

[Citation List]

[Non Patent Literature]

[0003]

[NPL 1] N Engl J Med 2007; 357:1731-1743

[NPL 2] J Biomed Sci. 2012; 19(1): 88

[NPL 3] N Engl J Med 2003; 348:2517-2524

[NPL 4] Gut 2003; 52:960-965

[NPL 5] Dig Dis Sci 2004; 49:1479-1484

[NPL 6] Gastroenterology 2011; 141:610-620

[NPL 7] Gut 2005; 54:1217-1223

[NPL 8] Gastroenterology 2014; 146:1649-58

[NPL 9] Nutrients 2013 Oct 5(10): 3975-3992

[NPL 10] J Clin Invest. 2007; 117(1):41-49

[NPL 11] Am J Clin Nutr 2007; 85: 160-6

[Summary ~~of Invention~~]

In one aspect, the present disclosure provides a multispecific antigen-binding molecule that binds to a complex formed by HLA-DQ2.5 and a gluten peptide and which comprises

a first antigen-binding moiety comprising first and second antibody variable regions and a second antigen-binding moiety comprising third and fourth antibody variable regions, wherein the multispecific antigen-binding molecule comprises any one of (1) to (14) below:

- (1) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;
- (2) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 98;
- (3) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (4) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

- (13) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100; and
- (14) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99.

In another aspect, the present disclosure provides a multispecific antigen-binding molecule that binds to a complex formed by HLA-DQ2.5 and a gluten peptide, comprising a combination of four polypeptide chains selected from the group consisting of (1) to (14) below:

- (1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (2) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 55;
- (3) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (4) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 58 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (5) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (6) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 55;

- (7) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 65 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (8) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (9) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 58 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (10) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (11) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 65 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (12) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (13) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61; and
- (14) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61.

In another aspect, the present disclosure provides a nucleic acid encoding the multispecific antigen-binding molecule of the disclosure.

In another aspect, the present disclosure provides a vector comprising the nucleic acid of the disclosure.

In another aspect, the present disclosure provides a cell comprising the nucleic acid of the disclosure.

In another aspect, the present disclosure provides a method of producing a multispecific antigen-binding molecule comprising culturing the cell of the disclosure so that the multispecific antigen-binding molecule is produced.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the multispecific antigen-binding molecule of the disclosure, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a use of the multispecific antigen-binding molecule of the disclosure in the manufacture of a medicament for treating and/or preventing celiac disease.

[Technical Problem]

[0004]

Under the above-mentioned circumstances with the need for adjunctive therapy, the present invention provides anti-HLA-DQ2.5 antigen-binding molecules.

[Solution to Problem]

[0005]

The antigen-binding molecules of the present invention have been altered and can bind to two or more complexes formed by HLA-DQ2.5 and a gluten peptide.

[0006]

More specifically, the present invention provides the following.

[1] A multispecific antigen-binding molecule comprising:

(i) a first antigen-binding moiety that has binding activity to HLA-DQ2.5 in the form of a complex with a gluten peptide; and

(ii) a second antigen-binding moiety that has binding activity to HLA-DQ2.5 in the form of a complex with a gluten peptide;

wherein the antigen-binding molecule binds to two or more complexes of HLA-DQ2.5 and gluten peptides,

wherein at least one of the gluten peptides in the complexes bound by the first antigen-binding moiety is different from at least one of the gluten peptides in the complexes bound by the second antigen-binding moiety; and

wherein the antigen-binding molecule has substantially no binding activity to either or both of a HLA-DQ2.5 positive PBMC B cell and a Ba/F3 cell that expresses HLA-DQ2.5,

wherein the antigen-binding molecule is humanized, and

wherein one or more amino acids in a heavy chain and/or a light chain of the first

of SEQ ID NO: 94; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(12) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(13) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(14) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(15) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in any one of (1) ~~or to~~ (14); a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in any one of (1) ~~or to~~ (14); a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (1) to (14); and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (1) to (14).

[27] A multispecific antigen-binding molecule comprising a combination of two polypeptide chains selected from the group consisting of (A1) to (A3) below:

(A1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43;

(A2) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46; and

(A3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first heavy chain sequence recited in (A1) or (A2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first light chain sequence recited in (A1) or (A2).

[27-2] A multispecific antigen-binding molecule comprising a combination of two polypeptide chains selected from the group consisting of (A1) to (A3) below:

(A1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 41 and a first

sequence of SEQ ID NO: 99;

(10) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(11) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 94; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(12) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(13) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(14) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(15) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in any one of (1) ~~or to~~ (14); a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in any one of (1) ~~or to~~ (14); a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (1) to (14); and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (1) to (14).

In some embodiments, the present disclosure provides a multispecific antigen-binding molecule comprising a combination of two polypeptide chains selected from the group consisting of (A1) to (A3) below:

(A1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first

[CLAIMS]

[Claim 1]

A multispecific antigen-binding molecule that binds to a complex formed by HLA-DQ2.5 and a gluten peptide and which comprises~~comprising~~:

~~(i)-a first antigen-binding moiety comprising first and second antibody variable regions and that has binding activity to HLA-DQ2.5 in the form of a complex with a gluten peptide; and~~
 (ii)-a second antigen-binding moiety comprising third and fourth antibody variable regions, wherein the multispecific antigen-binding molecule comprises any one of (1) to (14) below: that has binding activity to HLA-DQ2.5 in the form of a complex with a
~~gluten peptide;~~

- (1) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;
- (2) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 98;
- (3) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (4) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (5) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 94; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;
- (6) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96; a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

antibody variable region comprising the amino acid sequence of SEQ ID NO: 99.

~~wherein the antigen-binding molecule binds to two or more complexes of HLA-DQ2.5 and gluten peptides;
 wherein at least one of the gluten peptides in the complexes bound by the first antigen-binding moiety is different from at least one of the gluten peptides in the complexes bound by the second antigen-binding moiety; and
 wherein the antigen-binding molecule has substantially no binding activity to either or both of a HLA-DQ2.5 positive PBMC B cell and a Ba/F3 cell that expresses HLA-DQ2.5;
 wherein the antigen-binding molecule is humanized, and
 wherein one or more amino acids in a heavy chain and/or a light chain of the first antigen-binding moiety and/or second antigen-binding moiety in the multispecific antigen-binding molecule are altered.~~

[Claim 2] A multispecific antigen-binding molecule that binds to a complex formed by HLA-DQ2.5 and a gluten peptide, comprising a combination of four polypeptide chains selected from the group consisting of (1) to (14) below:

- (1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (2) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 55;
- (3) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (4) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 58 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (5) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (6) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID

- NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 55;
- (7) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 65 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (8) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (9) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 58 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (10) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (11) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 65 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;
- (12) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;
- (13) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61; and
- (14) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61.

[Claim 3] The multispecific antigen-binding molecule of claim 1 or 2, which is a bispecific antibody.

[Claim 2]

The multispecific antigen-binding molecule of claim 1, wherein the antigen-binding molecule has substantially no binding activity to a Ba/F3 cell that expresses HLA-DQ2.2.

[Claim 3]

The multispecific antigen-binding molecule of claim 1 or 2, wherein the gluten peptide is an immune dominant peptide related to celiac disease.

[Claim 4]

The multispecific antigen-binding molecule of any one of claims 1 to 3, wherein the gluten peptide is selected from the group consisting of: 33mer gliadin peptide, alpha 1 gliadin peptide, alpha 2 gliadin peptide, gamma 1 gliadin peptide, gamma 2 gliadin peptide, omega 1 gliadin peptide, omega 2 gliadin peptide, BC Hordein peptide, alpha 3 gliadin peptide, alpha 1b gliadin peptide, gamma 4a gliadin peptide, gamma 4b gliadin peptide, avenin 1 peptide, avenin 2 peptide, avenin 3 peptide, hordein 1 peptide, hordein 2 peptide, secalin 1 peptide, secalin 2 peptide, and 26mer gliadin peptide.

[Claim 5]

The multispecific antigen-binding molecule of any one of claims 1 to 4, which has substantially no binding activity to HLA-DQ2.5 in the form of a complex with an irrelevant peptide, wherein the irrelevant peptide is at least one peptide selected from the group consisting of: CLIP peptide, Hepatitis B virus 1 peptide, Salmonella peptide, Mycobacterium bovis peptide, and thyroperoxidase peptide.

[Claim 6]

The multispecific antigen-binding molecule of any one of claims 1 to 5, which has substantially no binding activity to HLA-DP, HLA-DR, HLA-DQ5.1, HLA-DQ6.3, HLA-DQ7.3, HLA-DQ7.5, and HLA-DQ8.

[Claim 7]

The multispecific antigen-binding molecule of any one of claims 1 to 6, which blocks (i) the interaction between HLA-DQ2.5/gluten peptide complex and HLA-DQ2.5/gluten peptide-restricted CD4+ T cell; and/or (ii) the interaction between HLA-DQ2.2/gluten peptide complex and HLA-DQ2.2/gluten peptide-restricted CD4+ T cell.

[Claim 8]

The multispecific antigen-binding molecule of claim 7, wherein the gluten peptide is selected from the group consisting of: alpha 1 gliadin peptide, alpha 1b gliadin peptide, alpha 2 gliadin peptide, omega 1 gliadin peptide, omega 2 gliadin peptide, gamma 1 gliadin peptide, gamma 2 gliadin peptide, gamma 3 gliadin peptide, gamma 4a gliadin peptide, gamma 4d gliadin peptide, and BC Hordein peptide.

[Claim 9]

The multispecific antigen-binding molecule of any one of claims 1 to 8, wherein the antigen-binding molecule has enhanced binding activity to the complex formed by HLA-DQ2.5 and the gluten peptide, compared to before said humanization and alteration.

[Claim 10]

The multispecific antigen-binding molecule of any one of claims 1 to 9, wherein the antigen-binding molecule has enhanced cross reactivity towards gluten peptides, compared to before said humanization and alteration.

[Claim 11]

The multispecific antigen-binding molecule of any one of claims 1 to 10, wherein one, two, three or all sets of amino acid residues selected from the group consisting of the

sets of amino acid residues shown in (a) to (d) below in the heavy chain and the light chain of the antigen-binding molecule are amino acid residues which electrostatically repel each other:

- (a) an amino acid residue in a heavy chain constant region (CH1) which is at position 175 according to EU numbering, and an amino acid residue in a light chain constant region (CL) which is at position 131 according to Kabat numbering;
- (b) an amino acid residue in CH1 which is at position 175 according to EU numbering, and an amino acid residue in CL which is at position 160 according to Kabat numbering;
- (c) amino acid residue in CH1 which is at position 175 according to EU numbering, and amino acid residues in CL which are at positions 131 and 160 according to Kabat numbering;
- (d) amino acid residues in CH1 which are at positions 147 and 175 according to EU numbering, and amino acid residues in CL which are at positions 131 and 160 according to Kabat numbering.

[Claim 12]

The multispecific antigen-binding molecule of claim 11, further wherein two or more amino acid residues that form an interface between a heavy chain variable region and a light chain variable region are amino acid residues which electrostatically repel each other.

[Claim 13]

The multispecific antigen-binding molecule of claim 12, wherein the amino acid residues which electrostatically repel each other are one or two sets of amino acid residues selected from the group consisting of the sets of amino acid residues of (a) and (b) below:

- (a) an amino acid residue in the heavy chain variable region which is at position 39 according to Kabat numbering, and an amino acid residue in the light chain variable region which is at position 38 according to Kabat numbering;
- (b) an amino acid residue in the heavy chain variable region which is at position 45 according to Kabat numbering, and an amino acid residue in the light chain variable region which is at position 44 according to Kabat numbering.

[Claim 14]

The multispecific antigen-binding molecule of any one of claims 11 to 13, wherein the amino acid residues which electrostatically repel each other are selected from the amino acid residues included in either set of (X) or (Y) below:

- (X) glutamic acid (E), aspartic acid (D);
- (Y) lysine (K), arginine (R), histidine (H).

[Claim 15]

The multispecific antigen-binding molecule of any one of claims 11 to 14, which further comprises an Fc domain that exhibits reduced binding affinity to human Fc gamma receptor, as compared to a native human IgG1 Fc domain.

[Claim 16]

The multispecific antigen-binding molecule of claim 15, wherein the Fc domain comprises Arg at position 235 and Arg at position 236, wherein the amino acid positions are numbered according to EU numbering.

[Claim 17]

The multispecific antigen-binding molecule of claim 15 or 16, wherein the Fe domain is composed of a first Fe-region subunit and a second Fe-region subunit that are capable of stable association.

[Claim 18]

The multispecific antigen-binding molecule of claim 17, wherein the Fe domain comprises (e1) or (e2) below:

(e1) the first Fe-region subunit comprising Cys at position 349, Ser at position 366, Ala at position 368 and Val at position 407, and the second Fe-region comprising Cys at position 354 and Trp at position 366;

(e2) the first Fe-region subunit comprising Glu at position 439, and the second Fe-region comprising Lys at position 356;

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

[Claim 19]

The multispecific antigen-binding molecule of any one of claims 15 to 18, wherein the Fe domain further exhibits stronger FeRn binding affinity to human FeRn, as compared to a native human IgG1-Fe domain.

[Claim 20]

The multispecific antigen-binding molecule of claim 18, wherein the first and/or Fe-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 numbering.

[Claim 21]

The multispecific antigen-binding molecule of any one of claims 1 to 20, wherein the multispecific antigen-binding molecule has substantially no binding activity to the gluten peptide itself.

[Claim 22]

The multispecific antigen-binding molecule of any one of claims 1 to 10, wherein the multispecific antigen-binding molecule comprises one or more of the amino acid residues of (i) to (xii) below:

(i) glutamic acid or lysine at position 175 (EU numbering) in the heavy-chain constant region;

(ii) glutamic acid at position 147 (EU numbering) in the heavy-chain constant region;

(iii) glutamic acid or lysine at position 131 (Kabat numbering) in the light-chain constant region;

(iv) glutamic acid or lysine at position 160 (Kabat numbering) in the light-chain constant region;

(v) arginine at position 235 (EU numbering) in the heavy-chain constant region;

(vi) arginine at position 236 (EU numbering) in the heavy-chain constant region;

(vii) lysine at position 356 (EU numbering) in the heavy-chain constant region;

(viii) leucine at position 428 (EU numbering) in the heavy-chain constant region;

(ix) alanine at position 434 (EU numbering) in the heavy-chain constant region;

(x) arginine at position 438 (EU numbering) in the heavy-chain constant region;

(xi) glutamic acid at position 439 (EU numbering) in the heavy-chain constant region;

(xii) glutamic acid at position 440 (EU numbering) in the heavy-chain constant region.

[Claim 23]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety and a second antigen-binding moiety;

wherein the first antigen-binding moiety comprises any one of (a1) to (a3) below:
 (a1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 129, the CDR 2 of SEQ ID NO: 130, the CDR 3 of SEQ ID NO: 131, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 132, the CDR 2 of SEQ ID NO: 133, the CDR 3 of SEQ ID NO: 134;
 (a2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 164, the CDR 2 of SEQ ID NO: 165, the CDR 3 of SEQ ID NO: 166, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 167, the CDR 2 of SEQ ID NO: 168, the CDR 3 of SEQ ID NO: 169; and
 (a3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in (a1) or (a2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in (a1) or (a2).
 [Claim 24]

The multispecific antigen-binding molecule of claim 23,
 wherein the second antigen-binding moiety comprises any one of (b1) to (b8) below:
 (b1) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137 and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 138, the CDR 2 of SEQ ID NO: 139, the CDR 3 of SEQ ID NO: 140;
 (b2) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;
 (b3) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 144, the CDR 2 of SEQ ID NO: 145, the CDR 3 of SEQ ID NO: 146, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;
 (b4) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 147, the CDR 2 of SEQ ID NO: 148, the CDR 3 of SEQ ID NO: 149, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;
 (b5) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 153, the CDR 2 of SEQ ID NO: 154, the CDR 3 of SEQ ID NO: 155, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;
 (b6) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 156, the CDR 2 of SEQ ID NO: 157, the CDR 3 of SEQ ID NO: 158, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;
 (b7) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 159, the CDR 2 of SEQ ID NO: 160, the CDR 3 of SEQ ID NO: 161, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143; and
 (b8) a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (b1) to (b7), and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95%

sequence identity to the fourth antibody variable region recited in any one of (b1) to (b7).

[Claim 25]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety and a second antigen-binding moiety;

wherein the second antigen-binding moiety comprises any one of (b1) to (b8) below:

(b1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137 and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 138, the CDR 2 of SEQ ID NO: 139, the CDR 3 of SEQ ID NO: 140;

(b2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;

(b3) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 144, the CDR 2 of SEQ ID NO: 145, the CDR 3 of SEQ ID NO: 146, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;

(b4) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 147, the CDR 2 of SEQ ID NO: 148, the CDR 3 of SEQ ID NO: 149, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(b5) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 153, the CDR 2 of SEQ ID NO: 154, the CDR 3 of SEQ ID NO: 155, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(b6) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 156, the CDR 2 of SEQ ID NO: 157, the CDR 3 of SEQ ID NO: 158, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(b7) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 159, the CDR 2 of SEQ ID NO: 160, the CDR 3 of SEQ ID NO: 161, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143; and

(b8) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in any one of (b1) to (b7), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in any one of (b1) to (b7).

[Claim 26]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety and a second antigen-binding moiety;

wherein the first antigen-binding moiety comprises any one of (c1) to (c3) below:

(c1) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 129, the CDR 2 of SEQ ID NO: 130, the CDR 3 of SEQ ID NO: 131, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 132, the CDR 2 of SEQ ID NO: 133, the CDR 3 of SEQ ID NO: 134;

(c2) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 164, the CDR 2 of SEQ ID NO: 165, the CDR 3 of SEQ ID NO: 166, and a second antibody variable region comprising the CDR 1 of SEQ ID NO: 167, the CDR 2 of SEQ ID NO: 168, the CDR 3 of SEQ ID NO: 169; and

(c3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in (c1) or (c2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in (c1) or (c2), wherein the second antigen-binding moiety comprises any one of (d1) to (d8) below:

(d1) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137 and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 138, the CDR 2 of SEQ ID NO: 139, the CDR 3 of SEQ ID NO: 140;

(d2) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 135, the CDR 2 of SEQ ID NO: 136, the CDR 3 of SEQ ID NO: 137, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;

(d3) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 144, the CDR 2 of SEQ ID NO: 145, the CDR 3 of SEQ ID NO: 146, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143;

(d4) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 147, the CDR 2 of SEQ ID NO: 148, the CDR 3 of SEQ ID NO: 149, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(d5) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 153, the CDR 2 of SEQ ID NO: 154, the CDR 3 of SEQ ID NO: 155, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(d6) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 156, the CDR 2 of SEQ ID NO: 157, the CDR 3 of SEQ ID NO: 158, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(d7) a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 159, the CDR 2 of SEQ ID NO: 160, the CDR 3 of SEQ ID NO: 161, and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143; and

(d8) a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (d1) to (d7), and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (d1) to (d7).

[Claim 27]

A multispecific antigen-binding molecule that comprises a first antigen-binding moiety comprising first and second antibody variable regions and a second antigen-binding moiety comprising third and fourth antibody variable regions, wherein the multispecific antigen-binding molecule comprises any one of (1) to (15) below:

NO: 153, the CDR 2 of SEQ ID NO: 154, the CDR 3 of SEQ ID NO: 155; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(13) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 164, the CDR 2 of SEQ ID NO: 165, the CDR 3 of SEQ ID NO: 166; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 167, the CDR 2 of SEQ ID NO: 168, the CDR 3 of SEQ ID NO: 169; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 156, the CDR 2 of SEQ ID NO: 157, the CDR 3 of SEQ ID NO: 158; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 150, the CDR 2 of SEQ ID NO: 151, the CDR 3 of SEQ ID NO: 152;

(14) a first antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 164, the CDR 2 of SEQ ID NO: 165, the CDR 3 of SEQ ID NO: 166; a second antibody variable region comprising the CDR 1 of SEQ ID NO: 167, the CDR 2 of SEQ ID NO: 168, the CDR 3 of SEQ ID NO: 169; a third antibody variable region comprising the complementarity determining region (CDR) 1 of SEQ ID NO: 159, the CDR 2 of SEQ ID NO: 160, the CDR 3 of SEQ ID NO: 161; and a fourth antibody variable region comprising the CDR 1 of SEQ ID NO: 141, the CDR 2 of SEQ ID NO: 142, the CDR 3 of SEQ ID NO: 143; and

(15) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in any one of (1) to (14); a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in any one of (1) to (14); a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (1) to (14); and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (1) to (14).
[Claim 28]

The multispecific antigen-binding molecule of any one of claims 23 to 27, wherein the antibody variable region comprised in the first and/or second antigen-binding moiety comprises human antibody frameworks or humanized antibody frameworks.

[Claim 29]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety and a second antigen-binding moiety;

wherein the first antigen-binding moiety comprises any one of (e1) to (e3) below:

(e1) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88, and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90;

(e2) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89, and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; and

(e3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in (e1) or (e2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in (e1) or (e2).

[Claim 30]

The multispecific antigen-binding molecule of claim 29, wherein the second antigen-binding moiety comprises any one of (f1) to (f8) below:

(f1) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 98;

(f2) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(f3) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(f4) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 94, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f5) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f6) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f7) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99; and

(f8) a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (f1) to (f7), and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (f1) to (f7).
[Claim 31]

A multispecific antigen-binding molecule comprising a first antigen-binding moiety and a second antigen-binding moiety;

wherein the first antigen-binding moiety comprises any one of (e1) to (e3) below:

(e1) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88, and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90;

(e2) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 89, and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 91; and

(e3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in (e1) or (e2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in (e1) or (e2), and

wherein the second antigen-binding moiety comprises any one of (f1) to (f8) below:

(f1) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 98;

(f2) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(f3) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(f4) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 94, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f5) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 95, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f6) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 96, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

(f7) a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97, and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99; and

(f8) a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (f1) to (f7), and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (f1) to (f7).

[Claim 32]

A multispecific antigen-binding molecule that comprises a first antigen-binding moiety comprising first and second antibody variable regions and a second antigen-binding moiety comprising third and fourth antibody variable regions, wherein the multispecific antigen-binding molecule comprises any one of (1) to (15) below:

- (1) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 98;
- (2) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; and a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 92; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (3) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 93; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (4) a first antibody variable region comprising the amino acid sequence of SEQ ID NO: 88; a second antibody variable region comprising the amino acid sequence of SEQ ID NO: 90; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 94; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 100;

ID NO: 91; a third antibody variable region comprising the amino acid sequence of SEQ ID NO: 97; and a fourth antibody variable region comprising the amino acid sequence of SEQ ID NO: 99;

(15) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first antibody variable region recited in (1) or (14); a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second antibody variable region recited in (1) or (14); a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the third antibody variable region recited in any one of (1) to (14); and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the fourth antibody variable region recited in any one of (1) to (14).

[Claim 33]

A multispecific antigen-binding molecule comprising a combination of two polypeptide chains selected from the group consisting of (A1) to (A3) below:

(A1) a first heavy chain comprising amino acid sequence of SEQ ID NO: 42 and a first light chain comprising amino acid sequence of SEQ ID NO: 43;

(A2) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46; and

(A3) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first heavy chain sequence recited in (A1) or (A2), and a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first light chain sequence recited in (A1) or (A2).

[Claim 34]

The multispecific antigen-binding molecule of claim 33, further comprising a combination of two polypeptide chains selected from the group consisting of (B1) to (B8) below:

(B1) a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 55;

(B2) a second heavy chain comprising amino acid sequence of SEQ ID NO: 54 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;

(B3) a second heavy chain comprising amino acid sequence of SEQ ID NO: 58 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;

(B4) a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;

(B5) a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;

(B6) a second heavy chain comprising amino acid sequence of SEQ ID NO: 65 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;

(B7) a second heavy chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56; and

(B8) a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second heavy chain sequence recited in any one of (B1) to (B7), and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second light chain sequence recited in any one of (B1) to (B7).

[Claim 35]

A multispecific antigen-binding molecule comprising a combination of four polypeptide chains selected from the group consisting of (1) to (15) below:

chain comprising amino acid sequence of SEQ ID NO: 67 and a second light chain comprising amino acid sequence of SEQ ID NO: 56;

(13) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 63 and a second light chain comprising amino acid sequence of SEQ ID NO: 61;

(14) a first heavy chain comprising amino acid sequence of SEQ ID NO: 45 and a first light chain comprising amino acid sequence of SEQ ID NO: 46, and a second heavy chain comprising amino acid sequence of SEQ ID NO: 60 and a second light chain comprising amino acid sequence of SEQ ID NO: 61; and

(15) a first amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first heavy chain sequence recited in any one of (1) to (14); a second amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the first light chain sequence recited in any one of (1) to (14); a third amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second heavy chain sequence recited in any one of (1) to (14); and a fourth amino acid sequence that has at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to the second light chain sequence recited in any one of (1) to (14).

[Claim 36]

A combination of any one of (i) to (iii) below:

(i) a multispecific antigen-binding molecule comprising the sequences recited in any one of (a1) to (a3) of claim 23, and a multispecific antigen-binding molecule comprising the sequences recited in any one of (b1) to (b8) of claim 24;

(ii) a multispecific antigen-binding molecule comprising the sequences recited in any one of (e1) to (e3) of claim 29, and a multispecific antigen-binding molecule comprising the sequences recited in any one of (f1) to (f8) of claim 30; and

(iii) a multispecific antigen-binding molecule comprising the sequences recited in any one of (A1) to (A3) of claim 33, and a multispecific antigen-binding molecule comprising the sequences recited in any one of (B1) to (B8) of claim 34.

[Claim 37]

A nucleic acid encoding the multispecific antigen-binding molecule of any one of claims 1 to 35.

[Claim 38]

A vector comprising the nucleic acid of claim 37.

[Claim 39]

A cell comprising the nucleic acid of claim 37 or the vector of claim 38.

[Claim 40]

A method of producing a multispecific antigen-binding molecule comprising culturing the cell of claim 39 so that the multispecific antigen-binding molecule is produced.

[Claim 41]

The method of claim 40, further comprising recovering the multispecific antigen-binding molecule from the culture of the cell.

[Claim 42]

A pharmaceutical composition comprising the multispecific antigen-binding molecule of any one of claims 1 to 35 or the combination of claim 36, and a pharmaceutically acceptable carrier.

[Claim 43]

The composition of claim ~~42~~9, which is a pharmaceutical composition for use in ~~the treatment and/or prevention of celiac disease~~therapy.

[Claim ~~44~~11]

Use of the multispecific antigen-binding molecule of any one of claims 1 to ~~35~~ or the combination of claim 36 in the manufacture of a medicament.

[Claim ~~45~~]

The use of claim ~~44~~, wherein the medicament is a medicament for ~~treatment~~ treating and/or ~~prevention~~ preventing of celiac disease.

[Claim ~~46~~]

A method of ~~treating an individual having celiac disease comprising administering to the individual an effective amount of the multispecific antigen-binding molecule of any one of claims 1 to 35 or the combination of claim 36.~~

[Claim ~~47~~]

A kit for use in the ~~treatment and/or prevention of celiac disease, which comprising at least the multispecific antigen-binding molecule of any one of claims 1 to 35 or the combination of claim 36, and instructions for use.~~