLL3), which comprises an antibody variable region comprising a heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 233, a heavy chain CDR 2 of SEQ ID NO: 234, a heavy chain CDR 3 of SEQ ID NO: 235, a light chain CDR 1 of SEQ ID NO: 237, a light chain CDR 2 of SEQ ID NO: 238 and a light chain CDR 3 of SEQ ID NO: 239,

and

at least one disulfide bond formed between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety.

[Claim 2] The multispecific antigen-binding molecule of claim 1, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising any one of (a1) to (a15) below:

~~(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 17, the heavy chain CDR 2 of SEQ ID NO: 31, the heavy chain CDR 3 of SEQ ID NO: 45, the light chain CDR 1 of SEQ ID NO: 64, the light chain CDR 2 of SEQ ID NO: 69 and the light chain CDR 3 of SEQ ID NO: 74;~~

~~(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 18, the heavy chain CDR 2 of SEQ ID NO: 32, the heavy chain CDR 3 of SEQ ID NO: 46, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;~~

~~(a3) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 19, the heavy chain CDR 2 of SEQ ID NO: 33, the heavy chain CDR 3 of SEQ ID NO: 47, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;~~

~~(a4) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 19, the heavy chain CDR 2 of SEQ ID NO: 33, the heavy chain CDR 3 of SEQ ID NO: 47, the light chain CDR 1 of SEQ ID NO: 65, the light chain CDR 2 of SEQ ID NO: 70 and the light chain CDR 3 of SEQ ID NO: 75;~~

[Claim ~~32~~1] The multispecific antigen-binding molecule of ~~any one of claims 1 to 2~~claim 1, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising any one of (a1) to (~~a15~~a2) below:

~~(a1) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 3, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 59;~~

~~(a2) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a3) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a4) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 60;~~

~~(a5~~a1~~) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58; and~~

~~(a6) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 8, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a7) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 9, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a8) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 9, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;~~

~~(a9) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 10, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a10) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 11, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;~~

~~(a11) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 12, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 61;~~

~~(a12) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 12, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a13) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 13, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58;~~

~~(a~~2~~14) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 14, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58; and~~

~~(a15) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 81, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 60.~~

~~[Claim 4] The multispecific antigen-binding molecule of any one of claims 1 to 3, wherein each of the first antigen-binding moiety and the second antigen-binding moiety is a Fab molecule and comprises at least one disulfide bond formed between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety.~~

[Claim 53] The multispecific antigen-binding molecule of claim ~~41~~ or 2, ~~wherein each of the first antigen-binding moiety and the second antigen-binding moiety is a Fab molecule and wherein the at least one disulfide bond~~ comprises one disulfide bond formed between the amino acid residues at position 191 according to EU numbering in the respective CH1 region of the first antigen-binding moiety and the second antigen-binding moiety.

[Claim 64] The multispecific antigen-binding molecule of any one of claims 1 to 53, wherein ~~each of the first, second and the~~ third antigen binding moiety is a Fab molecule, wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain (CH1) to the N-terminus of the Fab heavy chain of either one of the first antigen binding moiety or the second antigen binding moiety, ~~optionally~~ via a peptide linker.

[Claim 75] The multispecific antigen-binding molecule of claim 64, wherein said peptide linker is selected from the group consisting of the amino acid sequence of SEQ ID NO: 248, SEQ ID NO: 249 or SEQ ID NO: 259.

[Claim 86] The multispecific antigen-binding molecule of ~~any one of claims 1 to 7~~ claim 5, wherein the third antigen binding moiety is a crossover Fab molecule in which the variable regions of the Fab light chain and the Fab heavy chain are exchanged, and wherein each of the first and second antigen binding moiety is a conventional Fab molecule.

[Claim 97] The multispecific antigen-binding molecule of claim 86, wherein in the constant domain CL of the light chain of each of the first and second antigen binding moiety, the amino acids at position 123 and 124 are arginine (R) and lysine (K) respectively (numbering according to Kabat), and wherein in the constant domain CH1 of the heavy chain of each of the first and second antigen binding moiety the amino acids at position 147 and 213 are glutamic acid (E) (numbering according to EU numbering).

[Claim 8] The multispecific antigen-binding molecule of any one of claims 1 to 7, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain CDR 1 comprising SEQ ID NO: 20, a heavy chain CDR 2 comprising SEQ ID NO: 34, a heavy chain CDR 3 comprising SEQ ID NO: 48, a light chain CDR 1 comprising SEQ ID NO: 63, a light chain CDR 2 comprising SEQ ID NO: 68, and a light chain CDR 3 comprising SEQ ID NO: 73.

[Claim 9] The multispecific antigen-binding molecule of claim 8, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

~~[Claim 10] The multispecific antigen-binding molecule of any one of claims 1 to 9, wherein the third antigen-binding moiety comprises an antibody variable region comprising a heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 233, a heavy chain CDR 2 of SEQ ID NO: 234, a heavy chain CDR 3 of SEQ ID NO: 235, a light chain CDR 1 of SEQ ID NO: 237, a light chain CDR 2 of SEQ ID NO: 238 and a light chain CDR 3 of SEQ ID NO: 239.~~

[Claim ~~11~~10] The multispecific antigen-binding molecule of any one of claims 1 to ~~10~~9, wherein the third antigen-binding moiety comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 232, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 236.

[Claim ~~12~~11] The multispecific antigen-binding molecule of any one of claims 1 to ~~11~~10, further comprises a Fc domain.

[Claim 12] A multispecific antigen-binding molecule that comprises:
(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which is a Fab molecule that binds to human CD137 and comprises an antibody variable region comprising any one of (a1) to (a2) below:
(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 20, the heavy chain CDR 2 of SEQ ID NO: 34, the heavy chain CDR 3 of SEQ ID NO: 48, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73; and
(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 28, the heavy chain CDR 2 of SEQ ID NO: 42, the heavy chain CDR 3 of SEQ ID NO: 56, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;
and
(b) a third antigen-binding moiety that binds to human Delta-like 3 (DLL3), which comprises an antibody variable region comprising a heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 233, a heavy chain CDR 2 of SEQ ID NO: 234, a heavy chain CDR 3 of SEQ ID NO: 235, a light chain CDR 1 of SEQ ID NO: 237, a light chain CDR 2 of SEQ ID NO: 238 and a light chain CDR 3 of SEQ ID NO: 239,
and
at least one disulfide bond formed between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety.

[Claim 13] The multispecific antigen-binding molecule of claim 12, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising any one of (a1) to (a2) below:
(a1) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58; and
(a2) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 14, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

[Claim 14] The multispecific antigen-binding molecule of claim 12 or 13, wherein the at least one disulfide bond comprises one disulfide bond formed between the amino acid residues at position 191 according to EU numbering in the respective CH1 region of the first antigen-binding moiety and the second antigen-binding moiety.

[Claim 15] The multispecific antigen-binding molecule of any one of claims 12 to 14, wherein the third antigen binding moiety is a Fab molecule, wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain (CH1) to the N-terminus of the Fab heavy chain of either one of the first antigen binding moiety or the second antigen binding moiety, via a peptide linker.

[Claim 16] The multispecific antigen-binding molecule of claim 15, wherein said peptide linker is selected from the group consisting of the amino acid sequence of SEQ ID NO: 248, SEQ ID NO: 249 or SEQ ID NO: 259.

[Claim 17] The multispecific antigen-binding molecule of claim 16, wherein the third antigen binding moiety is a crossover Fab molecule in which the variable regions of the Fab light chain and the Fab heavy chain are exchanged, and wherein each of the first and second antigen binding moiety is a conventional Fab molecule.

[Claim 18] The multispecific antigen-binding molecule of claim 17, wherein in the constant domain CL of the light chain of each of the first and second antigen binding moiety, the amino acids at position 123 and 124 are arginine (R) and lysine (K) respectively (numbering according to Kabat), and wherein in the constant domain CH1 of the heavy chain of each of the first and second antigen binding moiety the amino acids at position 147 and 213 are glutamic acid (E) (numbering according to EU numbering).

[Claim 19] The multispecific antigen-binding molecule of any one of claims 12 to 18, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain CDR 1 comprising SEQ ID NO: 20, a heavy chain CDR 2 comprising SEQ ID NO: 34, a heavy chain CDR 3 comprising SEQ ID NO: 48, a light chain CDR 1 comprising SEQ ID NO: 63, a light chain CDR 2 comprising SEQ ID NO: 68, and a light chain CDR 3 comprising SEQ ID NO: 73.

[Claim 20] The multispecific antigen-binding molecule of claim 19, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

[Claim 21] The multispecific antigen-binding molecule of any one of claims 12 to 20, wherein the third antigen-binding moiety comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 232, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 236.

[Claim 22] The multispecific antigen-binding molecule of any one of claims 12 to 21, further comprises a Fc domain.

[Claim 23] A multispecific antigen-binding molecule that comprises:
(a) a first antigen-binding moiety and a second antigen-binding moiety, each of which is capable of binding to human CD3 and human CD137, wherein each of the first antigen-binding moiety and the second antigen-binding moiety is a Fab molecule that binds to either one of human CD3 and human CD137, and comprises an antibody variable region comprising any one of (a1) to (a2) below:
(a1) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 20, the heavy chain CDR 2 of SEQ ID NO: 34, the heavy chain CDR 3 of SEQ ID NO: 48, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73; and
(a2) the heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 28, the heavy chain CDR 2 of SEQ ID NO: 42, the heavy chain CDR 3 of SEQ ID NO: 56, the light chain CDR 1 of SEQ ID NO: 63, the light chain CDR 2 of SEQ ID NO: 68 and the light chain CDR 3 of SEQ ID NO: 73;
and
(b) a third antigen-binding moiety that binds to human Delta-like 3 (DLL3), which comprises an antibody variable region comprising a heavy chain complementarity determining region (CDR) 1 of SEQ ID NO: 233, a heavy chain CDR 2 of SEQ ID NO: 234, a heavy chain CDR 3 of SEQ ID NO: 235, a light chain CDR 1 of SEQ ID NO: 237, a light chain CDR 2 of SEQ ID NO: 238 and a light chain CDR 3 of SEQ ID NO: 239,
and
at least one disulfide bond formed between the CH1 region of the first antigen-binding moiety and the CH1 region of the second antigen-binding moiety.

[Claim 24] The multispecific antigen-binding molecule of claim 23, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising any one of (a1) to (a2) below:
(a1) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58; and

(a2) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 14, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

[Claim 25] The multispecific antigen-binding molecule of claim 23 or 24, wherein the at least one disulfide bond comprises one disulfide bond formed between the amino acid residues at position 191 according to EU numbering in the respective CH1 region of the first antigen-binding moiety and the second antigen-binding moiety.

[Claim 26] The multispecific antigen-binding molecule of any one of claims 23 to 25, wherein the third antigen binding moiety is a Fab molecule, wherein the third antigen binding moiety is fused at the C-terminus of the Fab heavy chain (CH1) to the N-terminus of the Fab heavy chain of either one of the first antigen binding moiety or the second antigen binding moiety, via a peptide linker.

[Claim 27] The multispecific antigen-binding molecule of claim 26, wherein said peptide linker is selected from the group consisting of the amino acid sequence of SEQ ID NO: 248, SEQ ID NO: 249 or SEQ ID NO: 259.

[Claim 28] The multispecific antigen-binding molecule of claim 27, wherein the third antigen binding moiety is a crossover Fab molecule in which the variable regions of the Fab light chain and the Fab heavy chain are exchanged, and wherein each of the first and second antigen binding moiety is a conventional Fab molecule.

[Claim 29] The multispecific antigen-binding molecule of claim 28, wherein in the constant domain CL of the light chain of each of the first and second antigen binding moiety, the amino acids at position 123 and 124 are arginine (R) and lysine (K) respectively (numbering according to Kabat), and wherein in the constant domain CH1 of the heavy chain of each of the first and second antigen binding moiety the amino acids at position 147 and 213 are glutamic acid (E) (numbering according to EU numbering).

[Claim 30] The multispecific antigen-binding molecule of any one of claims 23 to 29, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain CDR 1 comprising SEQ ID NO: 20, a heavy chain CDR 2 comprising SEQ ID NO: 34, a heavy chain CDR 3 comprising SEQ ID NO: 48, a light chain CDR 1 comprising SEQ ID NO: 63, a light chain CDR 2 comprising SEQ ID NO: 68, and a light chain CDR 3 comprising SEQ ID NO: 73.

[Claim 31] The multispecific antigen-binding molecule of claim 30, wherein the first antigen-binding moiety and the second antigen-binding moiety each comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 58.

[Claim 32] The multispecific antigen-binding molecule of any one of claims 23 to 31, wherein the third antigen-binding moiety comprises an antibody variable region comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 232, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 236.

[Claim 33] The multispecific antigen-binding molecule of any one of claims 23 to 32, further comprises a Fc domain.

[Claim ~~1334~~34] A multispecific antigen-binding molecule comprising five polypeptide chains in any one of the combination selected from (a1) to (~~a15a3~~) below:

(a1) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 201 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 208 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);

(a2) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 203 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 209 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5); and

(a3) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 204 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 209 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);

~~(a4) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 205 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 209 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);~~

~~(a5) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 216 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 229 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);~~

~~(a6) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 217 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 210 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);~~

~~(a7) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 219 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 211 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);~~

(a8) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 220 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 211 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);

(a9) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 221 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 211 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);

(a10) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 222 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 230 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 214 (chain 4 & chain 5);

(a11) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 223 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 212 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 215 (chain 4 & chain 5);

(a12) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 225 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 213 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 215 (chain 4 & chain 5);

(a13) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 226 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 213 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 215 (chain 4 & chain 5);

(a14) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 227 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 213 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 215 (chain 4 & chain 5); and

(a15) a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 228 (chain 1), a polypeptide chain comprising an amino acid sequence of SEQ ID NO: 206 (chain 2), a polypeptide chain comprising an amino acid sequence of SEQ ID NOs: 231 (chain 3) and two polypeptide chains each comprising an amino acid sequence of SEQ ID NOs: 215 (chain 4 & chain 5).

[Claim ~~1435~~] An isolated polynucleotide or plurality of polynucleotides encoding the multispecific antigen-binding molecule of any one of claims 1 to ~~1334~~.

[Claim ~~1536~~] A host cell comprising the polynucleotide or plurality of polynucleotides of claim ~~1435~~.

[Claim ~~16~~37] A method of producing the multispecific antigen-binding molecule of any one of claims 1 to ~~13~~34, comprising the steps of a) culturing the host cell of claim ~~15~~36 under conditions suitable for the expression of the antigen-binding molecule and b) recovering the antigen-binding molecule.