

- [0005] [NPL 1] Furuse and Tsukita, TRENDS in Cell Biology 2006, 16: 181
 [NPL 2] Wilcox, et al., Cell 2001, 104: 165
 [NPL 3] Rahner, et al., GASTROENTEROLOGY 2001, 120: 411
 [NPL 4] Morita, et al., Proc. Natl. Acad. Sci. USA 1999, 96: 511
 [NPL 5] Dev Dyn. 2004 Oct; 231(2):4 25-31.
 [NPL 6] Am J Physiol Renal Physiol. 2006 Dec; 291(6):F113 2-41.
 [NPL 7] Int J Cancer. 2014 Nov 1;135(9): 2206-14.
 [NPL 8] Histopathology. 201 2 Dec;61(6):1043-56.
 [NPL 9] J Gastrointest Cancer. 2010 Mar;41(1):5 2-9.
 [NPL 10] Oncoimmunology. 2015 Oct 29;5(3):e1091555.

Summary

The present disclosure provides aspects as disclosed in the claims.

Technical Problem

- [0006] An objective of the present disclosure is to provide multispecific antigen-binding molecules that can recruit T cells efficiently and specifically to the target cancer cells, especially CLDN6-expressing cells such as cancer cells, and can treat cancer through the cytotoxic activity of T cells against target cancer tissues containing CLDN6-expressing cells; methods for producing the antigen-binding molecules; and pharmaceutical compositions comprising the antigen-binding molecules as active ingredient. The disclosure also provides methods to obtain multispecific antigen-binding molecules which induce T-cell dependent cytotoxicity more efficiently whilst circumventing adverse toxicity concerns or side effects that prior art multispecific antigen-binding molecules may have.

Solutions to Problem

- [0007] Specifically, the present disclosure provides an antigen-binding molecule comprising: a first antigen-binding moiety that is capable of binding to CD3 and CD137 (4-1BB), but does not bind to CD3 and CD137 at the same time (i.e. dual-binding to CD3 and CD137 but not simultaneously); and a second antigen-binding moiety capable of binding to a molecule specifically expressed in a cancer tissue, specifically Claudin-6 (CLDN6).
- [0008] Advantageously, by having a Dual binding capability to CD137 in addition to binding capability to CD3, the multispecific antigen-binding molecule of the present disclosure exhibits enhanced T-cell dependent cytotoxicity activity contributed by the synergistic co-stimulator CD137 signaling on the CD3 signaling, compared to a T-cell recruiting bispecific antibody which binds to CD3 alone. In addition, since the binding of the antigen-binding molecule to CD3 and CD137 is non-simultaneous (i.e. not binding to CD3 and CD137 at the same time), the simultaneous binding of CD3 and/or CD137 expressed on different immune cells (e.g. T cells) by the same antigen-binding

molecule will not occur, thereby circumventing systemic toxicity concerns due to undesirable cross-linking between different immune cells which is considered to be responsible for adverse reactions when a conventional multispecific antigen-binding molecule capable of simultaneously binding to CD3 and a second molecule expressed on T cells (e.g. CD137) is administered in vivo.

[0009] Additionally, by engineering and improving the binding activity to CD137 without adversely affecting the Dual-binding activity to CD3 of the antigen-binding molecules of the present disclosure, the inventors have selected, out of more than 1000 variants, antigen binding molecules comprising specific heavy chain complementarity determining regions (HCDRs) or heavy chain variable region (VH) together with specific light chain complementarity determining regions (LCDRs) or light chain variable region (VL), that exhibit superior T-cell dependent cytotoxicity activity to tumors in a cancer antigen (CLDN6)-dependent manner. In one example, the inventors surprisingly found that, by engineering the optimal CD3 and CD137 binding profile, the selected antigen-binding molecules exhibit strong T-cell dependent cytotoxicity activity with low toxicity.

[0010] Finally, a common challenge in the development of multispecific antibodies has been the production of multispecific antibody constructs at a clinically sufficient quantity and purity, due to the mispairing of antibody heavy and light chains of different specificities upon co-expression, which decreases the yield of the correctly assembled construct and results in a number of non-functional side products from which the desired multispecific antibody may be difficult to separate. In one example, by way of careful antibody engineering and molecular format design (including charged mutations in the constant region, VH/VL exchanged, and Fc region selection), the present disclosure provides multispecific antigen-binding molecules designed for T cell activation and re-direction that combine good anticancer efficacy and low toxicity with favorable stability, manufacturability/producibility and structural homogeneity.

[0011] As a result of all the above efforts, the antigen-binding molecules and pharmaceutical compositions thereof can be used for targeting cells expressing CLDN6, for use in immunotherapy for treating various cancers, especially those associated with CLDN6 such as CLDN6-positive tumors.

[0012] More specifically, the present disclosure provides the following:

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

- (i) a first antigen-binding moiety that is capable of binding to CD3 and CD137, but does not bind to CD3 and CD137 at the same time; and
- (ii) a second antigen-binding moiety that is capable of binding to claudin-6 (CLDN6).

[2-1] A multispecific antigen-binding molecule comprising:

Claims

[Claim 1]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that binds to CD3 and is composed of a first antibody variable region and a second antibody variable region, and a second antigen-binding moiety that is capable of binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (1) to (6) below:

(1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;

(2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 9, the CDR 2 of SEQ ID NO: 15, and the CDR 3 of SEQ ID NO: 21; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;

(3) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 10, the CDR 2 of SEQ ID NO: 16, and the CDR 3 of SEQ ID NO: 22; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region

comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;

(4) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;

(5) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19;

(6) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19.

[Claim 2]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that binds to CD137 and is composed of a first antibody variable region and a second antibody variable region, and a second antigen-binding moiety that is capable of binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (1) to (6) below:

- (1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;
- (2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 9, the CDR 2 of SEQ ID NO: 15, and the CDR 3 of SEQ ID NO: 21; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;
- (3) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 10, the CDR 2 of SEQ ID NO: 16, and the CDR 3 of SEQ ID NO: 22; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;
- (4) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;
- (5) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2

of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19;

(6) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19.

[Claim 3]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that is capable of binding to CD3 and CD137 and binds to either CD3 or CD137, and is composed of a first antibody variable region and a second antibody variable region, and a second antigen-binding moiety that is capable of binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (1) to (6) below:

(1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;

(2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 9, the CDR 2 of SEQ ID NO: 15, and the CDR 3 of SEQ ID NO: 21; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;

(3) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 10, the CDR 2 of SEQ ID NO: 16, and the CDR 3 of SEQ ID NO: 22; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 31, the CDR 2 of SEQ ID NO: 35, and the CDR 3 of SEQ ID NO: 39; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 8, the CDR 2 of SEQ ID NO: 14, and the CDR 3 of SEQ ID NO: 20; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 30, the CDR 2 of SEQ ID NO: 34, and the CDR 3 of SEQ ID NO: 38;

(4) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37;

(5) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 11, the CDR 2 of SEQ ID NO: 17, and the CDR 3 of SEQ ID NO: 23; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19;

(6) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 12, the CDR 2 of SEQ ID NO: 18, and the CDR 3 of SEQ ID NO: 24; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 32, the CDR 2 of SEQ ID NO: 36, and the CDR 3 of SEQ ID NO: 40; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 29, the CDR 2 of SEQ ID NO: 33, and the CDR 3 of SEQ ID NO: 37; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 7, the CDR 2 of SEQ ID NO: 13, and the CDR 3 of SEQ ID NO: 19.

[Claim 4]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that binds to CD3 and is composed of a first antibody variable region and a second antibody variable region, and a second antigen-binding moiety that is capable of

binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (I) to (VI) below:

- (I) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;
- (II) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 3; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;
- (III) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 4; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;
- (IV) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;
- (V) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1;
- (VI) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1.

[Claim 5]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that binds to CD137 and is composed of a first antibody variable region and a second antibody variable region, and a

second antigen-binding moiety that is capable of binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (I) to (VI) below:

(I) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;

(II) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 3; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;

(III) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 4; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;

(IV) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;

(V) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1;

(VI) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1.

[Claim 6]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety that is capable of binding to CD3 and CD137 and binds to either CD3 or CD137, and is composed of a first antibody

variable region and a second antibody variable region, and a second antigen-binding moiety that is capable of binding to claudin-6 and is composed of a third antibody variable region and a fourth antibody variable region, wherein the multispecific antigen-binding molecule comprises any one of (I) to (VI) below:

(I) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;

(II) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 3; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;

(III) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 4; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 27; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 2; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 26;

(IV) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 1; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 25;

(V) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 5; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1;

(VI) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 6; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 28; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 25; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 1.

[Claim 7]

The multispecific antigen-binding molecule of any one of claims 1 to 6, which further comprises:

an Fc domain which exhibits reduced binding affinity to human Fc gamma receptor, as compared to a native human IgG1 Fc domain, wherein the Fc domain comprises an amino acid substitution at at least one position selected from the group of E233, L234, L235, N297, P331 and P329, wherein the amino acid positions are numbered according to EU index.

[Claim 8] The multispecific antigen-binding molecule of claim 7, wherein the Fc domain is composed of a first Fc-region subunit and a second Fc-region subunit, and wherein the Fc domain comprises (e1) or (e2) below:

(e1) the first Fc-region subunit comprising Glu at position 439, and the second Fc-region subunit comprising Lys at position 356;

(e2) the first Fc-region subunit comprising Cys at position 349, Ser at position 366, Ala at position 368 and Val at position 407, and the second Fc-region subunit comprising Cys at position 354 and Trp at position 366;

wherein the amino acid positions are numbered according to EU index.

[Claim 9] The multispecific antigen-binding molecule of claim 8, wherein the first and/or the second Fc-region subunit comprises (f1) or (f2) below:

(f1) Ala at position 234, Ala at position 235 and Ala at position 297;

(f2) Ala at position 234 and Ala at position 235;

wherein the amino acid positions are numbered according to EU index.

[Claim 10] The multispecific antigen-binding molecule of any one of claims 7 to 9, wherein the Fc domain further exhibits stronger FcRn binding affinity to human FcRn, as compared to a native human IgG1 Fc domain, wherein the first and/or the second Fc-region subunit comprises Leu at position 428, Ala at position 434, Arg at position 438, and Glu at position 440, wherein the amino acid positions are numbered according to EU index.

[Claim 11] The multispecific antigen-binding molecule of any one of claims 1 to 6, wherein the first antibody variable region of the first antigen-binding moiety is fused with a first heavy chain constant region, the second antibody variable region of the first antigen-binding moiety is fused with a first light chain constant region, the third antibody variable region of the second antigen-binding moiety is fused with a second heavy chain constant region, the fourth antibody variable region of the second antigen-binding moiety is fused with a second light chain constant region, wherein the constant regions are any one of (g1) to (g7) below:

(g1) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 74, a first light chain constant region

comprising the amino acid sequence of SEQ ID NO: 87, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 73, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 88;

(g2) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 74, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 85, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 81, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 86;

(g3) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 79, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 72, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 80, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 89;

(g4) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 83, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 87, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 82, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 88;

(g5) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 83, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 85, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 84, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 86;

(g6) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 77, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 72, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 78, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 89;

(g7) a first heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 75, a first light chain constant region comprising the amino acid sequence of SEQ ID NO: 72, a second heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 76, and a second light chain constant region comprising the amino acid sequence of SEQ ID NO: 89.

[Claim 12]

A multispecific antigen-binding molecule comprising any one of (h03), (h09), (h15), (h01), (h02), (h04) to (h08), (h10) to (h14), and (h16) to (h18) below:

(h03) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h09) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h15) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h01) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h02) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 55 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h04) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57

(chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h05) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 60 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h06) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 61 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h07) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h08) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 63 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h10) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h11) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h12) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 67 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h13) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h14) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h16) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h17) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 58 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4); and

(h18) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 59 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4),

wherein the first antigen-binding moiety binds to CD3 and the second antigen-binding moiety is capable of binding to claudin-6.

[Claim 13]

A multispecific antigen-binding molecule comprising any one of (h03), (h09), (h15), (h01), (h02), (h04) to (h08), (h10) to (h14), and (h16) to (h18) below:

(h03) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h09) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h15) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h01) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h02) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 55 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h04) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57 (chain

3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h05) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 60 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h06) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 61 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h07) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h08) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 63 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h10) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h11) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h12) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 67 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h13) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h14) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h16) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h17) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 58 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4); and

(h18) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 59 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4),

wherein the first antigen-binding moiety binds to CD137 and the second antigen-binding moiety is capable of binding to claudin-6.

[Claim 14]

A multispecific antigen-binding molecule comprising any one of (h03), (h09), (h15), (h01), (h02), (h04) to (h08), (h10) to (h14), and (h16) to (h18) below:

(h03) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h09) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h15) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 64 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h01) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h02) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 55 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h04) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 42 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57

(chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h05) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 60 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h06) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 44 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 61 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h07) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h08) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 50 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 63 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 68 (chain 4);

(h10) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 51 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 69 (chain 4);

(h11) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 66 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h12) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 47 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 67 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4);

(h13) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 56 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h14) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 48 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 57 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h16) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 49 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 53 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 65 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 71 (chain 4);

(h17) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 58 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4); and

(h18) a second antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 43 (chain 1) and a light chain comprising the amino acid sequence of SEQ ID NO: 52 (chain 2), and a first antigen-binding moiety composed of a heavy chain comprising the amino acid sequence of SEQ ID NO: 59 (chain 3) and a light chain comprising the amino acid sequence of SEQ ID NO: 70 (chain 4),

wherein the first antigen-binding moiety is capable of binding to CD3 and CD137 and binds to either CD3 or CD137 and the second antigen-binding moiety is capable of binding to claudin-6.

[Claim 15] An isolated nucleic acid encoding the multispecific antigen-binding molecule of any one of claims 1 to 14.

[Claim 16] A host cell comprising the nucleic acid of claim 15.

[Claim 17] A method of producing a multispecific antigen-binding molecule comprising culturing the host cell of claim 16 so that the multispecific antigen-binding molecule is produced.

[Claim 18] The method of claim 17, further comprising recovering the multispecific antigen-binding molecule from the culture of the host cell.

[Claim 19] A pharmaceutical composition comprising the multispecific antigen-binding molecule of any one of claims 1 to 14, and a pharmaceutically acceptable carrier.