

The present inventors have generated a large repertoire of fully human mAbs against several immune-regulatory checkpoints using a strategy for rapid, parallel screening of phage displayed antibody libraries by directly panning on activated human lymphocytes. It was demonstrated that the thus selected mAbs are endowed with high binding affinity for their targets and improved functional activity on lymphocytes.

Summary

In ~~a first~~one aspect~~example~~, the present disclosure provides an antagonistic antigen binding protein that specifically binds to PD-1, wherein said antigen binding protein competes for binding to PD-1 with an antibody

- (i) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 2; and a light chain variable region of the amino acid sequence in SEQ ID NO: 3; or
- (ii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 11; and a light chain variable region of the amino acid sequence in SEQ ID NO: 12.

In ~~another a second~~example~~aspect~~, the present disclosure relates to an antagonistic antigen binding protein that specifically binds to PD-L1, wherein said antigen binding protein competes for binding to PD-L1 with an antibody

- (i) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 20; and a light chain variable region of the amino acid sequence in SEQ ID NO: 21; or
- (ii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 29; and a light chain variable region of the amino acid sequence in SEQ ID NO: 30;
- (iii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 83; and a light chain variable region of the amino acid sequence in SEQ ID NO: 84; or
- (iv) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 92; and a light chain variable region of the amino acid sequence in SEQ ID NO: 93; or
- (v) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 101; and a light chain variable region of the amino acid sequence in SEQ ID NO: 102.

In ~~another a third example~~ aspect, the present disclosure relates to an antagonistic antigen binding protein that specifically binds to LAG-3, wherein said antigen binding protein competes for binding to LAG-3 with an antibody

- (i) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 38; and a light chain variable region of the amino acid sequence in SEQ ID NO: 39;
- (ii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 47; and a light chain variable region of the amino acid sequence in SEQ ID NO: 48;
- (iii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 56; and a light chain variable region of the amino acid sequence in SEQ ID NO: 57;
- (iv) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 65; and a light chain variable region of the amino acid sequence in SEQ ID NO: 66; or
- (v) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 74; and a light chain variable region of the amino acid sequence in SEQ ID NO: 75.

In ~~another a fourth example~~ aspect, the present disclosure relates to an antagonistic antigen binding protein that specifically binds to PD-1, wherein said antigen binding protein comprises either

- (i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 3 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 2;
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 12 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 11;
- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 8
and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 9;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 17

5 and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 18, preferably further comprising one or more selected from the group consisting of a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 4 or 13, a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NOs: 6 or 15, CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 5 or 14 and a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NOs: 7 or 16.

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In one example, the present disclosure relates to an antagonistic antigen binding protein that specifically binds to PD-1, wherein said antigen binding protein comprises either

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- (i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:

a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 3 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 2;

20

a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 12 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 11;

25

- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 8
and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 9;

30

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 17
and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 18.

In ~~another a fifth example~~ aspect, the present disclosure refers to an antagonistic antigen binding protein that specifically binds to PD-L1, wherein said antigen binding protein comprises either

- (i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:
- a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 21 and
 - 5 a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 20;
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 30 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 29;
 - 10 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 84 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 83;
 - 15 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 93 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 92;
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 102 and
 - 20 a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 101;
- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:
- a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 26 and
 - a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;
 - a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 35 and
 - 30 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 36;
 - a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 89 and
 - a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 90;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 98
and a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO:
99;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 107
and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 108, preferably
further comprising one or more selected from the group consisting of a CDRH1 comprising or
consisting of the amino acid sequence of SEQ ID NOS: 22, 31, 85, 94 or 103, a CDRH2
comprising or consisting of the amino acid sequence of SEQ ID NOS: 24, 33, 87, 96 or 105, a
CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NOS: 23, 32, 86, 95
or 104 and a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NOS: 25,
34, 88, 97 or 106.

In another example, the present disclosure relates to an antagonistic antigen binding
protein that specifically binds to PD-L1, wherein said antigen binding protein comprises either

(i) a combination of a light chain variable domain and a heavy chain variable domain
selected from the group of combinations consisting of:

a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 21 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 20;

a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 30 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 29;

a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 84 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 83;

a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 93 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 92;

a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 102 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 101;

- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3)

selected from the group of combinations consisting of:

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 26
and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 35

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 36;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 89

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 90;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 98

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 99;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 107

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 108.

In ~~another~~ sixth example aspect, the present disclosure refers to an antagonistic antigen binding protein that specifically binds to LAG-3, wherein said antigen binding protein comprises either

- (i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:

a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 39 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 38;

a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 48 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 47;

- a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 57 and
- a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 56;
- 5 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 66 and
- a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 65;
- 10 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 75 and
- a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 74;
- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3)
- 15 selected from the group of combinations consisting of:
- a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 44 and
- a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 45;
- a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 53
- 20 and
- a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 54;
- a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 62 and
- and
- a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 63;
- 25 a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 71 and
- a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 72;
- a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 80 and
- 30 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 81, preferably further comprising one or more selected from the group consisting of a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 40, 49, 58, 67, or 76, a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NOs: 42, 51, 60, 69, or 78, CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 41, 50, 59, 68,

or 77 and a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NOs: 43, 52, 61, 70, or 79.

In another example, the present disclosure relates to an antagonistic antigen binding protein that specifically binds to LAG-3, wherein said antigen binding protein comprises either

- 5 (i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 39 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 38;
 - 10 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 48 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 47;
 - 15 a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 57 and
 - a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 56;
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 66 and
 - 20 a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 65;
 - a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 75 and
 - 25 a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 74;
- (ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:
 - 30 a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 44 and
 - a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 45;

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 53 and
 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 54;
 a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 62 and
 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 63;
 5 a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 71 and
 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 72;
 a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 80 and
 a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 81.

10 In ~~a-seventh~~another aspect, the present disclosure relates to a nucleic acid encoding the
 antagonistic antigen binding protein ~~of any one of aspects 1 to 6 of the present disclosure~~as described
herein.

In ~~another~~an eighth aspect, the present disclosure relates to a recombinant expression vector
 comprising a nucleic acid molecule as described herein~~according to the seventh aspect~~.

15 In ~~another~~a ninth aspect, the present disclosure relates to a host cell comprising the vector as
~~described herein~~of the eighth aspect of the present disclosure.

In ~~another~~a tenth aspect, the present disclosure relates to a method of making the antagonistic
 antigen binding protein as described herein~~of any one of aspects 1 to 6 of the present disclosure~~
 comprising the step of preparing said antigen binding protein from a host cell expressing said antigen
 binding protein.

20 In ~~another~~an eleventh aspect, the present disclosure relates to an antagonistic antigen binding
 protein produced by the expression of recombinant DNA in the host cell as described herein~~of the ninth~~
~~aspect of the present disclosure~~.

25 In a further aspect, the present disclosure relates to a pharmaceutical composition comprising at
least one antagonistic antigen binding protein as described herein, the nucleic acid as described herein,
or the vector as described herein and a pharmaceutically acceptable carrier, preferably wherein the
composition comprises at least one further active agent. In another example~~a twelfth aspect~~, the present
 disclosure relates to a pharmaceutical composition comprising at least one antagonistic antigen binding
 protein ~~according to any one of aspects 1 to 6 of the present disclosure~~as described herein, the nucleic
 acid as described herein~~according to the seventh aspect of the present disclosure~~ or the vector as
 30 described herein~~according to the eighth aspect of the present disclosure~~ and a pharmaceutically
 acceptable carrier.

In ~~a-thirteenth~~another aspect, the present disclosure relates to a kit comprising the
 pharmaceutical composition as described herein~~according to the twelfth aspect of the present disclosure~~
 and optionally at least one further active agent.

In ~~a-fourteenth~~another aspect, the present disclosure refers to the antagonistic antigen binding protein as described herein, the nucleic acid as described herein, the vector as described herein, or the pharmaceutical composition as described herein for use in therapy.

In another example, the present disclosure relates to the antagonistic antigen binding protein as described herein~~according to any one of aspects 1 to 6 of the present disclosure~~, the nucleic acid as described herein~~of the seventh aspect of the present disclosure~~, the vector as described herein~~of the eighth aspect of the present disclosure~~ or the pharmaceutical composition as described herein~~of the twelfth aspect of the present disclosure~~ for use in the treatment of cancer and/or chronic infectious disease.

In a ~~fifteenth~~further aspect, the present disclosure refers to use of the antagonistic antigen binding protein as described herein, the nucleic acid as described herein, the vector as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer and/or chronic infectious disease, preferably wherein

(i) the cancer is selected from the group consisting of:

- (a) Malignant neoplasms of lip, oral cavity and pharynx; and/or
- (b) Malignant neoplasms of digestive organs; and/or
- (c) Malignant neoplasms of respiratory and intrathoracic organs; and/or
- (d) Malignant neoplasms of bone and articular cartilage; and/or
- (e) Melanoma and other malignant neoplasms of skin; and/or
- (f) Malignant neoplasms of mesothelial and soft tissue; and/or
- (g) Malignant neoplasm of breast; and/or
- (h) Malignant neoplasms of female genital organs; and/or
- (i) Malignant neoplasms of male genital organs; and/or
- (j) Malignant neoplasms of urinary tract; and/or
- (k) Malignant neoplasms of eye, brain and other parts of central nervous system; and/or
- (l) Malignant neoplasms of thyroid and other endocrine glands; and/or
- (m) Malignant neoplasms of lymphoid, hematopoietic and related tissue; and/or

(ii) the chronic infectious disease is selected from the group consisting of HBV, HCV, HIV, HSV, HPV, EBV, CMV and Chlamydia.

In a ~~sixteenth~~further aspect, the present disclosure refers to use of the antagonistic antigen binding protein as described herein, the nucleic acid as described herein, the vector as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for use in combination therapy for treating cancer and/or chronic infectious

Claims

1. ~~An antagonistic antigen binding protein that specifically binds to PD-L1, wherein said antigen binding protein competes for binding to PD-L1 with an antibody~~
 - (i) ~~comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 20; and a light chain variable region of the amino acid sequence in SEQ ID NO: 21; or~~
 - (ii) ~~comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 29; and a light chain variable region of the amino acid sequence in SEQ ID NO: 30;~~
 - (iii) ~~comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 83; and a light chain variable region of the amino acid sequence in SEQ ID NO: 84; or~~
 - (iv) ~~comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 92; and a light chain variable region of the amino acid sequence in SEQ ID NO: 93; or~~
 - (v) ~~comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 101; and a light chain variable region of the amino acid sequence in SEQ ID NO: 102.~~
2. ~~An antagonistic antigen binding protein that specifically binds to PD-L1, wherein said antigen binding protein comprises either~~
 - (i) ~~a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:~~
 - ~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 21 and~~
 - ~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 20;~~
 - ~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 30 and~~
 - ~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 29;~~
 - ~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 84 and~~

~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 83;~~

~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 93 and~~

~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 92;~~

~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 102 and~~

~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 101;~~

~~(ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 26 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 35 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 36;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 89 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 90;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 98 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 99;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 107 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 108, preferably further comprising one or more selected from the group consisting of a~~

~~CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 22, 31, 85, 94 or 103, a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NOs: 24, 33, 87, 96 or 105, a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 23, 32, 86, 95 or 104 and a CDRL2~~

~~comprising or consisting of the amino acid sequence of SEQ ID NOs: 25, 34, 88, 97 or 106.~~

1. An antagonistic antigen binding protein that specifically binds to PD-L1, wherein said antigen binding protein comprises

i) a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NO: 22
and

a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NO: 23,

a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NO: 24

and

a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NO: 25,

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 26

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;

ii) a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NO: 31
and

a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NO: 32,

a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NO: 33

and

a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NO: 34,

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 35

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 36;

iii) a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NO: 22
and

a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NO: 23,

a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NO: 24

and

a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NO: 25,

a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 89

and

a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;

iv) a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NO: 22
and

- 5 a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NO: 23,
a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NO: 24
and
a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NO: 25,
a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 98
and
a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27;
v) a CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NO: 22
and
10 a CDRL1 comprising or consisting of the amino acid sequence of SEQ ID NO: 23,
a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NO: 24
and
a CDRL2 comprising or consisting of the amino acid sequence of SEQ ID NO: 25,
a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 107
15 and
a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 27.

2. The antagonistic antigen binding protein of claim 1, wherein said antigen binding protein
comprises

- 20 i) a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 21 and
a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 20;
ii) a light chain variable domain having a sequence with at least 90% identity to SEQ
25 ID NO: 30 and
a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 29;
iii) a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 21 and
30 a heavy chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 83;
iv) a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 21 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 92;

v) a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 21 and

a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 101.

~~3. An antagonistic antigen binding protein that specifically binds to PD-1, wherein said antigen binding protein competes for binding to PD-1 with an antibody~~

~~(i) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 2; and a light chain variable region of the amino acid sequence in SEQ ID NO: 3; or~~

~~(ii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 11; and a light chain variable region of the amino acid sequence in SEQ ID NO: 12.~~

~~4. An antagonistic antigen binding protein that specifically binds to PD-1, wherein said antigen binding protein comprises either~~

~~(i) a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of:~~

~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 3 and~~

~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 2;~~

~~a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 12 and~~

~~a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 11;~~

~~(ii) a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 8 and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 9;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 17
and~~

~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 18,
preferably further comprising one or more selected from the group consisting of a
CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 4 or
13, a CDRH2 comprising or consisting of the amino acid sequence of SEQ ID NOs:
6 or 15, CDRL1 comprising or consisting of the amino acid sequence of SEQ ID
NOs: 5 or 14 and a CDRL2 comprising or consisting of the amino acid sequence of
SEQ ID NOs: 7 or 16.~~

~~5. An antagonistic antigen binding protein that specifically binds to LAG-3, wherein said
antigen binding protein competes for binding to LAG-3 with an antibody~~

~~(i) comprising a heavy chain variable region of the amino acid sequence in SEQ ID
NO: 38; and a light chain variable region of the amino acid sequence in SEQ ID
NO: 39;~~

~~(ii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID
NO: 47; and a light chain variable region of the amino acid sequence in SEQ ID
NO: 48;~~

~~(iii) comprising a heavy chain variable region of the amino acid sequence in SEQ ID
NO: 56; and a light chain variable region of the amino acid sequence in SEQ ID
NO: 57;~~

~~(iv) comprising a heavy chain variable region of the amino acid sequence in SEQ ID
NO: 65; and a light chain variable region of the amino acid sequence in SEQ ID
NO: 66; or~~

~~(v) comprising a heavy chain variable region of the amino acid sequence in SEQ ID
NO: 74; and a light chain variable region of the amino acid sequence in SEQ ID
NO: 75.~~

~~6. An antagonistic antigen binding protein that specifically binds to LAG-3, wherein said
antigen binding protein comprises either~~

~~(i) a combination of a light chain variable domain and a heavy chain variable domain
selected from the group of combinations consisting of:
a light chain variable domain having a sequence with at least 90% identity to SEQ
ID NO: 39 and~~

	a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 38; a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 48 and
5	a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 47; a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 57 and
10	a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 56; a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 66 and
15	a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 65; a light chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 75 and
	a heavy chain variable domain having a sequence with at least 90% identity to SEQ ID NO: 74;
20	(ii) ~~a combination of a complementarity determining region 3 of the heavy chain (CDRH3) and a complementarity determining region 3 of the light chain (CDRL3) selected from the group of combinations consisting of:~~
	~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 44 and~~
25	~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 45;~~
	~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 53 and~~
30	~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 54;~~ ~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 62 and~~ ~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 63;~~ ~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 71 and~~ ~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 72;~~

~~a CDRH3 comprising or consisting of the amino acid sequence of SEQ ID NO: 80 and~~
~~a CDRL3 comprising or consisting of the amino acid sequence of SEQ ID NO: 81,~~
~~preferably further comprising one or more selected from the group consisting of a~~
~~CDRH1 comprising or consisting of the amino acid sequence of SEQ ID NOs: 40,~~
~~49, 58, 67, or 76, a CDRH2 comprising or consisting of the amino acid sequence of~~
~~SEQ ID NOs: 42, 51, 60, 69, or 78, CDRL1 comprising or consisting of the amino~~
~~acid sequence of SEQ ID NOs: 41, 50, 59, 68, or 77 and a CDRL2 comprising or~~
~~consisting of the amino acid sequence of SEQ ID NOs: 43, 52, 61, 70, or 79.~~

- ~~7.3.~~ The antagonistic antigen binding protein of any one of the preceding claims, wherein
- (a) the antigen binding protein is an antibody, an antibody-like protein or a fragment thereof,
 preferably, wherein the antibody is selected from the group consisting of a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a multispecific antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a single chain variable fragment antibody, a diabody, a Fab fragment, an F(ab)₂ fragment, an antibody mimetic, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody; and/or
 - (b) the antigen binding protein has at least one of the following characteristics:
 - (i) binds to ~~PD-1~~, PD-L1 ~~or LAG-3~~ with a K_d of less than 100 nM, of less than 50 nM, of less than 10 nM, of less than 1 nM, of less than 100 pM, of less than 10 pM, or of less than 5 pM;
 - (ii) can block the binding of a ligand to ~~PD-1~~, PD-L1 ~~or LAG-3~~ with an IC₅₀ of less than 10 nM, less than 1nM, or less than 200 pM;
 - (iii) stimulates T cell proliferation;
 - (iv) induces the proliferation of lymphocytes;
 - (v) induces secretion of IL-2 and/or IFN γ ; and/or
 - (vi) reduces tumor volume by at least 50%, at least 60%, at least 70%, at least 80% or at least 90% compared to baseline value.

~~8.4.~~ A nucleic acid encoding the antagonistic antigen binding protein of any one of the preceding claims.

~~9.5.~~ A recombinant expression vector comprising a nucleic acid molecule according to claim ~~84.~~

~~10.6.~~ A host cell comprising the vector of claim ~~95.~~

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~~11.7.~~ A method of making the antagonistic antigen binding protein of any one of claims 1-~~73.~~ comprising the step of preparing said antigen binding protein from a host cell expressing said antigen binding protein.

10 ~~12.8.~~ An antagonistic antigen binding protein produced by the expression of recombinant DNA in the host cell of claim ~~106.~~

15 ~~13.9.~~ A pharmaceutical composition comprising at least one antagonistic antigen binding protein according to any one of claims 1 to ~~73~~ or ~~128.~~ the nucleic acid according to claim ~~84.~~ or the vector according to claim ~~59~~ and a pharmaceutically acceptable carrier, preferably wherein the composition comprises at least one further active agent.

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~~14.10.~~ A kit comprising the pharmaceutical composition of claim ~~13-9~~ and optionally at least one further active agent.

~~15.11.~~ The antagonistic antigen binding protein of any one of claims 1 to ~~73~~ or ~~128.~~ the nucleic acid of claim ~~84.~~ the vector of claim ~~95.~~ or the pharmaceutical composition of claim ~~13-9~~ for use in therapy.

25 ~~16.12.~~ Use of the antagonistic antigen binding protein of any one of claims 1 to ~~73~~ or ~~128.~~ the nucleic acid of claim ~~84.~~ the vector of claim ~~95.~~ or the pharmaceutical composition of claim ~~13-9~~ in the manufacture of a medicament for treating cancer and/or chronic infectious disease, preferably wherein

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(i) the cancer is selected from the group consisting of:

- (a) Malignant neoplasms of lip, oral cavity and pharynx; and/or
- (b) Malignant neoplasms of digestive organs; and/or
- (c) Malignant neoplasms of respiratory and intrathoracic organs; and/or
- (d) Malignant neoplasms of bone and articular cartilage; and/or
- 35 (e) Melanoma and other malignant neoplasms of skin; and/or
- (f) Malignant neoplasms of mesothelial and soft tissue; and/or

- (g) Malignant neoplasm of breast; and/or
- (h) Malignant neoplasms of female genital organs; and/or
- (i) Malignant neoplasms of male genital organs; and/or
- (j) Malignant neoplasms of urinary tract; and/or
- 5 (k) Malignant neoplasms of eye, brain and other parts of central nervous system; and/or
- (l) Malignant neoplasms of thyroid and other endocrine glands; and/or
- (m) Malignant neoplasms of lymphoid, hematopoietic and related tissue; and/or
- 10 (ii) the chronic infectious disease is selected from the group consisting of HBV, HCV, HIV, HSV, HPV, EBV, CMV and Chlamydia.

15 ~~17,13.~~ Use of the antagonistic antigen binding protein of any one of claims 1 to ~~73~~ or ~~128~~, the nucleic acid of claim ~~84~~, the vector of claim ~~95~~, or the pharmaceutical composition of claim ~~13-9~~ in the manufacture of a medicament for use in combination therapy for treating cancer and/or chronic infectious disease, wherein said medicament is to be administered in combination with at least one further active agent to a subject in need thereof, preferably,

20 wherein the at least one further active agent and the antagonistic antigen binding protein of any one of claims 1 to ~~7-3~~ or ~~128~~, the nucleic acid of claim ~~84~~, the vector of claim ~~95~~, or the pharmaceutical composition of claim ~~13-9~~ are to be administered either simultaneously or sequentially or a combination thereof, preferably wherein

- (i) the cancer is selected from the group consisting of:
 - 25 (a) Malignant neoplasms of lip, oral cavity and pharynx; and/or
 - (b) Malignant neoplasms of digestive organs; and/or
 - (c) Malignant neoplasms of respiratory and intrathoracic organs; and/or
 - (d) Malignant neoplasms of bone and articular cartilage; and/or
 - (e) Melanoma and other malignant neoplasms of skin; and/or
 - (f) Malignant neoplasms of mesothelial and soft tissue; and/or
 - 30 (g) Malignant neoplasm of breast; and/or
 - (h) Malignant neoplasms of female genital organs; and/or
 - (i) Malignant neoplasms of male genital organs; and/or
 - (j) Malignant neoplasms of urinary tract; and/or

- (k) Malignant neoplasms of eye, brain and other parts of central nervous system; and/or
 - (l) Malignant neoplasms of thyroid and other endocrine glands; and/or
 - (m) Malignant neoplasms of lymphoid, hematopoietic and related tissue; and/or
- 5 (ii) the chronic infectious disease is selected from the group consisting of HBV, HCV, HIV, HSV, HPV, EBV, CMV and Chlamydia.