

A developing class of therapeutic antibodies are bispecific antibodies, which comprise two different binding sites that bind different antigens or different epitopes on the same antigen. Bispecific antibodies can be designed for several applications. Firstly, bispecific antibodies may provide greater tissue-specificity than a monospecific antibody. Several tumor-associated antigens are not only (over)expressed by tumor cells but are also expressed on normal, healthy cells. A bispecific antibody directed against two different tumor-associated antigens involved in a particular type of cancer can specifically target the antibody to the tumor site where the antibody induces tumor cell killing, thereby preventing binding to non-tumor cells expressing only one of the antigens and thus reducing off-site toxicity. Other mechanisms of action include for instance the engagement of immune cells to tumor cells, and the disruption of two signaling pathways required for tumor growth.

Immune checkpoint proteins, like for instance PD-1, PD-L1, CTLA-4, LAG-3, and TIM-3, are an interesting target for antibody therapy. To date, a number of monospecific antibodies targeting PD-1 have been described, as well as certain bispecific antibodies comprising a PD-1 targeting binding domain. However, each of these bispecific antibodies has its own challenges in the production of an effective therapeutic drug. There thus remains a need for the development of novel, effective PD-1xLAG-3 bispecific antibodies.

SUMMARY

One of the objects of the present disclosure is to provide a new pharmaceutical agent for the treatment of human disease, in particular for the treatment of cancer. This object is met by the provision of multispecific binding moieties comprising novel anti-human PD-1 binding domains, and in particular by bispecific antibodies comprising a novel anti-human PD-1 binding domain and an anti-human LAG-3 binding domain.

In certain [embodimentexamples](#), the present disclosure provides a multispecific binding moiety comprising an anti-human PD-1 binding domain having higher binding affinity for human PD-1 than a reference anti-human PD-1 binding domain, wherein the reference anti-human PD-1 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34 and a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35.

In certain [embodimentexamples](#), the present disclosure also provides a multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1

binding domain provides at least comparable, or equal or higher, potency in blocking ligand binding to PD-1 than a reference anti-human PD-1 antibody, wherein the reference anti-human PD-1 antibody comprises two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 34 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 35.

In certain embodiment examples, the present disclosure further provides a multispecific antibody comprising a PD-1 binding domain as described herein and a binding domain that binds to human LAG-3.

In certain embodiment examples, the present disclosure further provides a pharmaceutical composition comprising an effective amount of a multispecific binding moiety as described herein.

In certain embodiment examples, the present disclosure also provides for the multispecific binding moiety as described herein, and pharmaceutical composition as described herein, for use in the treatment of - a disease, for example a disease associated with a suppressed immune system or cancer.

In certain embodiment examples, the present disclosure provides a method for treating a disease, comprising administering an effective amount of a multispecific binding moiety, or pharmaceutical composition, as described herein, to an individual in need thereof.

In certain embodiment examples, the present disclosure provides a method for treating cancer, comprising administering an effective amount of a multispecific binding moiety, or pharmaceutical composition, as described herein, to an individual in need thereof.

In certain embodiment examples, the present disclosure further provides a vector comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as described herein, and a nucleic acid sequence encoding the heavy chain variable region of an anti-human LAG-3 binding domain as described herein.

In certain embodiment examples, the present disclosure further provides a cell comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as described herein, and a nucleic acid sequence encoding the heavy chain variable region of an anti-human LAG-3 binding domain as described herein.

The present disclosure further provides a cell producing a multispecific binding moiety as described herein.

In certain embodiment examples, the present disclosure provides a method for producing a multispecific binding moiety as described herein, as well as a method for producing variants thereof.

In one aspect, the present disclosure relates to a multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain has higher binding affinity for human PD-1 than a reference anti-human PD-1 binding domain, wherein the reference anti-human PD-1 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34 and a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35, in particular wherein the binding affinity is measured by surface plasmon resonance.

In another aspect, the present disclosure relates to a multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain provides comparable, or equal or higher, potency in blocking ligand binding to PD-1 than a reference anti-human PD-1 antibody, wherein the reference anti-human PD-1 antibody comprises two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 34 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 35, in particular wherein the potency in blocking ligand binding to PD-1 is measured in a PD-1/PD-L1 or PD-1/LAG-3 reporter assay.

In another aspect, the present disclosure relates to a multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain comprises a heavy chain variable region, wherein the heavy chain variable region comprises a heavy chain CDR1 (HCDR1) from a heavy chain variable region having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8, a heavy chain CDR2 (HCDR2) from a heavy chain variable region having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8, and a heavy chain CDR3 (HCDR3) from a heavy chain variable regions having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising an effective amount of the multispecific binding as disclosed herein, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure relates to the multispecific binding moiety as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in therapy.

In another aspect, the present disclosure relates to use of the multispecific binding moiety as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disease associated with a suppressed immune system.

In another aspect, the present disclosure relates to use of the multispecific binding moiety as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of cancer.

In yet another aspect, the present disclosure relates to a vector comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as disclosed herein and a nucleic acid sequence encoding the heavy chain variable region of an anti-

human LAG-3 binding domain as disclosed herein, in particular wherein the vector further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.

In another aspect, the present disclosure relates to a cell comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as disclosed herein and a nucleic acid sequence encoding the heavy chain variable region of an anti-human LAG-3 binding domain as disclosed herein, in particular wherein the cell further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.

In another aspect, the present disclosure relates to a cell producing a multispecific binding moiety as disclosed herein, in particular wherein the cell is a recombinant cell, which has been transformed with the vector as disclosed herein.

DETAILED DESCRIPTION

The present disclosure describes several anti-human PD-1 binding domains, the heavy chain variable region having an amino acid sequence as set forth in SEQ ID NOS: 1-8, and multispecific binding moieties comprising such anti-human PD-1 binding domains.

Programmed Cell Death 1 protein (PD-1) is a cell surface receptor that belongs to the CD28 family of receptors and is expressed on T cells and pro-B cells. PD-1 is presently known to bind two ligands, PD-L1 and PD-L2. PD-1, functioning as an immune checkpoint, plays an important role in down regulating the immune system by inhibiting the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. The inhibitory effect of PD-1 is thought to be accomplished through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (suppressor T cells). PD-1 is also known under a number of different aliases such as PDCD1; Programmed Cell Death 1; Systemic Lupus Erythematosus Susceptibility 2; Protein PD-1; HPD-1; PD1; Programmed Cell Death 1 Protein; CD279 Antigen; CD279; HPD-L; HSLE1; SLEB2; and PD-1. External Ids for PD-1 are HGNC: 8760; Entrez Gene: 5133; Ensembl: ENSG00000188389; OMIM: 600244; and UniProtKB: Q15116. New classes of drugs that block the activity of PD-1, the PD-1 inhibitors, activate the immune system to attack tumors and are therefore used with a certain level of success to treat some types of cancer.

LAG-3 is known under a number of different names such as Lymphocyte Activating 3; Lymphocyte-Activation Gene 3; CD223 Antigen; Protein FDC; CD223; LAG-3; or FDC. External Ids for LAG3 are: HGNC: 6476; Entrez Gene: 3902; Ensembl: ENSG00000089692; OMIM: 153337; and UniProtKB: P18627. LAG-3 is closely related to CD4. LAG-3 is located on the human chromosome 12 (12p13.32) adjacent to the CD4 gene, and its sequence is approximately 20% identical to CD4. The LAG-3 protein binds a nonholomorphic region of major histocompatibility complex 2 (MHC class II) with greater affinity than CD4. LAG-3 is one of the various immune-checkpoint receptors that are coordinately upregulated on both

CLAIMS

1. A multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain has higher binding affinity for human PD-1 than a reference anti-human PD-1 binding domain, wherein the reference anti-human PD-1 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34 and a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35, in particular wherein the binding affinity is measured by surface plasmon resonance.

2. A multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain provides comparable, or equal or higher, potency in blocking ligand binding to PD-1 than a reference anti-human PD-1 antibody, wherein the reference anti-human PD-1 antibody comprises two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 34 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 35, in particular wherein the potency in blocking ligand binding to PD-1 is measured in a PD-1/PD-L1 or PD-1/LAG-3 reporter assay.

3. The multispecific binding moiety according to claim 1 or 2, wherein the anti-human PD-1 binding domain comprises at least a heavy chain variable region and a light chain variable region, and wherein the light chain variable region preferably is a light chain variable region of a light chain that is capable of pairing with multiple heavy chains having different epitope specificities.

~~4. The multispecific binding moiety according to claim 1 or 3, wherein the binding affinity is measured by surface plasmon resonance.~~

~~5~~4. The multispecific binding moiety according to any one of claims 1-~~4~~3, wherein the anti-human PD-1 binding domain has at least a ten-fold higher binding affinity for human PD-1 than the reference anti-human PD-1 binding domain, or wherein the anti-human PD-1 binding domain has a ten-fold higher binding affinity for human PD-1 than the reference anti-human PD-1 binding domain.

~~6. The multispecific binding moiety according to any one of claims 1-4, wherein the anti-human PD-1 binding domain has a ten fold higher binding affinity for human PD-1 than the reference anti-human PD-1 binding domain.~~

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~~7~~5. The multispecific binding moiety according to any one of claims 1-~~6~~4, wherein the anti-human PD-1 binding domain has a binding affinity for human PD-1 in a range of about 0.1-1.0 nM, in particular in a range of about 0.3-0.8 nM, more in particular in a range of about 0.38-0.78 nM.

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~~8~~6. The multispecific binding moiety according to any one of claims 1, and 3-~~7~~5, wherein the binding affinity is measured with both the anti-human PD-1 binding domain and the reference anti-human PD-1 binding domain in a bivalent monospecific IgG format, or wherein the binding affinity is measured with the anti-human PD-1 binding domain in a bivalent bispecific IgG format and the reference anti-human PD-1 binding domain in a bivalent monospecific IgG format.

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~~9. The multispecific binding moiety according to any one of claims 1, and 3-7, wherein the binding affinity is measured with the anti-human PD-1 binding domain in a bivalent bispecific IgG format and the reference anti-human PD-1 binding domain in a bivalent monospecific IgG format.~~

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~~10. The multispecific binding moiety according to any one of claims 2, 3, or 5-9, wherein the potency in blocking ligand binding to PD-1 is measured in a PD-1/PD-L1 or PD-1/LAG-3 reporter assay.~~

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~~11~~7. The multispecific binding moiety according to any one of claims 2, ~~3, or 5-10~~6, wherein a comparable potency in blocking ligand binding to PD-1 is a potency within a 5 fold range of the potency in blocking ligand binding to PD-1 of the reference anti-human PD-1 antibody, including a 5, 4, 3, and 2 fold, deviation from the potency in blocking ligand binding to PD-1 of the reference anti-human PD-1 antibody.

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128. The multispecific binding moiety according to any one of claims 1-**117**, wherein the heavy chain variable region comprises:

a) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively;

b) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, respectively;

c) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44, respectively;

d) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively;

e) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively;

f) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 51, SEQ ID NO: 52, and SEQ ID NO: 53, respectively;

g) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56, respectively; or

h) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 57, SEQ ID NO: 58, and SEQ ID NO: 59, respectively;

wherein each of the HCDRs may comprise at most three, two, or one amino acid substitutions.

129. The multispecific binding moiety according to any one of claims 1-**128**, comprising a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NOS: 1-8, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

~~14. The multispecific binding moiety according to any one of claims 3-13, wherein the anti-human PD-1 binding domain further comprises a CH1 and CL region.~~

5 ~~15~~10. A multispecific binding moiety comprising an anti-human PD-1 binding domain, wherein the anti-human PD-1 binding domain comprises a heavy chain variable region, wherein the heavy chain variable region comprises a heavy chain CDR1 (HCDR1) from a heavy chain variable region having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8, a heavy chain CDR2 (HCDR2) from a heavy chain variable region
10 having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8, and a heavy chain CDR3 (HCDR3) from a heavy chain variable regions having an amino acid sequence from the group consisting of SEQ ID NOS: 1-8.

~~16~~11. The multispecific binding moiety according to claim ~~15~~10, wherein the heavy
15 chain variable region comprises:

a) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively;

b) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain
20 CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, respectively;

c) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44, respectively;

d) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain
25 CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively;

e) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 48, SEQ ID
30 NO: 49, and SEQ ID NO: 50, respectively;

f) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 51, SEQ ID NO: 52, and SEQ ID NO: 53, respectively;

g) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56, respectively; or

h) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), having an amino acid sequence as set forth in SEQ ID NO: 57, SEQ ID NO: 58, and SEQ ID NO: 59, respectively;

wherein each of the HCDRs may comprise at most three, two, or one amino acid substitutions.

10 ~~17~~12. The multispecific binding moiety according to claim ~~15~~10 or ~~16~~11, comprising a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 1-8, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

15 ~~18~~13. The multispecific binding moiety according to any one of claims ~~15-17~~3-12, wherein the anti-human PD-1 binding domain further comprises a CH1 and CL region.

~~19~~14. The multispecific binding moiety according to any one of claims 1-~~18~~13, further comprising a binding domain that binds to a cell surface moiety expressed on an immune effector cell, in particular further comprising an anti-human LAG-3 binding domain.

~~20. The multispecific binding moiety according to any one of claims 1-19, further comprising an anti-human LAG-3 binding domain.~~

25 ~~21~~15. The multispecific binding moiety according to claim ~~20~~14, wherein the anti-human LAG-3 binding domain comprises a heavy chain variable region comprising:

a) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 11;

30 b) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 12;

c) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 13;

d) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 14;

e) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 15;

f) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 16; or

g) heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17,

wherein each of the HCDRs may comprise at most three, two, or one amino acid substitutions.

2216. The multispecific binding moiety according to claim 2014 or 2115, wherein the anti-human LAG-3 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NOS: 11-17, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

2317. The multispecific binding moiety according to any one of claims 202214-16, wherein the anti-human LAG-3 binding domain further comprises a light chain variable region, preferably a light chain variable region of a light chain that is capable of pairing with multiple heavy chains having different epitope specificities, in particular the same light chain variable region as that of the anti-human PD-1 binding domain.

2418. The multispecific binding moiety according to any one of claims 202314-17, wherein the anti-human LAG-3 binding domain further comprises a CH1 and CL region.

2519. The multispecific binding moiety according to any one of claims ~~15-24~~10-18, wherein the binding moiety has comparable, or equal or higher, potency in blocking ligand binding to PD-1 than a bivalent monospecific anti-human PD-1 antibody, wherein the bivalent monospecific anti-human PD-1 antibody comprises two binding domains comprising
 5 a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34 and a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:35, in particular wherein the potency in blocking ligand binding to PD-1 is measured in a PD-1/PD-L1 or PD-1/LAG-3 reporter assay.

~~26. The multispecific binding moiety according to claim 25, wherein the potency in blocking ligand binding to PD-1 is measured in a PD-1/PD-L1 or PD-1/LAG-3 reporter assay.~~

2720. The multispecific binding moiety according to claim ~~25 or 26~~19, wherein a
 15 comparable potency in blocking ligand binding to PD-1 is a potency within a 5 fold range of the potency in blocking ligand binding to PD-1 of the reference anti-human PD-1 antibody, including a 5 to 2 fold, preferably a 5, 4, 3, or 2 fold, deviation from the potency in blocking ligand binding to PD-1 of the reference anti-human PD-1 antibody.

2821. The multispecific binding moiety according to any one of claims 1-~~27~~20, wherein the binding moiety is monovalent for binding to human PD-1.

2922. A pharmaceutical composition comprising an effective amount of the multispecific binding moiety according to any one of claims 1-~~28~~21, and a pharmaceutically
 25 acceptable carrier.

3023. The multispecific binding moiety according to any one of claims 1-~~28~~21, or the pharmaceutical composition according to claim 2922, for use in therapy.

3124. Use of Tthe multispecific binding moiety according to any one of claims 1-~~28~~21, or the pharmaceutical composition according to claim 2922, ~~for use in~~ the manufacture of a medicament for the treatment of a disease associated with a suppressed immune system.

~~3225.~~ Use of Tthe multispecific binding moiety according to any one of claims 1-~~28~~21, or the pharmaceutical composition according to claim ~~29~~22, ~~for use in~~ the manufacture of a medicament for the treatment of cancer.

~~33. A method for treating a disease, comprising administering an effective amount of a multispecific binding moiety as claimed in any one of claims 1-28, or the pharmaceutical composition as claimed in claim 29, to an individual in need thereof.~~

~~34. A method for treating a disease associated with a suppressed immune system, comprising administering an effective amount of a multispecific binding moiety as claimed in any one of claims 1-28, or the pharmaceutical composition as claimed in claim 29, to an individual in need thereof.~~

~~35. A method for treating cancer, comprising administering an effective amount of a multispecific binding moiety as claimed in any one of claims 1-28, or the pharmaceutical composition as claimed in claim 29, to an individual in need thereof.~~

~~36~~26. A vector comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as defined in any one of claims 1-~~28~~21 and a nucleic acid sequence encoding the heavy chain variable region of an anti-human LAG-3 binding domain as defined in claim ~~21~~15 or ~~22~~16, in particular wherein the vector further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.

~~37. The vector according to claim 36, wherein the vector further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.~~

~~38~~27. The vector according to claim ~~36 or 37~~26, wherein the vector further comprises at least one nucleic acid sequence encoding a light chain variable region, and preferably a CL region, in particular wherein the light chain variable region is a light chain variable region of a light chain that is capable of pairing with multiple heavy chains having different epitope specificities.

~~39. The vector according to claim 38, wherein the light chain variable region is a light chain variable region of a light chain that is capable of pairing with multiple heavy chains having different epitope specificities.~~

5 ~~40~~28. A cell comprising a nucleic acid sequence encoding the heavy chain variable region of an anti-human PD-1 binding domain as defined in any one of claims 1-~~28~~21 and a nucleic acid sequence encoding the heavy chain variable region of an anti-human LAG-3 binding domain as defined in claim ~~21~~15 or ~~22~~16, in particular wherein the cell further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and
10 CH3 region.

~~41. The cell according to claim 40, wherein the cell further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.~~

15 ~~42~~29. The cell according to claim ~~40 or 41~~28, wherein the cell further comprises at least one nucleic acid sequence encoding a light chain variable region, and preferably a CL region.

20 ~~43~~30. A cell producing a multispecific binding moiety as claimed in any one of claims 1-~~28~~21, in particular wherein the cell is a recombinant cell, which has been transformed with the vector as claimed in claim 26 or 27.

~~44. The cell according to claim 43, wherein the cell is a recombinant cell, which has been transformed with the vector as claimed in any one of claims 36-39.~~

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