

host-mediated tumor-promoting mechanisms, restricting immune cell infiltration and production of cytotoxicity and cytokines (such as interferon), and causes strong immunosuppression (Ohta, A. *et al.*, (2016), *Front Immunol*, 7, 109). Immunosuppression is a typical characteristic of cancer, and it is important to overcome the inhibitory barrier. Therefore, it is a highly potential therapeutic direction of inhibiting the production of adenosine in the tumor microenvironment by inhibiting CD73, thereby activating immunity and inhibiting tumor growth.

Antibodies can inhibit the enzymatic activity of CD73 by antagonizing CD73 allosteric to the active form, but there is no report of any antibody that can directly bind to the CD73 active site to inhibit its enzyme activity. Meanwhile, although CD73 is a very potential therapeutic target, more research is needed to verify the prognosis of CD73 targets and to develop related drugs and combination therapies.

Summary

The disclosure provide an isolated antibody or antigen-binding fragment specifically binding for CD73 and uses thereof in the treatment diseases.

In one aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof comprising a heavy chain variable region that comprises HCDR1, HCDR2, HCDR3; and a light chain variable region that comprises LCDR1, LCDR2, LCDR3, wherein:

1) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 43, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 44, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 45, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 48, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 49, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 50;

2) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 5, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 6, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 7, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 10, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 11, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 12;

3) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 18, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 19, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 20, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 23, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 24, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 25;

4) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 31, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 32, (c) HCDR3 comprises an amino

acid sequence of SEQ ID NO: 33, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 36, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 37, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 38; or

5) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 56, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 57, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 58, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 61, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 62, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 63.

In one example, the disclosure provide an isolated antibody or antigen-binding fragment thereof comprising a heavy chain variable region that comprises HCDR1, HCDR2, HCDR3; and a light chain variable region that comprises LCDR1, LCDR2, LCDR3, wherein:

- (a) HCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 5, 18, 31, 43 and 56, and conservative modifications thereof;
- (b) HCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 19, 32, 44 and 57, and conservative modifications thereof;
- (c) HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 7, 20, 33, 45 and 58, and conservative modifications thereof;
- (d) LCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 10, 23, 36, 48 and 61, and conservative modifications thereof;
- (e) LCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 11, 24, 37, 49 and 62, and conservative modifications thereof; and
- (f) LCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 12, 25, 38, 50 and 63, and conservative modifications thereof.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises:

- 1) (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 11, and (f) LCDR3 comprising SEQ ID NO: 12;
- 2) (a) HCDR1 comprising SEQ ID NO: 18, (b) HCDR2 comprising SEQ ID NO: 19, (c) HCDR3 comprising SEQ ID NO: 20, (d) LCDR1 comprising SEQ ID NO: 23, (e) LCDR2 comprising SEQ ID NO: 24, and (f) LCDR3 comprising SEQ ID NO: 25;
- 3) (a) HCDR1 comprising SEQ ID NO: 31, (b) HCDR2 comprising SEQ ID NO: 32, (c) HCDR3 comprising SEQ ID NO: 33, (d) LCDR1 comprising SEQ ID NO: 36, (e) LCDR2 comprising SEQ ID NO: 37, and (f) LCDR3 comprising SEQ ID NO: 38;
- 4) (a) HCDR1 comprising SEQ ID NO: 43, (b) HCDR2 comprising SEQ ID NO: 44, (c) HCDR3 comprising SEQ ID NO: 45, (d) LCDR1 comprising SEQ ID NO: 48, (e) LCDR2 comprising SEQ ID NO: 49, and (f) LCDR3 comprising SEQ ID NO: 50; or
- 5) (a) HCDR1 comprising SEQ ID NO: 56, (b) HCDR2 comprising SEQ ID NO: 57, (c) HCDR3 comprising SEQ ID NO: 58, (d) LCDR1 comprising SEQ ID

NO: 61, (e) LCDR2 comprising SEQ ID NO: 62, and (f) LCDR3 comprising SEQ ID NO: 63.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 11, and (f) LCDR3 comprising SEQ ID NO: 12.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 18, (b) HCDR2 comprising SEQ ID NO: 19, (c) HCDR3 comprising SEQ ID NO: 20, (d) LCDR1 comprising SEQ ID NO: 23, (e) LCDR2 comprising SEQ ID NO: 24, and (f) LCDR3 comprising SEQ ID NO: 25.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 31, (b) HCDR2 comprising SEQ ID NO: 32, (c) HCDR3 comprising SEQ ID NO: 33, (d) LCDR1 comprising SEQ ID NO: 36, (e) LCDR2 comprising SEQ ID NO: 37, and (f) LCDR3 comprising SEQ ID NO: 38.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 43, (b) HCDR2 comprising SEQ ID NO: 44, (c) HCDR3 comprising SEQ ID NO: 45, (d) LCDR1 comprising SEQ ID NO: 48, (e) LCDR2 comprising SEQ ID NO: 49, and (f) LCDR3 comprising SEQ ID NO: 50.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 56, (b) HCDR2 comprising SEQ ID NO: 57, (c) HCDR3 comprising SEQ ID NO: 58, (d) LCDR1 comprising SEQ ID NO: 61, (e) LCDR2 comprising SEQ ID NO: 62, and (f) LCDR3 comprising SEQ ID NO: 63.

In some examples, the isolated antibody or antigen-binding fragment thereof comprises:

- (i) the heavy chain variable region(VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 3, 16, 29, 41, 54, 66, 67, 76, 77 and 78, and conservative modifications thereof; and
- (ii) the light chain variable region(VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 21, 34, 46, 59, 68, 69, 70, 79 and 80, and conservative modifications thereof.

In some examples, the heavy chain variable regions comprise an amino acid sequence which has at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy variable regions selected from the group of (i), and the light chain variable regions comprise an amino acid sequence which has at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the light variable regions selected from the group of (ii).

In some examples, the isolated antibody or antigen-binding fragment thereof comprises:

- 1) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 3, and a light chain variable region(VL) that comprises an amino acid sequence

- which has at least 85% identity to the amino acid sequences of SEQ ID NO: 8;
- 2) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 16, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identical to the amino acid sequences of SEQ ID NO:21;
 - 3) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 29, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 34;
 - 4) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 41, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 46;
 - 5) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 54, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 59;
 - 6) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 68;
 - 7) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 69;
 - 8) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 70;
 - 9) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 67, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 68;
 - 10) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO:

- 67, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 69;
- 11) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 67, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 70;
 - 12) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 76, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
 - 13) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 76, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80;
 - 14) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 77, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
 - 15) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 77, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80;
 - 16) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 78, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
 - 17) a heavy chain variable region(VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 78, and a light chain variable region(VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80.

In some examples, the isolated antibody or antigen-binding fragment thereof, wherein the heavy and light chain variable regions comprise an amino acid sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy and light chain variable regions, respectively, selected from the group consisting of 1)-17).

In some examples, the isolated antibody is an IgG.

In some examples, the isolated antibody is an IgG1, IgG2 or IgG4.

In some examples, the isolated antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, Fv, a single chain antibody (scFv), Fab, Fab', Fab'-SH or F(ab')₂.

In some examples, the isolated antibody or antigen-binding fragment thereof comprising a heavy chain and a light chain, wherein:

- (I) the heavy chain comprising an amino acid sequence which is at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 13, 15, 26, 27, 39, 51, 52, 64, 71, 72, 81, 82, 83, 86, 87, 90, 91, 124, 125, 126 and 127, and conservative modifications thereof; and
- (II) the light chain comprising an amino acid sequence which is at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 14, 28, 40, 53, 65, 73, 74, 75, 84, 85, 88 and 89, and conservative modifications thereof.

In some examples, the heavy chain comprises an amino acid sequence which has at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 100% identity to the heavy chains selected from the group of (I), and the light chain comprises an amino acid sequence which has at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 100% identity to the light chain selected from the group of (II).

In some examples, the isolated antibody or antigen-binding fragment thereof comprises:

- 1) a heavy chain that comprises an amino acid sequence which is at least 85% identity to the amino acid sequences of SEQ ID NO: 13, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 14;
- 2) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 15, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 14;
- 3) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 26, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 28;
- 4) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 27, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 28;
- 5) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 39, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 40;
- 6) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 51, and a light chain that

[illegible]

comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEO ID NO: 84;

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- comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 89;
- 29) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 124, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
 - 30) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 124, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
 - 31) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 125, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84; or
 - 32) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 125, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85.

In some examples, the heavy and light chain comprise an amino acid sequence at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy and light chain variable regions, respectively, selected from the group consisting of 1)-32).

In another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain of SEQ ID NO: 71 and a light chain of SEQ ID NO: 73.

In yet another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 72 and a light chain consisting essentially of SEQ ID NO: 74.

In one example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain of SEQ ID NO: 72 and a light chain of SEQ ID NO: 75.

In another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 81 and a light chain consisting essentially of SEQ ID NO: 85.

In yet another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 82 and a light chain consisting essentially of SEQ ID NO: 84.

In one example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 83 and a light chain consisting essentially of SEQ ID NO: 85.

In another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 124 and a light chain consisting essentially of SEQ ID NO: 85.

In yet another example, the disclosure provides an isolated antibody or antigen-binding fragment thereof, which comprises a heavy chain consisting essentially of SEQ ID NO: 125 and a light chain consisting essentially of SEQ ID NO: 85.

In some examples, the isolated antibody or antigen-binding fragment thereof is an antagonist of CD73 or 5'-nucleotidase of CD73.

In some examples, the CD73 is human CD73.

In another aspect, the present disclosure refers to the use of the isolated antibody or antigen-binding fragment thereof as disclosed herein in the manufacture of a medicament for decreasing adenosine levels in a tumor cell and/or a tumor microenvironment, for stimulating a T cell response in a subject with tumor, for stimulating an immune response in a subject, or for inhibiting the growth of tumor cells in a subject.

In another aspect, the present disclosure refers to the isolated antibody or antigen-binding fragment thereof as disclosed herein for use in decreasing adenosine levels in a tumor cell and/or a tumor microenvironment, for use in stimulating a T cell response in a subject with tumor, for use in stimulating an immune response in a subject, or for use in inhibiting the growth of tumor cells in a subject.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as disclosed herein, and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to the use of the isolated antibody or antigen-binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein for the manufacture of a medicament for a treatment of tumor, preferably, the tumor is selected from solid tumor or hematological tumor, more preferably, the tumor is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

In another aspect, the present disclosure refers to the isolated antibody or antigen-binding fragment thereof as disclosed herein, or the pharmaceutical composition as disclosed herein for use in a treatment of tumor, preferably, the tumor is selected from solid tumor or hematological tumor, more preferably, the cancer is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

In one example, the disclosure provides a method of decreasing adenosine levels in a subject with tumor, comprising administering a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof.

In another example, the disclosure provides a method of improving a T cell response in a subject with tumor, comprising administering a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof.

In yet another example, the disclosure provides a method of stimulating an immune response in a subject comprising administering a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof.

In some examples, the subject is the subject with tumor.

In some examples, the subject has a tumor cell expressing CD73 and/or a tumor microenvironment containing CD73.

In one example, the disclosure provides a method for inhibiting the growth of tumor cells in a subject comprising administering to the subject a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof

In another example, the disclosure provides use of the isolated antibody or antigen-binding fragment thereof in the manufacture of a medicament for decreasing adenosine levels in a tumor cell and/or a tumor microenvironment.

In yet another example, the disclosure provides use of the isolated antibody or antigen-binding fragment thereof in the manufacture of a medicament for stimulating a T cell response in a subject with tumor.

In one example, the disclosure provides use of the isolated antibody or antigen-binding fragment thereof in the manufacture of a medicament for stimulating an immune response in a subject.

In some examples, the subject is a subject with tumor.

In some examples, the subject has a tumor cell expressing CD73 and/or a tumor microenvironment containing CD73.

In another example, the disclosure provides use of the isolated antibody or antigen-binding fragment thereof in the manufacture of a medicament for inhibiting the growth of tumor cells in a subject.

In yet another example, the disclosure provides the isolated antibody or antigen-binding fragment thereof for use in decreasing adenosine levels in a tumor cell and/or a tumor microenvironment.

In one example, the disclosure provides the isolated antibody or antigen-binding fragment thereof for use in stimulating a T cell response in a subject with tumor.

In another example, the disclosure provides the isolated antibody or antigen-binding fragment thereof for use in stimulating an immune response in a subject.

In some examples, the subject is a subject with tumor.

In some examples, the subject has a tumor cell expressing CD73 and/or a tumor microenvironment containing CD73.

In another example, the disclosure provides the isolated antibody or antigen-binding fragment thereof for use in inhibiting the growth of tumor cells in a subject.

In another aspect, the present disclosure refers to a nucleic acid composition, which comprises:

(I) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 47, 105 and 106;

(II) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 4; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 9;

(III) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 22, 94, 95 and 96;

(IV) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 30; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 35;

(V) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 55; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60;

(VI) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115; or

(VII) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101; preferably, the nucleic acid composition comprises:

1) the first nucleic acid comprising SEQ ID NO: 4 and the second nucleic acid comprising SEQ ID NO: 9;

2) the first nucleic acid comprising SEQ ID NO: 17 and the second nucleic acid comprising SEQ ID NO: 22;

3) the first nucleic acid comprising SEQ ID NO: 30 and the second nucleic acid comprising SEQ ID NO: 35;

4) the first nucleic acid comprising SEQ ID NO: 42 and the second nucleic acid comprising SEQ ID NO: 47;

5) the first nucleic acid comprising SEQ ID NO: 55 and the second nucleic acid comprising SEQ ID NO: 60;

6) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 94;

7) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 95;

8) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 96;

9) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 94;

10) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 95;

11) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 96;

12) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 105;

13) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 106;

- 14) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 105;
- 15) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 106;
- 16) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 105;
- 17) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 106;
- 18) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 99;
- 19) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 100;
- 20) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 101;
- 21) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 99;
- 22) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 100;
- 23) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 101;
- 24) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 110;
- 25) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 111;
- 26) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 110;
- 27) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 111;
- 28) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 110;
- 29) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 111;
- 30) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 110;
- 31) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 111;
- 32) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 110;
- 33) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 111;
- 34) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 114;
- 35) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 115;

36) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 114; or

37) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 115.

In another aspect, the present disclosure refers to an expression vector composition, which comprises:

(I) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 47, 105 and 106;

(II) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9;

(III) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 22, 94, 95 and 96;

(IV) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 30; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 35;

(V) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 55; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 60;

(VI) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115; or

(VII) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101;

preferably, the expression vector composition comprises:

1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9;

2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 17 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 22;

3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 30 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 35;

4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 42 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 47;

5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 55 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 60;

6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 94;

7) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 95;

- [illegible]

30) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;

31) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;

32) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;

33) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;

34) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 114;

35) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 115;

36) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 114; or

37) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 115.

In another aspect, the present disclosure refers to an expression vector, which comprises:

(I) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 47, 105 and 106;

(II) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 4; and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 9;

(III) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 22, 94, 95 and 96;

(IV) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30; and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 35; or

(V) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 55; and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 60,

(VI) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115; or

(VII) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101;

preferably, the expression vector comprises:

- 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 4 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 9;
- 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 17 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 22;
- 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 35;
- 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 42 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 47;
- 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 55 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 60;
- 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 8) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 9) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 10) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 11) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 12) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 13) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 14) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 15) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;

- 16) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 17) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 18) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 19) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 20) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 21) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 22) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 23) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 24) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 25) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 26) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 27) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 28) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 29) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;

30) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;

31) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;

32) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;

33) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;

34) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114;

35) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115;

36) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114; or

37) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115.

In another aspect, the present disclosure refers to a cell comprising the expression vector composition as disclosed herein or the expression vector as disclosed herein.

In yet another aspect, the present disclosure refers to a method of preparing the isolated antibody or antigen-binding fragment thereof as disclosed herein, comprising expressing the isolated antibody or antigen-binding fragment thereof in the cell as disclosed herein, and isolating the isolated antibody or antigen-binding fragment from the cell.

In yet another aspect, the present disclosure refers to a kit comprising the isolated antibody or antigen-binding fragment thereof as disclosed herein.

In yet another example, the disclosure provides an isolated nucleic acid composition, which comprises:

- (I) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4, 17, 30, 42, 55, 92, 93, 102, 103 and 104; and
- (II) a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 9, 22, 35, 47, 60, 94, 95, 96, 105 and 106.

In some examples, the isolated nucleic acid composition comprises:

- 1) the first nucleic acid comprising SEQ ID NO: 4 and the second nucleic acid comprising SEQ ID NO: 9;
- 2) the first nucleic acid comprising SEQ ID NO: 17 and the second nucleic acid comprising SEQ ID NO: 22;

- 3) the first nucleic acid comprising SEQ ID NO: 30 and the second nucleic acid comprising SEQ ID NO: 35;
- 4) the first nucleic acid comprising SEQ ID NO: 42 and the second nucleic acid comprising SEQ ID NO: 47;
- 5) the first nucleic acid comprising SEQ ID NO: 55 and the second nucleic acid comprising SEQ ID NO: 60;
- 6) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 94;
- 7) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 95;
- 8) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 96;
- 9) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 94;
- 10) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 95;
- 11) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 96;
- 12) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 105;
- 13) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 106;
- 14) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 105;
- 15) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 106;
- 16) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 105; or
- 17) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 106.

In one example, the disclosure provides an expression vector composition, which comprises:

- (I) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4, 17, 30, 42, 55, 92, 93, 102, 103 and 104; and
- (II) a second expression vector comprising a nucleotide sequences selected from the group consisting of SEQ ID NOs: 9, 22, 35, 47, 60, 94, 95, 96, 105 and 106.

In some examples, the expression vector composition comprises:

- 1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9;
- 2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 17 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 22;

- 3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 30 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 35;
- 4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 42 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 47;
- 5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 55 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 60;
- 6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 94;
- 7) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 95;
- 8) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 96;
- 9) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 94;
- 10) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 95;
- 11) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 96;
- 12) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 102 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 105;
- 13) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 102 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 106;
- 14) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 103 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 105;
- 15) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 103 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 106;
- 16) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 104 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 105; or
- 17) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 104 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 106.

In another example, the disclosure provides an expression vector, which comprises:

- (I) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4, 17, 30, 42, 55, 92, 93, 102, 103 and 104 ;and
- (II) a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 9, 22, 35, 47, 60, 94, 95, 96, 105 and 106.

In some examples, the expression vector, comprises:

- 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 4 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 9;
- 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 17 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 22;
- 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 35;
- 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 42 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 47;
- 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 55 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 60;
- 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 8) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 9) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 10) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 11) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 12) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 13) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 14) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;

- 15) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 16) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 17) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106.

In yet another example, the disclosure provides an isolated nucleic acid composition, which comprises:

- (I) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97, 98, 107, 108, 109, 112, 113, 116 and 117; and
- (II) a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100, 101, 110, 111, 114 and 115.

In some examples, the isolated nucleic acid composition, comprises:

- 1) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 99;
- 2) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 100;
- 3) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 101;
- 4) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 99;
- 5) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 100;
- 6) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 101;
- 7) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 110;
- 8) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 111;
- 9) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 110;
- 10) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 111;
- 11) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 110;
- 12) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 111;
- 13) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 110;
- 14) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 111;

- 15) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 110;
- 16) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 111;
- 17) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 114;
- 18) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 115;
- 19) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 114; or
- 20) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 115.

In one example, the disclosure provides an expression vector composition, which comprises:

- (I) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97, 98, 107, 108, 109, 112, 113, 116 and 117; and
- (II) a second expression vector comprising a nucleotide sequences selected from the group consisting of SEQ ID NOs: 99, 100, 101, 110, 111, 114 and 115.

In some examples, the disclosure provides the expression vector composition, which comprises:

- 1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 99;
- 2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 100;
- 3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 101;
- 4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 99;
- 5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 100;
- 6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 101;
- 7) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 107 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;
- 8) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 107 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;

- 9) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 108 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;
- 10) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 108 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;
- 11) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 109 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;
- 12) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 109 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;
- 13) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;
- 14) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;
- 15) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 110;
- 16) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 111;
- 17) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 114;
- 18) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 115;
- 19) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 114; or
- 20) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 115.

In another example, the disclosure provides an expression vector, which comprises:

- (I) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97, 98, 107, 108, 109, 112, 113, 116 and 117 ;and
- (II) a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100, 101, 110, 111, 114 and 115.

In some examples, the expression vector, comprises:

- 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 8) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 9) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 10) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 11) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 12) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 13) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 14) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;

- 15) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 16) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 17) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114;
- 18) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115;
- 19) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114; or
- 20) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115.

In yet another example, the disclosure provides a cell comprising any one of the expression vector composition.

In one example, the disclosure provides a method of preparing the isolated antibody or antigen-binding fragment thereof, comprising expressing the isolated antibody or antigen-binding fragment thereof in the cell, and isolating the isolated antibody or antigen-binding fragment from the cell.

In another example, the disclosure provides a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof, and a pharmaceutically acceptable excipient.

In yet another example, the disclosure provides a kit comprising the isolated antibody or antigen-binding fragment thereof.

In one example, the disclosure provides a method of treating tumor comprising administering a subject in need a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof, or the pharmaceutical composition. In some examples, the tumor is selected from solid tumor or hematological tumor. In some examples, the tumor is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

In another example, the disclosure provides use of the isolated antibody or antigen-binding fragment thereof, or the pharmaceutical composition for the manufacture of a medicament for a treatment of tumor. In some examples, the tumor is selected from solid tumor or hematological tumor. In some examples, the tumor is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular

cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

In yet another example, the disclosure provides the isolated antibody or antigen-binding fragment thereof, or the pharmaceutical composition for use in a treatment of tumor. In some examples, the tumor is selected from solid tumor or hematological tumor. In some examples, the cancer is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

Table I Description of the antibody sequence listing of the invention

SEQ ID NO:	Sequence Description	Sequence
1	huCD73	WELTILHTNDVHSRLEQTSSEDSSKCVNASRCMGG VARLFTKVQQIRRAEPNVLLLDAGDQYQGTIWF VYKGAEVAHFMNALRYDAMALGNHEFDNGVEG LIEPLLKEAKFPILSANIKAKGPLASQISGLYLPYK VLPVGDEVVGIVGYTSKETPFLSNPGTNLVFEDEI TALQPEVDKLKTLNVNKKIHALGHSGFEMDKLIAQ KVRGVDVVVGHSNTFLYTGNPPSKEVPAGKYP FIVTSDDGRKVPVVQAYAFGKYLGYLKIEFDERG NVISSHGNPILLNSSIPEDPSIKADINKWRIKLDNYS TQELGKTIVYLDGSSQSCRFRECNMGNLICDAMIN NNLRHTDEMFWNHVSMCILNGGGIRSPIDERNNG TITWENLAAVLPFGGTFDLVQLKGSTLKKAFEHS VHRYGQSTGEFLQVGGIHVVDLSRKPGDRVVK LDVLCCTKCRVPSYDPLKMDEVYKVILPNFLANGG DGFQMIKDELLRHDSGDQDINVVSTYISKMKVIYP AVEGRIKAHHHHHHHHHH

VH region are abbreviated as HCDR, that is, the three CDRs of the VH region can be abbreviated as HCDR1, HCDR2, and HCDR3; the CDRs of the VL region are abbreviated as LCDR, that is, the three CDRs of the VL region can be abbreviated as LCDR1, LCDR2, LCDR3. Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component of the classical complement system (C1q).

The heavy chain of an antibody may or may not contain a terminal lysine (K), or a terminal glycine and lysine (GK). Thus, any of the heavy chain sequences and heavy chain constant region sequences provided herein can end in either GK or K, or lack K or GK, regardless of what the last amino acid of the sequence provides. This is because the terminal lysine and sometimes glycine and lysine are cleaved during expression of the antibody.

Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K_D) of 10^{-7} to 10^{-11} M or less. Any K_D greater than about 10^{-6} M is generally considered to indicate binding nonspecifically. As used herein, an antibody that "binds specifically" to an antigen refers to an antibody that binds to the antigen and substantially identical antigens with high affinity, which means having a K_D of 10^{-7} M or less, preferably 10^{-8} M or less, even more preferably 5×10^{-9} M or less, and most preferably between 10^{-8} M and 10^{-10} M or less, but does not bind with high affinity to unrelated antigens. An antigen is "substantially identical" to a given antigen if it exhibits a high degree of sequence identity to the given antigen, for example, if it exhibits at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% or greater sequence identity to the sequence of the given antigen. By way of example, an antibody that binds specifically to human CD73 may also cross-react with CD73 from some non-human primate species (e.g., cynomolgus),

JB94H2L1	380.4	875	0.002
JB94H3L3	245.9	1419	0.003
JB94Chi	267.4	1550	0.004

Example 12: Inhibition of 5'exonuclease activity in A375 xenograft model by humanized antibody

B-NDG mice (Biocytogen) were subcutaneously inoculated with A375 cells, and 3 days later, the antibodies JB94H1L3, 94H3L3 hIgG1 (SEQ ID NOS: 91 and 85) or PBS were injected intraperitoneally (i.p.) 2 times / week, and dosing for two weeks, tumors were harvested at 1d, 2d, 3d, and 7d after administration. Place fresh tissue in a small cup filled with liquid nitrogen to freeze the tissue quickly, embed it in OCT, cut into 5-6 μ m thickness and dry at room temperature. The tumor section is fixed with 4 °C pre-cooled acetone for 20 min. Store at -80 °C after drying . Take the tumor section out of the refrigerator at -80 °C, equilibrate at room temperature for 5-10min, put it into 50mM Tris-maleic acid buffer (PH7.4, containing 2mM CaCl₂ and 0.25M sucrose), pre-incubate at room temperature for 1h, remove the pre-incubation buffer after 1 h, and again add 50 mM Tris-maleic acid buffer (PH7.4, containing 5 mM MnCl₂, 2 mM lead nitrate, 2.5% dextran T200, 2.5 mM levamisole and 400 μ M AMP), incubate at 37 °C for 1.5h; rinse three times with water, incubate the sections with 1% (NH₄)₂S for 1 min at room temperature, and then quickly rinse three times with water; the sections were counterstained with hematoxylin and eosin, dehydrated, xylene transparent, and photographed under a microscope. Brown indicates the presence of activated CD73, and deletion of brown indicates that the antibody blocks the enzyme activity of CD73. Results are shown in Figure 15A and Figure 15B.

The above results show that both JB94H1L3 and 94H3L3 hIgG1 can significantly reduce the 5'exonuclease activity of tumors in xenograft animal models,

THE CLAIMS

1. An isolated antibody or antigen-binding fragment thereof comprising a heavy chain variable region that comprises HCDR1, HCDR2, HCDR3; and a light chain variable region that comprises LCDR1, LCDR2, LCDR3, wherein:
 - 1) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 43, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 44, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 45, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 48, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 49, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 50;
 - 2) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 5, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 6, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 7, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 10, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 11, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 12;
 - 3) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 18, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 19, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 20, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 23, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 24, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 25;
 - 4) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 31, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 32, (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 33, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 36, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 37, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 38; or
 - 5) (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 56, (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 57, (c)

HCDR3 comprises an amino acid sequence of SEQ ID NO: 58, (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 61, (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 62, and (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 63.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, which comprises:

- (i) a heavy chain variable region (VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 41, 76, 77 and 78, and a light chain variable region (VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 46, 79 and 80;
- (ii) a heavy chain variable region (VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 3, and a light chain variable region (VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 8;
- (iii) a heavy chain variable region (VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 16, 66 and 67, and a light chain variable region (VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 21, 68, 69, and 70;
- (iv) a heavy chain variable region (VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 29, and a light chain variable region (VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 34; or
- (v) a heavy chain variable region (VH) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO:

54, and a light chain variable region (VL) comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 59,

preferably, the isolated antibody or antigen-binding fragment thereof comprises:

- 1) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 3, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 8;
- 2) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 16, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identical to the amino acid sequences of SEQ ID NO:21;
- 3) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 29, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 34;
- 4) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 41, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 46;
- 5) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 54, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 59;

- 6) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 68;
- 7) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 69;
- 8) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 66, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 70;
- 9) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 67, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 68;
- 10) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 67, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 69;
- 11) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 67, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 70;

- 12) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 76, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
- 13) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 76, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80;
- 14) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 77, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
- 15) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 77, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80;
- 16) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 78, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 79;
- 17) a heavy chain variable region (VH) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 78, and a light chain variable region (VL) that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 80.

3. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 2, wherein the isolated antibody is
- i) an IgG;
 - ii) an IgG1, IgG2 or IgG4; and/or
 - iii) a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, Fv, a single chain antibody (scFv), Fab, Fab', Fab'-SH or F(ab')₂.
4. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 3, comprising
- (I) a heavy chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 51, 52, 81, 82, 83, 86, 87, 90, 91, 120, 124, 125, 126 and 127; and a light chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 53, 84, 85, 88, 89 and 121;
 - (II) a heavy chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 13 and 15; and a light chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 14;
 - (III) a heavy chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 26, 27, 71 and 72; and a light chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 28, 74 and 75;
 - (IV) a heavy chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 39 and 118; and a light chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 40 and 119;

- (V) a heavy chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 64 and 122; and a light chain comprising an amino acid sequence which has at least 85% identity to the amino acid sequences selected from the group consisting of SEQ ID NOs: 65 and 123;

preferably, the isolated antibody or antigen-binding fragment thereof comprises:

- 1) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 13, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 14;
- 2) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 15, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 14;
- 3) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 26, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 28;
- 4) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 27, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 28;
- 5) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 39, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 40;
- 6) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 51, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 53;

- 7) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 52, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 53;
- 8) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 64, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 65;
- 9) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 71, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 73;
- 10) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 71, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 74;
- 11) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 71, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 75;
- 12) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 72, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 73;
- 13) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 72, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 74;
- 14) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 72, and a light chain that

- comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 75;
- 15) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 81, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
- 16) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 81, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 17) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 82, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
- 18) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 82, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 19) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 83, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
- 20) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 83, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 21) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 90, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;

- 22) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 90, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 23) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 91, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
- 24) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 91, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 25) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 86, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 88;
- 26) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 86, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 89;
- 27) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 87, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 88;
- 28) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 87, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 89;
- 29) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 124, and a light chain

- that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84;
- 30) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 124, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85;
- 31) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 125, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 84; or
- 32) a heavy chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequences of SEQ ID NO: 125, and a light chain that comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 85,
- more preferably, the isolated antibody or antigen-binding fragment thereof comprises
- a) a heavy chain consisting essentially of SEQ ID NO: 71 and a light chain consisting essentially of SEQ ID NO: 73;
- b) a heavy chain consisting essentially of SEQ ID NO: 72 and a light chain consisting essentially of SEQ ID NO: 74;
- c) a heavy chain consisting essentially of SEQ ID NO: 72 and a light chain consisting essentially of SEQ ID NO: 75;
- d) a heavy chain consisting essentially of SEQ ID NO: 81 and a light chain consisting essentially of SEQ ID NO: 85;
- e) a heavy chain consisting essentially of SEQ ID NO: 82 and a light chain consisting essentially of SEQ ID NO: 84;
- f) a heavy chain consisting essentially of SEQ ID NO: 83 and a light chain consisting essentially of SEQ ID NO: 85;
- g) a heavy chain consisting essentially of SEQ ID NO: 124 and a light chain consisting essentially of SEQ ID NO: 85; or

- h) a heavy chain consisting essentially of SEQ ID NO: 125 and a light chain consisting essentially of SEQ ID NO: 85.
5. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 4, which is an antagonist of CD73 or an antagonist of 5'-nucleotidase of CD73, preferably, the CD73 is human CD73.
 6. Use of the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5 in the manufacture of a medicament for decreasing adenosine levels in a tumor cell and/or a tumor microenvironment, for stimulating a T cell response in a subject with tumor, for stimulating an immune response in a subject, or for inhibiting the growth of tumor cells in a subject.
 7. The use of claim 6, wherein the subject is a subject with tumor, preferably, the subject has a tumor cell expressing CD73 and/or a tumor microenvironment containing CD73.
 8. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5 for use in decreasing adenosine levels in a tumor cell and/or a tumor microenvironment, for use in stimulating a T cell response in a subject with tumor, for use in stimulating an immune response in a subject, or for use in inhibiting the growth of tumor cells in a subject.
 9. The isolated antibody or antigen-binding fragment thereof for use according to claim 8, wherein the subject is a subject with tumor, preferably, the subject has a tumor cell expressing CD73 and/or a tumor microenvironment containing CD73.
 10. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5, and a pharmaceutically acceptable excipient.
 11. Use of the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5, or the pharmaceutical composition of claim 10 for the manufacture of a medicament for a treatment of tumor, preferably, the tumor is selected from solid tumor or hematological tumor, more preferably, the tumor is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer,

gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

12. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5, or the pharmaceutical composition of claim 10 for use in a treatment of tumor, preferably, the tumor is selected from solid tumor or hematological tumor, more preferably, the cancer is selected from bladder cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, pancreatic cancer, colorectal cancer, colon cancer, renal cancer, head and neck cancer, lung cancer (small cell lung cancer or non-small cell lung cancer), stomach cancer, bone cancer, liver cancer, thyroid cancer, skin cancer, central nervous system tumor, lymphoma, leukemia, myeloma, sarcoma, and virus-associated cancer.

13. A nucleic acid composition, which comprises:

- (I) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 47, 105 and 106;
- (II) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 4; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 9;
- (III) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 22, 94, 95 and 96;
- (IV) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 30; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 35;

- (V) a first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 55; and a second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60,
- (VI) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115; or
- (VII) a first nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101;

preferably, the nucleic acid composition comprises:

- 1) the first nucleic acid comprising SEQ ID NO: 4 and the second nucleic acid comprising SEQ ID NO: 9;
- 2) the first nucleic acid comprising SEQ ID NO: 17 and the second nucleic acid comprising SEQ ID NO: 22;
- 3) the first nucleic acid comprising SEQ ID NO: 30 and the second nucleic acid comprising SEQ ID NO: 35;
- 4) the first nucleic acid comprising SEQ ID NO: 42 and the second nucleic acid comprising SEQ ID NO: 47;
- 5) the first nucleic acid comprising SEQ ID NO: 55 and the second nucleic acid comprising SEQ ID NO: 60;
- 6) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 94;
- 7) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 95;
- 8) the first nucleic acid comprising SEQ ID NO: 92 and the second nucleic acid comprising SEQ ID NO: 96;
- 9) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 94;

- 10) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 95;
- 11) the first nucleic acid comprising SEQ ID NO: 93 and the second nucleic acid comprising SEQ ID NO: 96;
- 12) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 105;
- 13) the first nucleic acid comprising SEQ ID NO: 102 and the second nucleic acid comprising SEQ ID NO: 106;
- 14) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 105;
- 15) the first nucleic acid comprising SEQ ID NO: 103 and the second nucleic acid comprising SEQ ID NO: 106;
- 16) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 105;
- 17) the first nucleic acid comprising SEQ ID NO: 104 and the second nucleic acid comprising SEQ ID NO: 106;
- 18) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 99;
- 19) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 100;
- 20) the first nucleic acid comprising SEQ ID NO: 97 and the second nucleic acid comprising SEQ ID NO: 101;
- 21) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 99;
- 22) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 100;
- 23) the first nucleic acid comprising SEQ ID NO: 98 and the second nucleic acid comprising SEQ ID NO: 101;
- 24) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 110;

- 25) the first nucleic acid comprising SEQ ID NO: 107 and the second nucleic acid comprising SEQ ID NO: 111;
- 26) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 110;
- 27) the first nucleic acid comprising SEQ ID NO: 108 and the second nucleic acid comprising SEQ ID NO: 111;
- 28) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 110;
- 29) the first nucleic acid comprising SEQ ID NO: 109 and the second nucleic acid comprising SEQ ID NO: 111;
- 30) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 110;
- 31) the first nucleic acid comprising SEQ ID NO: 116 and the second nucleic acid comprising SEQ ID NO: 111;
- 32) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 110;
- 33) the first nucleic acid comprising SEQ ID NO: 117 and the second nucleic acid comprising SEQ ID NO: 111;
- 34) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 114;
- 35) the first nucleic acid comprising SEQ ID NO: 112 and the second nucleic acid comprising SEQ ID NO: 115;
- 36) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 114; or
- 37) the first nucleic acid comprising SEQ ID NO: 113 and the second nucleic acid comprising SEQ ID NO: 115.

14. An expression vector composition, which comprises:

- (I) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a second

expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 47, 105 and 106;

- (II) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9;
- (III) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 22, 94, 95 and 96;
- (IV) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 30; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 35;
- (V) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 55; and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 60,
- (VI) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115;
or
- (VII) a first expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second expression vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101;

preferably, the expression vector composition comprises:

- 1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9;

- 2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 17
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 22;
- 3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 30
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 35;
- 4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 42
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 47;
- 5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 55
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 60;
- 6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 94;
- 7) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 95;
- 8) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 92
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 96;
- 9) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 94;
- 10) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 95;
- 11) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 93
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 96;

- 12) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 102
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 105;
- 13) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 102
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 106;
- 14) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 103
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 105;
- 15) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 103
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 106;
- 16) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 104
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 105;
- 17) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 104
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 106;
- 18) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 99;
- 19) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 100;
- 20) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 97
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 101;
- 21) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 99;

- 22) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 100;
- 23) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 98
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 101;
- 24) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 107
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 110;
- 25) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 107
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 111;
- 26) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 108
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 110;
- 27) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 108
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 111;
- 28) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 109
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 110;
- 29) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 109
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 111;
- 30) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 110;
- 31) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 116
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 111;

- 32) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 110;
 - 33) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 117
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 111;
 - 34) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 114;
 - 35) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 112
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 115;
 - 36) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 114; or
 - 37) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 113
and a second expression vector comprising a nucleotide sequence of SEQ ID
NO: 115.
15. An expression vector, which comprises:
- (I) a first nucleic acid sequence comprising a nucleotide sequence selected
from the group consisting of SEQ ID NOs: 42, 102, 103 and 104; and a
second nucleic acid sequence comprising a nucleotide sequence selected
from the group consisting of SEQ ID NOs: 47, 105 and 106;
 - (II) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID
NO: 4; and a second nucleic acid sequence comprising a nucleotide
sequence of SEQ ID NO: 9;
 - (III) a first nucleic acid sequence comprising a nucleotide sequence selected
from the group consisting of SEQ ID NOs: 17, 92 and 93; and a second
nucleic acid sequence comprising a nucleotide sequence selected from the
group consisting of SEQ ID NOs: 22, 94, 95 and 96;

- (IV) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30; and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 35; or
- (V) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 55; and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 60,
- (VI) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 107, 109, 109, 112, 113, 116 and 117; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 110, 111, 114 and 115; or
- (VII) a first nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 97 and 98; and a second nucleic acid sequence comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 99, 100 and 101;

preferably, the expression vector comprises:

- 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 4 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 9;
- 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 17 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 22;
- 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 35;
- 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 42 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 47;

- 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 55 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 60;
- 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 8) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 92 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 9) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 94;
- 10) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 95;
- 11) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 93 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 96;
- 12) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 13) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 102 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 14) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;

- 15) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 103 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 16) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 105;
- 17) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 104 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 106;
- 18) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 19) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 20) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 97 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 21) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 99;
- 22) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 100;
- 23) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 98 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 101;
- 24) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;

- 25) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 107 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 26) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 27) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 108 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 28) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 29) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 109 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 30) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 31) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 116 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 32) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 110;
- 33) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 117 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 111;
- 34) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114;

- 35) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 112 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115;
- 36) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 114; or
- 37) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 113 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 115.
16. A cell comprising the expression vector composition of claim 14 or the expression vector of claim 15.
17. A method of preparing the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5, comprising expressing the isolated antibody or antigen-bind thereof in the cell of claim 16, and isolating the isolated antibody or antigen-binding fragment from the cell.
18. A kit comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 5.