(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 October 2022 (06.10.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/211625 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/NL2022/050174

(22) International Filing Date:
30 March 2022 (30.03.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2027891 31 March 2021 (31.03.2021) NL

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2022/211625 A1

(54) Title: NOVEL MULTISPECIFIC ANTIBODIES

(57) Abstract: The present disclosure relates to a multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1. Such multispecific antibody has comparable, or equal or higher, potency than a combination of LAG-3 and PD-L1 reference antibodies. Also provided is a method for treating a disease, in particular a disease associated with a suppressed immune system, such as cancer, with a multispecific antibody of the present disclosure. The present disclosure further relates to a vector and cell comprising nucleic acids encoding the heavy chain variable region of the LAG-3 and PD-L1 binding domains.

Title: NOVEL MULTISPECIFIC ANTIBODIES

FIELD

The present disclosure relates to the field of antibodies. In particular it relates to the field of therapeutic antibodies for the treatment of diseases involving aberrant cells. More in particular it relates to novel multispecific antibodies and variants thereof that bind to LAG-3 and a protein of the B7 family, in particular PD-L1.

BACKGROUND

Cancer is still a major cause of death in the world, in spite of the many advances that have been made in the treatment of the disease and the increased knowledge of the molecular events that lead to cancer. Traditionally, most cancer drug discovery has focused on agents that block essential cell functions and kill dividing cells. However, in cases of advanced cancer, no matter how aggressively applied, even to the point where patients suffer life-threatening side-effects from the treatment, chemotherapy rarely results in a complete cure. In most cases the tumors in the patients stop growing or temporarily shrink (referred to as remission) only to start proliferating again, sometimes more rapidly (referred to as relapse), and become increasingly more difficult to treat. Over the past years, the focus of cancer drug development has moved away from broadly cytotoxic chemotherapy to targeted cytostatic therapies with less toxicity. Treatment of advanced cancer with targeted therapies has been validated clinically in leukemia and some other cancers. However, in a majority of carcinomas, targeted approaches are still proving not effective enough to completely abolish cancer in the majority of the patients.

Targeting of cancers has been achieved using a variety of different methods including for instance small molecules directed towards signaling proteins on which the cancer depends for survival and/or growth; vaccines with tumor specific proteins; cell therapies with immune cells that actively kill tumor cells, and antibodies that target cytotoxic molecules to the tumor; interfere with signaling and/or that (re)direct the immune system of the host to the tumor cells.

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 LAG-3 or PD-L1 have been described, as well as certain bispecific antibodies that bind LAG-3 and PD-L1. 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 LAG-3xPD-L1 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 a multispecific antibody comprising an anti-human LAG-3 binding domain and an anti-human PD-L1 binding domain.

In certain embodiments, the present disclosure provides a multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has at least comparable, or equal or higher, potency than a combination of reference antibodies. In certain embodiments, the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid

sequence as set forth in SEQ ID NO: 28 (a relatlimab analog antibody), and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26 (an atezolizumab analog antibody).

In certain embodiments, the present disclosure further provides a multispecific antibody, or variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant thereof comprises a binding domain that specifically binds to an extracellular domain of LAG-3 and a binding domain that specifically binds to an extracellular domain of a protein of the B7 family, wherein the LAG-3 binding domain comprises a heavy chain variable region comprising 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 any one of SEQ ID NOs: 1-17 or SEQ ID NOs: 52-59.

In certain embodiments, the present disclosure further provides a pharmaceutical composition comprising an effective amount of the multispecific antibody or variant thereof as described herein.

In certain embodiments, the present disclosure further provides a multispecific antibody or variant thereof, or pharmaceutical composition, as described herein for use as a medicament.

In certain embodiments, the present disclosure further provides a multispecific antibody or variant thereof, or a pharmaceutical composition, as described herein, for use in the treatment of a disease associated with a suppressed immune system. In certain embodiments, the present disclosure provides a multispecific antibody or variant thereof, or a pharmaceutical composition, as described herein, for use in the treatment of cancer.

In certain embodiments, the present disclosure further provides a method for treating (a) a disease, or (b) a disease associated with a suppressed immune system, or c) cancer, comprising administering an effective amount of the multispecific antibody or variant thereof, or the pharmaceutical composition, as described herein, to an individual in need thereof.

In certain embodiments, the present disclosure further provides a vector comprising a nucleic acid sequence encoding a heavy chain variable region of a LAG-3 binding domain as described herein and a nucleic acid sequence encoding a heavy chain variable region of a PD-L1 binding domain as described herein.

In certain embodiments, the present disclosure further provides a cell comprising a nucleic acid sequence encoding a heavy chain variable region of a LAG-3 binding domain as described herein and a nucleic acid sequence encoding a heavy chain variable region of a PD-L1 binding domain as described herein

In certain embodiments, the present disclosure further provides a cell producing a multispecific antibody or variant thereof as described herein.

In certain embodiments, the present disclosure provides a method for producing a variant of a multispecific antibody as described herein, as well as a variant obtained by such method.

DETAILED DESCRIPTION

In certain embodiments, the present disclosure provides a multispecific antibody, comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has at least comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26.

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 regulatory T cells (Tregs) and anergic T cells. LAG-3 can negatively regulate T cell proliferation, activation and homeostasis.

PD-L1 is a type 1 transmembrane protein that plays a role in suppressing an immune response during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. PD-L1 is expressed in various types of cancers, especially in NSCLC (Boland et al., 2013; Velcheti et al., 2014), melanoma, renal cell carcinoma, gastric cancer, hepatocellular as well as various leukemias and multiple myeloma (Bernstein et al., 2014; Thompson et al., 2005). PD-L1 is present in the cytoplasm and plasma membrane of cancer cells, but not all cancers or all cells within a tumor express PD-L1 (Dong et al., 2002). Multiple tumor microenvironment cells contribute to immune suppression by upregulating PD-L1 expression. This effect is called "adaptive immune resistance", because the tumor protects itself by inducing PD-L1 in response to IFN-γ produced by activated T cells (Sharma et al., 2017). PD-L1 can also be regulated by oncogenes, this mechanism is known as inherent immune resistance (Akbay et al., 2013). Within the tumor microenvironment, PD-L1 is also expressed on myeloid cells and activated T cells (Tumeh et al., 2014). The expression of PD-L1 is induced by multiple proinflammatory molecules, including types I and II IFN-γ, TNF-α, LPS, GM-CSF and VEGF, as well as the cytokines IL-10 and IL-4, with IFN-γ being the most potent inducer (Sznol and Chen, 2013).

A multispecific antibody according to the present disclosure is an antibody, in any antibody format, that comprises at least two binding domains which have specificity for at least two different targets or epitopes. In certain embodiments, a multispecific antibody of the present disclosure is a bispecific antibody. In certain embodiments, a multispecific antibody of the present disclosure comprises an Fc region or a part thereof. In certain embodiments, a multispecific antibody of the present disclosure is an IgG1 antibody.

A "variant" of a multispecific antibody as described herein comprises a functional part, derivative, and/or analogue of the multispecific antibody. The variant may be a structural variant, including but not limited to a fragment of an antibody, such as for example a Fab fragment or a single-chain variable fragment (scFv). The variant may be a sequence variant. The variant may be a structural and sequence variant. The variant maintains the binding specificity, but not necessarily the binding affinity, of the antibody.

In certain embodiments, the LAG-3 and/or PD-L1 binding domain comprises at least a heavy chain variable region and a light chain variable region. The light chain variable region can be any suitable light chain variable region as described further herein. In certain embodiments,

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. Such light chain is also referred to in the art as a "common light chain".

In certain embodiments, the multispecific antibody or variant thereof comprises a single binding domain that binds to LAG-3 and/or a single binding domain that binds to PD-L1. In other words, in certain embodiments the multispecific antibody or variant thereof is monovalent for binding to LAG-3 and/or monovalent for binding to PD-L1. In certain embodiments, the multispecific antibody or variant thereof is monovalent for binding to both LAG-3 and PD-L1.

Determining if a multispecific antibody or variant has a comparable, or equal or higher, potency than the combination of reference antibodies can be done by measuring the potency of both the multispecific antibody and combination of antibodies in the same type of study, using the same study conditions. Thus, in certain embodiments, the potency of the multispecific antibody or variant thereof is measured in the same type of study, using the same study conditions.

In certain embodiments, an at least comparable potency is a potency within a 5 fold range of the potency of the combination of reference antibodies, and includes a 5, 4, 3, or 2 fold, preferably a 3 or 2 fold, deviation from the potency of the combination of reference antibodies.

In the context of the present disclosure, "potency" refers to the functional activity of the multispecific antibody or variant thereof, which can be determined in *in vitro* or in *in vivo* studies.

In certain embodiments, the potency of the multispecific antibody or variant thereof is determined in an *in vivo* study, preferably in an *in vivo* mouse model, such as for instance a HuNSG™ mouse model bearing human MDA-231 tumors. In certain embodiments, the potency of the multispecific antibody or variant thereof is determined by measuring tumor volume reduction in such an *in vivo* mouse study. The tumor volume reduction induced by the multispecific antibodies as provided herein is determined with the method as described in Example 4.

In certain embodiments, a comparable potency is a tumor volume reduction within a 5 fold range of the tumor volume reduction of the combination of reference antibodies, and includes a 5, 4, 3, or 2 fold, preferably a 3 or 2 fold, deviation from the tumor volume reduction of the combination of reference antibodies.

In certain embodiments, the potency is determined in an *in vitro* study, such as for instance a blocking assay, including but not limited to a PD-1/LAG-3 or PD-L1/LAG-3 reporter assay, preferably a PD-1/LAG-3 reporter assay, such as for instance described in Example 2; or a T cell activation assay, including but not limited to a SEB assay, preferably a SEB assay such as for instance described in Example 2; an antigen recall assay; or an MLR assay. In certain embodiments, the potency of the multispecific antibody or variant thereof and the combination of reference antibodies is determined by measuring their potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, preferably ligand or receptor binding to LAG-3 and PD-L1. The potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1 of the multispecific antibodies as provided herein is measured with the method as described in Example 2. In brief, the PD-1/LAG-3 reporter assay is performed using PD-1 and LAG-3 expressing Jurkat T cells as effector cells and PD-L1 expressing Raji cells as target cells. The PD-1 and LAG-3 effector cells are prepared and plated at 100,000 cells per well. Test and control IgG are added in a 6-step semi-log titration at equimolar amounts, followed by the Raji cells (25,000 per well). The T cells are activated by the addition of partially purified Staphylococcal enterotoxin D (ppSED, using a concentration that achieves a highest response with the positive assay control, such as 16.6 ng/mL in Example 2 or 150 ng/mL in Example 5). After 6 hours incubation at 37°C, luciferase reporter gene activity is determined.

In certain embodiments, a comparable potency is a potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, preferably LAG-3 and PD-L1, that is within a 5 fold range of the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, preferably LAG-3 and PD-L1, of the combination of reference antibodies, and includes a 5, 4, 3, or 2 fold, preferably a 3 or 2 fold, deviation from the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, preferably LAG-3 and PD-L1, of the combination of reference antibodies. In certain embodiments, the combination of reference antibodies comprises an analog of anti-LAG-3 antibody relatlimab and an analog of anti-PD-L1 antibody atezolizumab. A relatlimab analog has the same heavy chain variable region sequence (SEQ ID NO: 27) as relatlimab. A relatlimab analog antibody has the same light chain variable region sequence (SEQ ID NO: 28) as relatlimab. An atezolizumab analog has the same heavy chain variable region sequence (SEQ ID NO: 25) as atezolizumab. An atezolizumab analog antibody has the same light chain variable region sequence (SEQ ID NO: 26) as atezolizumab. The reference antibodies are preferably

produced using the same production method as the multispecific antibody or variant thereof. Preferably, the LAG-3 and PD-L1 binding domains of the multispecific antibody or variant thereof of the present disclosure and the combination of reference antibodies are used at equimolar concentrations, i.e. when the multispecific antibody or variant thereof is used at 100 µg/mL, the combination of reference antibodies comprises 50 µg/mL of the LAG-3 binding reference antibody and 50 µg/mL of the PD-L1 binding reference antibody.

In certain embodiments, the present disclosure provides a multispecific antibody, or variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant thereof comprises a binding domain that specifically binds to an extracellular domain of LAG-3 and a binding domain that specifically binds to an extracellular domain of a protein of the B7 family.

In certain embodiments, the LAG-3 binding domain of a multispecific antibody or variant thereof of the present disclosure comprises a heavy chain variable region, wherein the heavy chain variable region comprises the heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3) of one of the heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 1-17 or SEQ ID NO: 52-59. The HCDRs, according to Kabat, are indicated in bold and underlined in the list of sequences provided herein.CDR sequences can be defined using different methods, including, but not limited to, according to the Kabat numbering scheme (Kabat et al., J. Biol. Chem.252:6609-6616 (1977); and/or Kabat et al., U.S. Dept. of Health and Human Services, “Sequences of proteins of immunological interest” (1991)), the Chothia numbering scheme (Chothia et al., J. Mol. Biol.196:901-917 (1987); Chothia et al., Nature 342: 877-883, 1989; and/or Al-Lazikani B. et al., J. Mol. Biol., 273: 927-948 (1997)), the numbering system of Honegger and Plukthun (Honegger and Plückthun, J. Mol. Biol., 309:657-670 (2001)), the numbering system of MacCallum (MacCallum et al., J. Mol. Biol.262:732-745 (1996); and/or Abhinandan and Martin, Mol. Immunol., 45: 3832-3839 (2008)), the numbering system of Lefranc (Lefranc M.P. et al., Dev. Comp. Immunol., 27: 55-77 (2003); and/or Honegger and Plückthun, J. Mol. Biol., 309:657-670 (2001)), or according to IMGT (discussed in Giudicelli et al., Nucleic Acids Res. 25: 206-211 (1997)).

Each of these numbering schemes base their definition of CDRs on a predicted contribution of amino acid residues in the heavy or light chain variable region to antigen binding. Hence, each method to identify CDRs can be used to identify the CDRs of the binding domains

of the present disclosure. In certain embodiments, the heavy chain CDRs of a binding domain of the present disclosure is according to Kabat, Chothia, or IMGT. In certain embodiments, the heavy chain CDRs of a binding domain of the present disclosure is according to Kabat. In certain embodiments, the heavy chain CDRs of a binding domain of the present disclosure is according to Chothia. In certain embodiments, the heavy chain CDRs of a binding domain of the present disclosure is according to IMGT.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 1;

- 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: 2;

- 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: 3;

- 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: 4;

- 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: 5;

- 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: 6;

- 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: 7;

- 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: 8;

- 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: 9;

- 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: 10;

- 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;

- 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;

- 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;

- 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;

- 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;

- 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;

- 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,

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 60, SEQ ID NO: 61 and SEQ ID NO: 62, respectively;

- 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: 60, SEQ ID NO: 63 and SEQ ID NO: 62, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 67, SEQ ID NO: 68 and SEQ ID NO: 69, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 73, SEQ ID NO: 74 and SEQ ID NO: 75, respectively;

- 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: 76, SEQ ID NO: 77 and SEQ ID NO: 78, respectively;

- 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: 79, SEQ ID NO: 80 and SEQ ID NO: 81, respectively;

- 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: 82, SEQ ID NO: 83 and SEQ ID NO: 84, respectively;

- 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: 85, SEQ ID NO: 86 and SEQ ID NO: 87, respectively;

- heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89 and SEQ ID NO: 90, respectively;

- 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: 76, SEQ ID NO: 91 and SEQ ID NO: 92, respectively;

- 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: 76, SEQ ID NO: 91 and SEQ ID NO: 93, respectively;

- 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: 94, SEQ ID NO: 95 and SEQ ID NO: 96, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 99, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 100, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively,

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 1;

- 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: 3;

- 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: 5;

- 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: 6;

- 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;

- 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;

- 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;

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59;wherein each of the HCDRs may comprise at most three, two, or one amino acid substitution.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 60, SEQ ID NO: 61 and SEQ ID NO: 62, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 73, SEQ ID NO: 74 and SEQ ID NO: 75, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 99, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 100, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 5;

- 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;

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 5,

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 52,

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

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

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 1;

- 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: 2;

- 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: 3;

- 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: 4;

- 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: 5;

- 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: 6;

- 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: 7;

- 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: 8;

- 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: 9;

- 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: 10;

- 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;

- 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;

- 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;

- 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;

- 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;

- 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;

- 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;

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 60, SEQ ID NO: 61 and SEQ ID NO: 62, respectively;

- 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: 60, SEQ ID NO: 63 and SEQ ID NO: 62, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 67, SEQ ID NO: 68 and SEQ ID NO: 69, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 73, SEQ ID NO: 74 and SEQ ID NO: 75, respectively;

- 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: 76, SEQ ID NO: 77 and SEQ ID NO: 78, respectively;

- 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: 79, SEQ ID NO: 80 and SEQ ID NO: 81, respectively;

- 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: 82, SEQ ID NO: 83 and SEQ ID NO: 84, respectively;

- 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: 85, SEQ ID NO: 86 and SEQ ID NO: 87, respectively;

- 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: 88, SEQ ID NO: 89 and SEQ ID NO: 90, respectively;

- 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: 76, SEQ ID NO: 91 and SEQ ID NO: 92, respectively;

- 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: 76, SEQ ID NO: 91 and SEQ ID NO: 93, respectively;

- 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: 94, SEQ ID NO: 95 and SEQ ID NO: 96, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 99, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 100, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 1;

- 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: 3;

- 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: 5;

- 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: 6;

- 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;

- 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;

- 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;

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 60, SEQ ID NO: 61 and SEQ ID NO: 62, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 73, SEQ ID NO: 74 and SEQ ID NO: 75, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 99, respectively;

- 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: 97, SEQ ID NO: 98 and SEQ ID NO: 100, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 5;

- 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;

- 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: 52;

- 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: 53;

- 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: 54;

- 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: 55;

- 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: 56;

- 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: 57;

- 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: 58; or

- 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: 59.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising:

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 5.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 52.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 1-17 or SEQ ID NO: 52-59, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

In certain embodiments, a LAG-3 binding domain of the multispecific antibody or variant thereof includes LAG-3 binding domain variants, wherein each of the HCDRs may comprise at most three, two, or one amino acid substitution. Such variants are expected to retain LAG-3 binding specificity.

For example, suitable positions for introducing an amino acid variation include, but are not limited to, the second, and/or third amino acid of HCDR1; the third, seventh, tenth, thirteenth, and/or sixteenth amino acid of HCDR2; and/or the first amino acid of HCDR3. CDR sequences according to Kabat, are indicated in bold and underlined in the list of sequences provided herein.

In certain embodiments, the anti-human LAG-3 binding domain comprises:

- HCDR1 having amino acid sequence SX_1X_2WS, wherein

  X_1 can be Y or F;

  X_2 can be Y or S; and/or

- HCDR2 having amino acid sequence $YIX_1YSGX_2TNX_3NPX_4LKX_5$, wherein

  X_1 can be Y or D;

  X_2 can be S, or T;

  X_3 can be Y or F;

  X_4 can be S, or F;

  X_5 can be S or I; and/or

- HCDR3 having amino acid sequence $X_1LLYKWNYVEGFDI$, wherein

  X_1 can be D or H.

For example, suitable positions for introducing an amino acid variation include, but are not limited to, the first, third and/or fourth amino acid of HCDR1; the seventh, tenth, and/or twelfth amino acid of HCDR2; and/or the third amino acid of HCDR3. CDR sequences according to Kabat are indicated in bold and underlined in the list of sequences provided herein.

In certain embodiments, the anti-human LAG-3 binding domain comprises:

- HCDR1 having amino acid sequence $X_1YX_2X_3H$, wherein

  X_1 can be S, N, or R;

X_2 can be G or D;

X_3 can be M, T or I; and/or

- HCDR2 having amino acid sequence VISYDGX_1NKX_2YX_3DSVKG, wherein

  X_1 can be S or N;

  X_2 can be Y, F, or H;

  X_3 can be A, E, or V; and/or

- HCDR3 having amino acid sequence ERX_1WDVFDI, wherein

  X_1 can be G or D.

For example, suitable positions for introducing an amino acid variation include, but are not limited to, the first, and/or third amino acid of HCDR1; the fifth, and/or eighth amino acid of HCDR2; and/or the third amino acid of HCDR3. CDR sequences according to Kabat, are indicated in bold and underlined in the list of sequences provided herein.

In certain embodiments, the anti-human LAG-3 binding domain comprises:

- HCDR1 having amino acid sequence X_1YX_2MH, wherein

  X_1 can be S or N;

  X_2 can be G or A; and/or

- HCDR2 having amino acid sequence VISYX_1GSX_2KYYADSVKG, wherein

  X_1 can be D or H;

  X_2 can be N or D; and/or

- HCDR3 having amino acid sequence DGDNWDX_1FDI, wherein

  X_1 can be V or A.

In certain embodiments, a LAG-3 binding domain of the multispecific antibody or variant thereof also includes LAG-3 binding domain variants, which, in addition to variations in the HCDRs, comprise one or more variations in the framework regions. In certain embodiments, a LAG-3 binding domain variant of the multispecific antibody or variant thereof comprises no variations in the CDR regions but comprises one or more variations in the framework regions.

Such variants have at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the sequences disclosed herein, and are expected to retain LAG-3 binding specificity. Thus, in certain embodiments, a LAG-3 binding domain of the present disclosure comprises:

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 1, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 1;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 2, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 2;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 3, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 3;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 4;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 5, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 5;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 6, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 6;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ

ID NO: 7, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 7;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 8, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 8;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 9, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 9;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 10, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 10;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 11, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 11;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 12, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 12;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 13;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 14, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 14;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 15;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 16, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 16;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 17;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 52, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 52;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 53, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 53;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 54, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 54;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 55, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 55;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ

ID NO: 56, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 56;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 57, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 57;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 58, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 58; or

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 59, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 59.

In certain embodiments, a LAG-3 binding domain of the present disclosure comprises:

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 1, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 60, SEQ ID NO: 61 and SEQ ID NO: 62, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 2, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 60, SEQ ID NO: 63 and SEQ ID NO: 62, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 3, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 4, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 67, SEQ ID NO: 68 and SEQ ID NO: 69, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 5, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 6, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 75, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 7, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 77 and SEQ ID NO: 78, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 8, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 79, SEQ ID NO: 80 and SEQ ID NO: 81, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 9, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 82, SEQ ID NO: 83 and SEQ ID NO: 84, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 10, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 86 and SEQ ID NO: 87, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 11, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89 and SEQ ID NO: 90, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 12, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 91 and SEQ ID NO: 92, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 91 and SEQ ID NO: 93, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 14, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 94, SEQ ID NO: 95 and SEQ ID NO: 96, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98 and SEQ ID NO: 99, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 16, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98 and SEQ ID NO: 100, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 52, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 53, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 54, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 55, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 56, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 57, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 58, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; or

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 59, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively.

In certain embodiments, a LAG-3 binding domain of the multispecific antibody or variant thereof further comprises a light chain variable region. In certain embodiments, a LAG-3 binding domain of the multispecific antibody or variant thereof comprises a common light chain variable region. An example of a suitable light chain variable region is a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), having an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, wherein each of the LCDRs may comprise at most three, two, or one amino acid substitution. In certain embodiments, a suitable light chain variable region is a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), having an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively. In certain embodiments, such

light chain variable region may comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto. A light chain or light chain variable region comprising these LCDRs and/or light chain variable region is the light chain referred to in the art as VK1-39/JK1. This is a common light chain.

In certain embodiments, a LAG-3 binding domain of the present disclosure comprises a light chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 30, which light chain variable region comprises a LCDR1 amino acid sequence as set forth in SEQ ID NO: 31; a LCDR2 amino acid sequence as set forth in SEQ ID NO: 32; and a LCDR3 amino acid sequence as set forth in SEQ ID NO: 33.

The term 'common light chain' according to the invention refers to a light chain that is capable of pairing with multiple different heavy chains, i.e. heavy chains having different antigen or epitope binding specificities. A common light chain is particularly useful in the generation of, for instance, bispecific antibodies, where antibody production is more efficient when both binding domains comprise the same light chain. The term "common light chain" encompasses light chains that are identical or have some amino acid sequence differences while the binding specificity of the full length antibody is not affected. It is for instance possible within the scope of the definition of common light chains as used herein, to prepare or find light chains that are not identical but still functionally equivalent, e.g., by introducing and testing conservative amino acid changes, changes of amino acids in regions that do not or only partly contribute to binding specificity when paired with the heavy chain, and the like.

Apart from a common light chain comprising the LCDRs and/or light chain variable region referred to above, other common light chains known in the art may be used. Examples of such common light chains include, but are not limited to: VK1-39/JK5, comprising a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34. The LCDRs according to IMGT are indicated in bold and underlined therein. In certain embodiments, the light chain comprises a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID

NO: 34, wherein each of the LCDRs may comprise at most three, two, or one amino acid substitution. In certain embodiments, the light chain comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 34, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto; VK3-15/JK1, comprising a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35. The LCDRs according to IMGT are indicated in bold and underlined therein. In certain embodiments, the light chain comprises a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35, wherein each of the LCDRs may comprise at most three, two, or one amino acid substitution. In certain embodiments, the light chain comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 35, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto; VK3-20/JK1, comprising a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 36. The LCDRs according to IMGT are indicated in bold and underlined therein. In certain embodiments, the light chain comprises a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 36, wherein each of the LCDRs may comprise at most three, two, or one amino acid substitution. In certain embodiments, the light chain comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 36, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto; and VL3-21/JL3, comprising a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 37. The LCDRs according to IMGT are indicated in bold and underlined therein. In certain embodiments, the light chain comprises a light chain variable region comprising a light chain CDR1 (LCDR1), light chain CDR2 (LCDR2), and light chain CDR3 (LCDR3), of a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 37, wherein each of

the LCDRs may comprise at most three, two, or one amino acid substitution. In certain embodiments, the light chain comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 37, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

VK1-39 is short for Immunoglobulin Variable Kappa 1-39 Gene. The gene is also known as Immunoglobulin Kappa Variable 1-39; IGKV139; IGKV1-39; IgVκ1-39. External Ids for the gene are HGNC: 5740; Entrez Gene: 28930; Ensembl: ENSG00000242371. A preferred amino acid sequence for VK1-39 is given as SEQ ID NO: 38. This is the sequence of the V-region. The V-region can be combined with one of five J-regions. Two preferred joined sequences are indicated as VK1-39/JK1 and VK1-39/JK5; alternative names are IgVκ1-39_01/IGJκ1_01 or IgVκ1-39_01/IGJκ5_01 (nomenclature according to the IMGT database worldwide web at imgt.org). These names are exemplary and encompass allelic variants of the gene segments.

VK3-15 is short for Immunoglobulin Variable Kappa 3-15 Gene. The gene is also known as Immunoglobulin Kappa Variable 3-15; IGKV315; IGKV3-15; IgVκ3-15. External Ids for the gene are HGNC: 5816; Entrez Gene: 28913; Ensembl: ENSG00000244437. A preferred amino acid sequence for VK3-15 is given as SEQ ID NO: 39. This is the sequence of the V-region. The V-region can be combined with one of five J-regions. A preferred joined sequence is indicated as VK3-15/JK1; alternative name is Vκ3-15_01/IGJκ1_01 (nomenclature according to the IMGT database worldwide web at imgt.org). This name is exemplary and encompasses allelic variants of the gene segments.

VK3-20 is short for Immunoglobulin Variable Kappa 3-20 Gene. The gene is also known as Immunoglobulin Kappa Variable 3-20; IGKV320; IGKV3-20; IgVκ3-20. External Ids for the gene are HGNC: 5817; Entrez Gene: 28912; Ensembl: ENSG00000239951. A preferred amino acid sequence for VK3-20 is as SEQ ID NO: 40. This is the sequence of the V-region. The V-region can be combined with one of five J-regions. A preferred joined sequence is indicated as VK3-20/JK1; alternative name is IgVκ3-20_01/IGJκ1_01 (nomenclature according to the IMGT database worldwide web at imgt.org). This name is exemplary and encompasses allelic variants of the gene segments.

VL3-21 is short for Immunoglobulin Variable Lambda 3-21 Gene. The gene is also known as Immunoglobulin Lambda Variable 3-21; IGLV321; IGLV3-21; IgVλ3-21. External Ids for the gene are HGNC: 5905; Entrez Gene: 28796; Ensembl: ENSG00000211662.2. A

preferred amino acid sequence for VL3-21 is given as SEQ ID NO: 41. This is the sequence of the V-region. The V-region can be combined with one of five J-regions. A preferred joined sequence is indicated as VL3-21/JL3; alternative name is IgVλ3-21/IGJλ3 (nomenclature according to the IMGT database worldwide web at imgt.org). This name is exemplary and encompasses allelic variants of the gene segments.

Further, any light chain variable region of a LAG-3 antibody available in the art may be used, or any other light chain variable region that can readily be obtained, such as from, for instance, an antibody display library by showing antigen binding activity when paired with a LAG-3 binding domain of the invention.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof may further comprise a CH1 and CL region. Any CH1 domain may be used, in particular a human CH1 domain. An example of a suitable CH1 domain is provided by the amino acid sequence provided as SEQ ID NO: 42. Any CL domain may be used, in particular a human CL. An example of a suitable CL domain is provided by the amino acid sequence provided as SEQ ID NO: 43.

In certain embodiments, the multispecific antibody or variant thereof comprises a binding domain that specifically binds to an extracellular domain of LAG-3 and a binding domain that specifically binds to an extracellular domain of a protein of the B7 family.

The B7 family comprises a number of structurally related, cell-surface proteins, which bind to receptors on lymphocytes that regulate immune responses. Activation of lymphocytes is initiated by engagement of cell-surface, antigen-specific T-cell receptors or B-cell receptors. Additional signals delivered simultaneously by B7 ligands further determine the immune response of these cells. These so-called 'costimulatory' or 'coinhibitory' signals are delivered by B7 family members through the CD28 family of receptors on lymphocytes. Binding of B7-family members with costimulatory receptors augments immune responses, and binding with coinhibitory receptors attenuates immune responses. Presently the following members are believed to be part of this family : B7.1 (CD80), B7.2 (CD86), inducible costimulator ligand (ICOS-L), programmed death-1 ligand (PD-L1), programmed death-2 ligand (PD-L2), B7-H3 (CD276), B7-H4, B7-H5, B7-H6 and B7-H7. B7 family members are expressed in lymphoid and non-lymphoid tissues. Effects of members on regulating immune responses are shown in the development of immunodeficiency and autoimmune diseases in mice with mutations in B7-

family genes. Manipulation of the signals delivered by B7 ligands has shown potential in the treatment of autoimmunity, inflammatory diseases and cancer.

In certain embodiments, the protein of the B7 family is selected from the group consisting of PD-L1, PD-L2, CD80, CD86, B7-H4, TNFRSF14, and B7-H7. In certain embodiments the protein of the B7 family is PD-L1.

In certain embodiments, the variable domain that specifically binds to an extracellular domain of a protein of the B7 family blocks the binding of PD-L1 to its receptor. In certain embodiments, the receptor is PD-1 and/or CD80.

In certain embodiments, the PD-L1 binding domain of a multispecific antibody or variant thereof of the present disclosure comprises a heavy chain variable region, wherein the heavy chain variable region comprises the heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3) of one of the heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 20-24. The HCDRs according to Kabat are indicated in bold and underlined in the list of sequences provided herein.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20;
- 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: 21;
- 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: 22;
- 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: 23; or
- 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: 24,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively;

- 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: 110, SEQ ID NO: 111 and SEQ ID NO: 112, respectively;

- 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: 113, SEQ ID NO: 114 and SEQ ID NO: 115, respectively;

- 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: 107, SEQ ID NO: 116 and SEQ ID NO: 109, respectively; or

- 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20; or

- 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: 24,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively; or

- 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively,

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

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20;

- 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: 21;

- 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: 22;

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: 23; or

- 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: 24.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively;

- 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: 110, SEQ ID NO: 111 and SEQ ID NO: 112, respectively;

- 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: 113, SEQ ID NO: 114 and SEQ ID NO: 115, respectively;

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: 107, SEQ ID NO: 116 and SEQ ID NO: 109, respectively; or

- 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20; or

- 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: 24.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively; or

- 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 20.

In certain embodiments, the binding domain that binds to PD-L1 comprises a heavy chain variable region comprising:

- 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively.

In certain embodiments, the PD-L1 binding domain of the multispecific antibody or variant thereof comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 20-24, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

In certain embodiments, a PD-L1 binding domain of the multispecific antibody or variant thereof includes PD-L1 binding domain variants, wherein each of the HCDRs may comprise at most three, two, or one amino acid substitution. Such variants are expected to retain PD-L1 binding specificity.

In certain embodiments, a PD-L1 binding domain of the multispecific antibody or variant thereof also includes PD-L1 binding domain variants, which, in addition to variations in the HCDRs, comprise one or more variations in the framework regions. In certain embodiments, a PD-L1 binding domain variant of the multispecific antibody or variant thereof comprises no variations in the CDR regions but comprises one or more variations in the framework regions. Such variants have at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the sequences disclosed herein, and are expected to retain PD-L1 binding specificity. Thus, in certain embodiments, a PD-L1 binding domain of the present disclosure comprises:

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 20, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 20;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 21;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 22, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 22;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 23, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 23; or

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ

ID NO: 24, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 of the amino acid sequence as set forth in SEQ ID NO: 24.

In certain embodiments, a PD-L1 binding domain of the present disclosure comprises:

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 20, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 110, SEQ ID NO: 111 and SEQ ID NO: 112, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 22, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 113, SEQ ID NO: 114 and SEQ ID NO: 115, respectively;

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 23, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 107, SEQ ID NO: 116 and SEQ ID NO: 109, respectively; or

- a heavy chain variable region having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 24, which heavy chain variable region comprises the HCDR1, HCDR2, and HCDR3 amino acid sequence as set forth in SEQ ID NO: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In certain embodiments, a PD-L1 binding domain of the multispecific antibody or variant thereof further comprises a light chain variable region. An example of a suitable light chain variable region is a light chain variable region as described herein. Light chain variable regions of PD-L1 antibodies available in the art may be used, or any other light chain variable region that can readily be obtained, such as from, for instance, an antibody display library by showing antigen binding activity when paired with a PD-L1 binding domain of the present disclosure. Preferably, a PD-L1 binding domain of the present disclosure comprises a VK1-39/JK1, VK1-39/JK5, VK3-15/JK1, VK3-20/JK1, or VL3-21/JL3 light chain variable region.

In certain embodiments, the PD-L1 binding domain of the multispecific antibody or variant thereof may further comprise a CH1 and CL region. Any CH1 domain may be used, in particular a human CH1 domain. An example of a suitable CH1 domain is provided by the amino acid sequence provided as SEQ ID NO: 42. Any CL domain may be used, in particular a human CL. An example of a suitable CL domain is provided by the amino acid sequence provided as SEQ ID NO: 43.

In certain embodiments, a LAG-3 binding domain disclosed herein can be combined with any PD-L1 binding domain disclosed herein to produce a multispecific antibody or variant thereof of the present disclosure. In certain embodiments, the present disclosure provides multispecific antibodies PB1-PB125, or variants thereof, as presented in Table 1.

	SEQ ID NO: 21	SEQ ID NO: 22	SEQ ID NO: 23	SEQ ID NO: 24	SEQ ID NO: 20
SEQ ID NO: 1	PB1	PB2	PB3	PB4	PB69
SEQ ID NO: 2	PB5	PB6	PB7	PB8	PB70
SEQ ID NO: 3	PB9	PB10	PB11	PB12	PB71
SEQ ID NO: 4	PB13	PB14	PB15	PB16	PB72

SEQ ID NO: 5	PB17	PB18	PB19	PB20	PB73
SEQ ID NO: 6	PB21	PB22	PB23	PB24	PB74
SEQ ID NO: 7	PB25	PB26	PB27	PB28	PB75
SEQ ID NO: 8	PB29	PB30	PB31	PB32	PB76
SEQ ID NO: 9	PB33	PB34	PB35	PB36	PB77
SEQ ID NO: 10	PB37	PB38	PB39	PB40	PB78
SEQ ID NO: 11	PB41	PB42	PB43	PB44	PB79
SEQ ID NO: 12	PB45	PB46	PB47	PB48	PB80
SEQ ID NO: 13	PB49	PB50	PB51	PB52	PB81
SEQ ID NO: 14	PB53	PB54	PB55	PB56	PB82
SEQ ID NO: 15	PB57	PB58	PB59	PB60	PB83
SEQ ID NO: 16	PB61	PB62	PB63	PB64	PB84
SEQ ID NO: 17	PB65	PB66	PB67	PB68	PB85
SEQ ID NO: 52	PB86	PB87	PB88	PB89	PB90
SEQ ID NO: 53	PB91	PB92	PB93	PB94	PB95

SEQ ID NO: 54	PB96	PB97	PB98	PB99	PB100
SEQ ID NO: 55	PB101	PB102	PB103	PB104	PB105
SEQ ID NO: 56	PB106	PB107	PB108	PB109	PB110
SEQ ID NO: 57	PB111	PB112	PB113	PB114	PB115
SEQ ID NO: 58	PB116	PB117	PB118	PB119	PB120
SEQ ID NO: 59	PB121	PB122	PB123	PB124	PB125

Table 1. Binding moieties comprising combinations of heavy chain variable regions specific for LAG-3 and heavy chain variable regions specific for PD-L1. Each of PB1-PB125 can be combined with the light chain disclosed herein.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 1; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 3; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 5; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24. In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 6; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 52; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 53; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 54; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 55; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 56; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 57; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 58; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 59; and
- a PD-L1 binding domain of the present disclosure comprising 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: 20, 23 or 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 53; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 54; and
- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively; and
- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 55; and
- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 56; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 57; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 58; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 59; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 5; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 52; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively.In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 66, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 53; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 119, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 54; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 120, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 55; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 121, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 56; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 122, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 57; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain

CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 123, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 58; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 124, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 59; and

- a PD-L1 binding domain of the present disclosure comprising 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: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 64, SEQ ID NO: 65 and SEQ ID NO: 125, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 117 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 5; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 72, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 52; and

- a PD-L1 binding domain of the present disclosure comprising 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: 20,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising 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: 70, SEQ ID NO: 71 and SEQ ID NO: 118, respectively; and

- a PD-L1 binding domain of the present disclosure comprising 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: 107, SEQ ID NO: 108 and SEQ ID NO: 109, respectively,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise light chain CDR1 (LCDR1) having an amino acid sequence as set forth in SEQ ID NO: 31, light chain CDR2 (LCDR2) having an amino acid sequence as set forth in SEQ ID NO: 32, and light chain CDR3 (LCDR3) having an amino acid sequence as set forth in SEQ ID NO: 33.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 53; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 54; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 55; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 56; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 57; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 58; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 59; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 5; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 52; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20.In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 53; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 54; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 55; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 56; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 57; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 58; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 59; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 5; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

In one embodiment, the multispecific antibody or variant thereof comprises:

- a LAG-3 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 52; and

- a PD-L1 binding domain of the present disclosure comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20,

wherein the LAG-3 binding domain and PD-L1 binding domain comprise a light chain variable region having an amino acid sequence as set forth in SEQ ID NO: 30.

A LAG-3xPD-L1 multispecific antibody or variant thereof of the present disclosure targets two immune checkpoints in trans: it binds to PD-L1 expressed on tumor cells or antigen-presenting cells and, simultaneously, LAG-3 expressed on T-cells. It could also function in cis by binding to PD-L1 upregulated on exhausted T-effector cells in the tumor microenvironment. In this way, a LAG-3xPD-L1 multispecific antibody or variant thereof of the present disclosure prevents T-cells inhibitory signaling and enhances tumor immunity.

In certain embodiments, the multispecific antibody or variant thereof has a binding affinity for human LAG-3 in a range of about 1-2 nM, in particular in a range of about 1.45-1.93 nM, as measured by SPR as described herein. The term “about” allows for a deviation of 10% from the stated values.

In certain embodiments, the multispecific antibody or variant thereof has a binding affinity for human LAG-3 in a range of 1-2 nM, in particular in a range of 1.45-1.93 nM, as measured by SPR as described herein.

In certain embodiments, the multispecific antibody or variant thereof has a binding affinity for human PD-L1 in a range of 0.1-0.5 nM, in particular in a range of 0.17-0.41 nM, as measured by SPR as described herein.

In certain embodiments, the present disclosure provides a multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has a higher affinity for cynomolgus LAG-3 than a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a higher affinity for cynomolgus PD-L1 than a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26.

Determining if a multispecific antibody or variant thereof has a higher binding affinity than a reference antibody can be done by measuring the binding affinity of both the multispecific antibody or variant thereof and the reference antibody in the same type of assay, using the same assay conditions. Thus, in certain embodiments, the binding affinity of the multispecific antibody or variant thereof and the binding affinity of the reference antibody are measured in the same type of assay, using the same assay conditions. In certain embodiments, the assay is an assay that uses surface plasmon resonance (SPR).SPR is an assay that uses surface plasmon resonance (SPR) to measure binding affinity, such as the biosensor system of Biacore®, or Solution Equilibrium Titration (SET) (see Friguet B et al. (1985) J. Immunol Methods; 77(2): 305-319, and Hanel C et al. (2005) Anal Biochem; 339(1): 182-184).

The binding affinity values of the LAG-3 and PD-L1 binding domains as provided herein are obtained with the method described in Example 3. In brief, anti-huIgG Fcγ is covalently coupled to the surface of a CM5 sensor chip using free amine chemistry. Multispecific antibodies are injected at concentrations up to 20 nM at 30 µL/min for 2 minutes in the flow cell. Subsequently, antigen (0.6-20 nM) is flowed over the surface of the CM5 sensor chip at 30 µL/min for 2 minutes. Sensorgrams of the association and dissociation phases for the different

antigens are obtained. Using the BIA evaluation software and curve-fitting employing a 1: 1 interaction model (for monovalent interaction), the affinities of the individual Fab arms are determined.

In certain embodiments, the binding affinity is measured with the LAG-3xPD-L1 multispecific antibody of the present disclosure in bivalent bispecific format and the reference anti-human LAG-3 antibody in bivalent monospecific IgG format. The binding affinity of the multispecific antibody for human LAG-3 thus represents a monovalent binding affinity.

In certain embodiments, the binding affinity is measured with the LAG-3xPD-L1 multispecific antibody of the present disclosure in bivalent bispecific format and the reference anti-human PD-L1 antibody in bivalent monospecific IgG format. The binding affinity of the multispecific antibody for human PD-L1 thus represents a monovalent binding affinity.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof has at least a ten-fold, preferably a ten to twenty fold, higher binding affinity for cynomolgus LAG-3 than the reference anti-human LAG-3 binding domain as described herein, as measured by SPR as described herein.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant thereof has a ten-fold higher binding affinity for cynomolgus LAG-3 than the reference anti-human LAG-3 binding domain as described herein, as measured by SPR as described herein.

In certain embodiments, the PD-L1 binding domain of the multispecific antibody or variant has at least a ten-fold higher, preferably a ten to fifty fold, in particular a ten to forty, ten to thirty, ten to twenty, fold, higher binding affinity for cynomolgus PD-L1 than the reference anti-human PD-L1 binding domain as described herein, as measured by SPR as described herein.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant has a binding affinity for cynomolgus LAG-3 in a range of about 0.1-2 nM, in particular in a range of about 0.3-1.5 nM; about 0.35-1.5 nM or about 0.4-1.2 nM, more in particular in a range of about 0.41-1.15 nM, as measured by SPR as described herein. The term “about” allows for a deviation of 10% from the stated values.

In certain embodiments, the LAG-3 binding domain of the multispecific antibody or variant has a binding affinity for cynomolgus LAG-3 in a range of 0.1-2 nM, in particular in a

range of 0.3-1.5 nM; 0.35-1.5 nM or 0.4-1.2 nM, more in particular in a range of 0.41-1.15 nM, as measured by SPR as described herein.

In certain embodiments, the PD-L1 binding domain of the multispecific antibody or variant has a binding affinity for cynomolgus PD-L1 in a range of about 0.05-1 nM, in particular in a range of about 0.05-0.5 nM; about 0.1-0.4 nM or about 0.1-0.35 nM, more in particular in a range of about 0.15-0.34 nM, as measured by SPR as described herein. The term "about" allows for a deviation of 10% from the stated values.

In certain embodiments, the PD-L1 binding domain of the multispecific antibody or variant has a binding affinity for cynomolgus PD-L1 in a range of 0.05-1 nM, in particular in a range of 0.05-0.5 nM; 0.1-0.4 nM or 0.1-0.35 nM, more in particular in a range of 0.15-0.34 nM, as measured by SPR as described herein.

In certain embodiments, the binding affinity for cynomolgus LAG-3 is measured with both the LAG-3 binding domain of the multispecific antibody and the reference anti-LAG-3 binding domain in a bivalent bispecific IgG format. A bivalent bispecific IgG format may for instance comprise a LAG-3 binding domain of the present disclosure or of the reference antibody and a binding domain that binds PD-L1 or another unrelated target. It is thus the monovalent interaction with cynomolgus LAG-3 that is being measured.

In certain embodiments, the binding affinity for cynomolgus PD-L1 is measured with both the PD-L1 binding domain of the multispecific antibody and the reference PD-L1 binding domain in a bivalent bispecific IgG format. A bivalent bispecific IgG format may for instance comprise a PD-L1 binding domain of the present disclosure or of the reference antibody and a binding domain that binds LAG-3 or another unrelated target. It is thus the monovalent interaction with cynomolgus PD-L1 that is being measured.

In certain embodiments, the multispecific antibody or variant thereof is capable of enhancing the proliferation of $CD4^+$ and/or $CD8^+$ tumor-infiltrating T cells. In certain embodiments, the multispecific antibody or variant thereof is capable of increasing the number of $CD4^+$ and/or $CD8^+$ T cells, in particular proliferating $CD4^+$ and/or $CD8^+$ T cells, in the tumor microenvironment. This can for instance be determined by measuring the number of $CD4^+$ and/or $CD8^+$ T cells, in particular proliferating $CD4^+$ and/or $CD8^+$ T cells, in a tumor biopsy, as described for instance in Example 4.

In certain embodiments, the multispecific antibody or variant thereof results in a reduced number of regulatory T cells in the tumor microenvironment as compared to the number of regulatory T cells in response to a combination of the reference antibodies as described herein.

In certain embodiments, the multispecific antibody or variant thereof is a full length antibody, in particular a full length bispecific antibody, more in particular a full length bispecific IgG1 antibody.

In certain embodiments, the present disclosure provides a vector comprising a nucleic acid sequence encoding the heavy chain variable region of a LAG-3 binding domain as described herein and a nucleic acid sequence encoding the heavy chain variable region of a PD-L1 binding domain as described herein. In certain embodiments, the vector further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region. In certain embodiments, the vector further comprises at least one polynucleotide encoding a light chain variable region, and preferably a CL region. In certain embodiments, 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.

The present disclosure further provides a cell comprising a nucleic acid sequence encoding the heavy chain variable region of a LAG-3 binding domain as described herein and a nucleic acid sequence encoding the heavy chain variable region of a PD-L1 binding domain as described herein. In certain embodiments, the cell may further comprise a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region. In certain embodiments, the cell may further comprise at least one polynucleotide sequence encoding a light chain variable region, and preferably a CL region. In certain embodiments, 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.

The present disclosure also provides a cell producing a multispecific antibody or variant thereof as described herein. In certain embodiments, the cell is a recombinant cell, which has been transformed with a vector as described herein.

Further provided herein is a method for producing a multispecific antibody or variant thereof of the present disclosure, wherein the method comprises culturing a cell as described herein and recovering the multispecific antibody or variant thereof, from the cell or supernatant.

Further provided herein is a method for producing a variant of a LAG-3 binding domain and/or a PD-L1 binding domain of the present disclosure, wherein the method comprises:

- generating a sequence variant of a heavy chain variable region as described herein; and
- expressing the sequence variant or variants and a light chain variable region as described herein in a cell.

Methods for generating sequence variants are well known in the art. One can take a random approach in generating sequence variants or a targeted approach, where one can for instance aim at introducing variations that are likely to increase or decrease binding affinity. Routine methods for affinity maturing antibody binding domains are widely known in the art, see for instance Tabasinezhad M. *et al.* Immunol Lett. 2019;212:106-113. One can also aim at introducing variations that mitigate developability risks with a view on producing a binding domain, or multispecific antibody comprising such binding domain, at large scale. Variations may be introduced that are likely not to cause a loss in binding specificity and/or affect binding affinity. Permissive substitutions include, but are not limited to, those substitutions which result in similar biophysical properties of the variant, for example Isoleucine to Leucine or Valine, Threonine to Serine, Arginine to Lysine, Aspartate to Glutamate and Tryptophan to Tyrosine. Variations may also be introduced at certain positions based on frequency in germlines or natural repertoires.

Whether amino acid residues within the CDRs and/or framework regions can be substituted, for instance with a conservative amino acid residue, and without, or substantially without, loss in binding specificity and/or affinity, can be determined by methods well known in the art. Experimental examples include, but are not limited to, for instance, alanine scanning (Cunningham BC, Wells JA. Science. 1989;244(4908):1081-5), and deep mutational scanning (Araya CL, Fowler DM. Trends Biotechnol. 2011;29(9):435-42). Computational methods have also been developed that can predict the effect of amino acid variation, such as for instance described in Sruthi CK, Prakash M. PLoS One. 2020;15(1):e0227621, Choi Y. et al. PLoS One. 2012;7(10):e46688, and Munro D, Singh M. Bioinformatics. 2020;36(22-23):5322–9.

Further provided herein are multispecific antibodies comprising any variant LAG-3 and/or PD-L1 binding domains produced by the above described method; a pharmaceutical composition comprising a multispecific antibody that comprises any of said variant LAG-3 and/or PD-L1 binding domains; nucleic acids encoding any of said variant binding domains;

vectors and cells comprising said nucleic acids; and use of a multispecific antibody comprising any of said variant LAG-3 and/or PD-L1 binding domains or said pharmaceutical composition for the treatment of cancer.

Pharmaceutical Composition and Methods

In certain embodiments, the present disclosure provides a pharmaceutical composition comprising the multispecific antibody or variant thereof as described herein and a pharmaceutical acceptable carrier, diluent or excipient.

In certain embodiments, the present disclosure provides a multispecific antibody or variant thereof, or pharmaceutical composition, as described herein for use as a medicament.

In certain embodiments, the present disclosure provides a multispecific antibody or variant thereof as described herein, or the pharmaceutical composition, as described herein, for use in the treatment of a disease associated with a suppressed immune system, in particular cancer.

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

In certain embodiments, the present disclosure provides a method for treating a disease associated with a suppressed immune system, in particular cancer, comprising administering an effective amount of the multispecific antibody or variant thereof, or the pharmaceutical composition, as described herein to an individual in need thereof.

As used herein, the terms “individual”, "subject" and "patient" are used interchangeably and refer to a mammal such as a human, mouse, rat, hamster, guinea pig, rabbit, cat, dog, monkey, cow, horse, pig and the like (e.g., a patient, such as a human patient, having cancer).

The terms “treat,” “treating,” and “treatment,” as used herein, refer to any type of intervention or process performed on or administering an active agent or combination of active agents to a subject with the objective of curing or improving a disease or symptom thereof. This includes reversing, alleviating, ameliorating, inhibiting, or slowing down a symptom, complication, condition or biochemical indicia associated with a disease, as well as preventing

the onset, progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease.

As used herein, "effective treatment" or "positive therapeutic response" refers to a treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder, e.g., cancer. A beneficial effect can take the form of an improvement over baseline, including an improvement over a measurement or observation made prior to initiation of therapy according to the method. For example, a beneficial effect can take the form of slowing, stabilizing, stopping or reversing the progression of a cancer in a subject at any clinical stage, as evidenced by a decrease or elimination of a clinical or diagnostic symptom of the disease, or of a marker of cancer. Effective treatment may, for example, decrease in tumor size, decrease the presence of circulating tumor cells, reduce or prevent metastases of a tumor, slow or arrest tumor growth and/or prevent or delay tumor recurrence or relapse.

The term “therapeutic amount" or “effective amount” refers to an amount of an agent or combination of agents that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In some embodiments, a therapeutic amount is an amount sufficient to delay tumor development. In some embodiments, a therapeutic amount is an amount sufficient to prevent or delay tumor recurrence.

The effective amount of the agent or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

An effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual to be treated, and the ability of the agent or combination of agents to elicit a desired response in the individual.

An effective amount can be administered in one or more administrations.

A therapeutic amount also includes an amount that balances any toxic or detrimental effects of the agent or combination of agents and the therapeutically beneficial effects.

The term “agent” refers to a therapeutically active substance, in the present case a multispecific antibody or variant thereof of the present disclosure, or a pharmaceutical composition of the present disclosure.

General Terms

As used herein, "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded.

The articles “a” and “an” are used herein to refer to one or more of the grammatical object of the article. By way of example, “an element” means one or more elements.

A reference herein to a patent document or other matter is not to be taken as an admission that that document or matter was known or that the information it contains was part of the common general knowledge at the priority date of any of the claims.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

Note that in the present specification, unless stated otherwise, amino acid positions assigned to CDRs and frameworks in a variable region of an antibody or antibody fragment are specified according to Kabat's numbering (see Sequences of Proteins of Immunological Interest (National Institute of Health, Bethesda, Md., 1987 and 1991)). Amino acids in the constant regions are indicated according to the EU numbering system.

Accession numbers are primarily given to provide a further method of identification of a target, the actual sequence of the protein bound may vary, for instance because of a mutation in the encoding gene such as those occurring in some cancers or the like. The antigen binding site binds the antigen and a variety of variants thereof, such as those expressed by some antigen positive immune or tumor cells.

When herein reference is made to a gene, a protein, the reference is preferably to the human form of the gene or protein. When herein reference is made to a gene or protein reference is made to the natural gene or protein and to variant forms of the gene or protein as can be detected in tumors, cancers and the like, preferably as can be detected in human tumors, cancers and the like.

HGNC stands for the HUGO Gene nomenclature committee. The number following the abbreviation is the accession number with which information on the gene and protein encoded by the gene can be retrieved from the HGNC database. Entrez Gene provides the accession number or gene ID with which information on the gene or protein encoded by the gene can be retrieved from the NCBI (National Center for Biotechnology Information) database. Ensemble provides the accession number with which information on the gene or protein encoded by the gene can be obtained from the Ensemble database. Ensembl is a joint project between EMBL-EBI and the Wellcome Trust Sanger Institute to develop a software system which produces and maintains automatic annotation on selected eukaryotic genomes.

BRIEF DESCRIPTION OF THE DRAWINGS

In the Figures, bivalent monospecific antibodies are indicated in the format SEQ ID NO: A, where SEQ ID NO: A refers to the heavy chain variable sequence of both binding domains. Each binding domain of the monospecific antibodies comprises a light chain. In the Examples, which are used to illustrate the present disclosure but are not intended to limit the disclosure in any way, each binding domain of the monospecific antibodies comprises a light chain variable region variable region having an amino acid sequence as set forth in SEQ ID NO: 30 and a light chain constant region having an amino acid sequence as set forth in SEQ ID NO: 43. The monospecific antibodies preferably are IgG1 antibodies comprising a CH1, hinge, CH2, and CH3. In the Examples, which are used to illustrate the present disclosure but are not intended to limit the disclosure in any way, monospecific antibodies were screened in IgG1 format, wherein the LAG-3 and PD-L1 binding heavy chains comprise a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 47.

Bispecific antibodies are indicated in the format SEQ ID NO: A x SEQ ID NO: B, where both SEQ ID NO: A and B refer to heavy chain variable sequences. Each binding domain of the bispecific antibodies comprises a light chain. In the Examples, which are used to illustrate the present disclosure but are not intended to limit the disclosure in any way, each binding domain of the bispecific antibodies comprises a light chain variable region variable region having an amino acid sequence as set forth in SEQ ID NO: 30 and a light chain constant region having an amino

acid sequence as set forth in SEQ ID NO: 43. The bispecific antibodies are IgG1 antibodies, comprising a CH1, hinge, CH2, and CH3.

In Example 1, which is used to illustrate the present disclosure but is not intended to limit the disclosure in any way, bispecific antibodies were screened in IgG1 format, wherein the PD-L1 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 that may have an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 that may have an amino acid sequence as set forth in SEQ ID NO: 50; and the LAG-3 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 51.

In Example 2, which is used to illustrate the present disclosure but is not intended to limit the disclosure in any way, bispecific antibodies were screened in IgG1 format, wherein the PD-L1 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 50; and the LAG-3 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 51.

In Examples 3 and 4, which are used to illustrate the present disclosure but are not intended to limit the disclosure in any way, bispecific antibodies were screened in IgG1 format.

For SEQ ID NO:17 x SEQ ID NO:24, the PD-L1 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 50; and the LAG-3 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 51.

For SEQ ID NO: 5 x SEQ ID NO: 20, the PD-L1 binding heavy chain may comprise a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 51; and the LAG-3 binding heavy chain comprises a CH1 having an amino acid

sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 50.

In Example 5, which is used to illustrate the present disclosure but is not intended to limit the disclosure in any way, bispecific antibodies were screened in IgG format, wherein the PD-L1 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 50 or 51; and the LAG-3 binding heavy chain comprises a CH1 having an amino acid sequence as set forth in SEQ ID NO: 42, a CH2 having an amino acid sequence as set forth in SEQ ID NO: 45, and a CH3 having an amino acid sequence as set forth in SEQ ID NO: 51 or 50, as indicated in (Table 10).Bivalent monospecific relatlimab analog antibody and bivalent monospecific atezolizumab analog antibody are indicated in the format SEQ ID NO: A/SEQ ID NO: B, where SEQ ID NO: A refers to the respective heavy chain sequence and SEQ ID NO: B refers to the respective light chain sequence. Bivalent monospecific relatlimab analog antibody comprises two LAG-3 binding domains. Bivalent monospecific atezolizumab analog antibody comprises two PD-L1 binding domains. Each binding domain of the analog antibodies comprises a light chain. A combination of relatlimab and atezolizumab analogs is indicated in the format SEQ ID NO: A/SEQ ID NO: B + SEQ ID NO: C/SEQ ID NO: D, where SEQ ID NO: A refers to the heavy chain sequence and SEQ ID NO: B refers to the light chain sequence of either relatlimab or atezolizumab analog, and SEQ ID NO: C to the heavy chain sequence and SEQ ID NO: D to the light chain sequence of the other.

Figure 1A shows the results of LAG-3 binding using FACS. Bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1 and SEQ ID NO: 23 (a), SEQ ID NO: 3 and SEQ ID NO: 23 (b), SEQ ID NO: 5 and SEQ ID NO: 23 (c), SEQ ID NO: 6 and SEQ ID NO: 23 (d), SEQ ID NO: 15 and SEQ ID NO: 23 (e), and SEQ ID NO: 16 and SEQ ID NO: 23 (f) were compared with bivalent monospecific antibodies comprising the respective LAG-3 binding domains, positive control relatlimab analog (SEQ ID NO: 27/SEQ ID NO: 28), and a negative control antibody (SEQ ID NO: 29/SEQ ID NO: 30). Each graph shows the result for binding to human and rhesus LAG-3.

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the level of binding expressed in Mean Fluorescence Intensity (MFI).

Figure 1B shows the results of PD-L1 binding using FACS. Bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1 and SEQ ID NO: 23, SEQ ID NO: 3 and SEQ ID NO: 23, SEQ ID NO: 5 and SEQ ID NO: 23, SEQ ID NO: 6 and SEQ ID NO: 23, SEQ ID NO: 15 and SEQ ID NO: 23, and SEQ ID NO: 16 and SEQ ID NO: 23 were compared with a bivalent monospecific antibody comprising the PD-L1 binding domain having an amino acid sequence as set forth in SEQ ID NO: 23, positive control atezolizumab analog (SEQ ID NO: 25/SEQ ID NO: 26), and a negative control antibody (SEQ ID NO: 29/SEQ ID NO: 30). The top graph shows the result for binding to human PD-L1; the bottom graph shows the result for binding to rhesus PD-L1.

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the level of binding expressed in Mean Fluorescence Intensity (MFI).

Figure 2 shows the results from the PD-1/LAG-3 reporter assay. Bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1 and SEQ ID NO: 23, SEQ ID NO: 3 and SEQ ID NO: 23, SEQ ID NO: 5 and SEQ ID NO: 23, SEQ ID NO: 6 and SEQ ID NO: 23, SEQ ID NO: 15 and SEQ ID NO: 23, and SEQ ID NO: 16 and SEQ ID NO: 23 were compared with positive control atezolizumab analog (SEQ ID NO: 25/SEQ ID NO: 26), positive control relatlimab analog (SEQ ID NO: 27/SEQ ID NO: 28), a combination of atezolizumab and relatlimab analogs (SEQ ID NO: 25/SEQ ID NO:26 + SEQ ID NO: 27/SEQ ID NO: 28), and a negative control antibody (SEQ ID NO: 29/SEQ ID NO: 30).

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the fold induction.

Figure 3 shows the results from the SEB assay from donor 1 (Figure 3A) and donor 2 (Figure 3B).

Figures 3A1 and 3B1 show a comparison in fold induction of IL-2 of bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1 and SEQ ID NO: 23, SEQ ID NO: 3 and SEQ ID NO: 23, SEQ ID NO: 5 and SEQ ID NO: 23, SEQ ID NO: 6 and SEQ ID NO: 23, SEQ ID NO: 15 and SEQ ID NO: 23, and SEQ ID NO: 16 and SEQ ID NO: 23 with positive control atezolizumab analog (SEQ ID NO: 25/SEQ ID NO: 26), a combination of atezolizumab and relatlimab analogs (SEQ ID NO:

25/SEQ ID NO:26 + SEQ ID NO: 27/SEQ ID NO: 28), and a negative control antibody (SEQ ID NO: 29/SEQ ID NO: 30).

Figures 3A2 and 3B2 show a comparison in fold induction of TNFa of the same antibodies.

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the fold induction of IL-2 or TNFa. Fold induction of each antibody was calculated relative to control wells containing no IgG.

Figure 4 shows the binding affinity data of two bispecific antibodies.

Figure 5 shows the results of two bispecific antibodies in FACS binding, PD-1/LAG-3 reporter, and SEB assays.

Figure 5A compares the binding to human LAG-3 of the bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20 with that of positive control relatlimab analog (SEQ ID NO: 27/SEQ ID NO:28) and a negative control antibody.

Figure 5B compares the binding to rhesus LAG-3 of the same antibodies.

Figure 5C compares the binding to human PD-L1 of the bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20 with that of positive control atezolizumab analog (SEQ ID NO: 25/SEQ ID NO:26) and a negative control antibody.

Figure 5D compares the binding to rhesus PD-L1 of the same antibodies.

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the level of binding expressed in Mean Fluorescence Intensity (MFI).

Figure 5E shows the results of the PD-1/LAG-3 reporter assay, wherein bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20 are compared with positive controls atezolizumab analog (SEQ ID NO: 25/SEQ ID NO:26) and relatlimab analog (SEQ ID NO: 27/SEQ ID NO:28), a combination of relatlimab and atezolizumab analogs (SEQ ID NO: 27/SEQ ID NO:28 + SEQ ID NO: 25/SEQ ID NO: 26, and a negative control antibody.

Figure 5F shows the results of the SEB assay, comparing the fold induction of IL-2 of bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as

set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20 with that of positive controls atezolizumab analog (SEQ ID NO: 25/SEQ ID NO:26) and relatlimab analog (SEQ ID NO: 27/SEQ ID NO:28), a combination of relatlimab and atezolizumab analogs (SEQ ID NO: 27/SEQ ID NO:28 + SEQ ID NO: 25/SEQ ID NO: 26, and a negative control antibody, in four different donors. The four graphs represent the results of four different donors. The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the concentration of IL-2 in pg/mL.

Figure 6 shows the data from the an *in vivo* study. The effect on tumor volume of hu-CD34 NSG™ mice with MDA-MB-231 tumors was assessed for bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20, and compared with atezolizumab analog (Atezolizumab*), relatlimab analog (Relatlimab*, and a combination of relatlimab and atezolizumab analogs (Relatlimab* + Atezolizumab*).

Figure 6A1 shows the data from mice immunized with $CD34^+$ HSC from donor 1, Figure 6A2 from mice immunized with $CD34^+$ HSC from donor 2, and Figure 6A3 from mice immunized with $CD34^+$ HSC from donor 3. Figure 6A4 shows the data from all donors combined.

Figure 6B shows the results from the analysis of $CD4^+$ and $CD8^+$ T cell and regulatory T cell (Treg) populations in MDA-MB-231 tumor samples. The effect on the percentage CD3+ T cells (Figure 6B1), CD8+ T cells (Figure 6B2), FOXP3+ regulatory T cells (Figure 6B3), proliferating CD8+ T cells (Figure 6B4), and proliferating CD4+ T-cells (Figure 6B5), was assessed for bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and SEQ ID NO: 24, and SEQ ID NO: 5 and SEQ ID NO: 20, and compared with atezolizumab analog, relatlimab analog, and a combination of relatlimab and atezolizumab analogs.

Figure 7 shows the results of a binding assay using FACS. Bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in Table 10 were tested along with RSV control antibody (SEQ ID NO: 29/SEQ ID NO: 30). The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows fold induction obtained by normalizing mean MFI values with respect to that of wells without antibody.

Figure 7A shows the results of binding to human LAG-3.

Figure 7B shows the results of binding to rhesus LAG-3.

Figure 7C shows the results of binding to human PD-L1.

Figure 8 shows the results from a PD-1/LAG-3 reporter assay. Bispecific antibodies comprising a heavy chain variable region having an amino acid sequence as set forth in Table 10 were compared with a combination of atezolizumab and relatlimab analogs (SEQ ID NO: 25/SEQ ID NO:26 + SEQ ID NO: 27/SEQ ID NO: 28), and RSV control antibody (SEQ ID NO: 29/SEQ ID NO: 30).

The X-axis shows the concentration of antibody in µg/mL. The Y-axis shows the fold induction.

The following Examples illustrate the present disclosure but are not intended to limit the disclosure in any way.

EXAMPLES

Example 1 – Production and identification of LAG-3xPD-L1 bispecific antibodies

Anti-human LAG-3 binding domains can be obtained by methods known in the art, such as for instance as described in WO 2019/009728. A large panel of heavy chain variable regions were obtained by immunizing transgenic mice comprising a common IGKV1-39 light chain (MeMo® mice) with human LAG-3 antigenic moieties, including the use of different forms of DNA, protein and cell-based antigen delivery.

Anti-human PD-L1 binding domains can be obtained by methods known in the art, such as for instance as described in WO 2018/056821 and WO 2019/009726. A large panel of heavy chain variable regions were obtained by immunizing transgenic mice comprising a common IGKV1-39 light chain (MeMo® mice) with human PD-L1 antigenic moieties, including the use of different forms of DNA, protein and cell-based antigen delivery.

A number of anti-human LAG-3 Fabs were selected, the heavy chain variable regions of which were used for the production of bispecific anti-LAG-3 x anti-PD-L1 antibodies. The amino acid sequences of these heavy chain variable regions are set forth in SEQ ID NOs: 1-16. Fabs comprising these heavy chain variable regions bind domain 1 or domain 2 of human LAG-3

and showed functional activity in a LAG-3 reporter assay (data not shown). Two additional Fabs were selected, the heavy chain variable regions of which comprise the amino acid sequences as set forth in SEQ ID Nos: 18 and 19. Fabs comprising these heavy chain variable regions bind domain 3 and domain 4 of human LAG-3. These two Fabs did not show functional activity in the LAG-3 reporter and were selected for the production of negative control bispecific antibodies.

A number of anti-human PD-L1 Fabs were selected, the heavy chain variable regions of which were used for the production of the bispecific antibodies. The amino acid sequences of these heavy chain variable regions are as set forth in SEQ ID NOs: 21-23. Fabs comprising these heavy chain variable regions block binding of PD-L1 to PD-1 (data not shown). The heavy chain variable domains exhibit different affinities as determined in a bispecific IgG format comprising one PD-L1 binding Fab and one other Fab (binding tetanus toxoid (TT) or anti-PD-1), as measured using SPR. It is thus the binding affinity of a monovalent interaction with PD-L1 that has been measured.

The affinity for PD-L1 of the anti-PD-L1 Fab arms was determined using surface plasmon resonance (SPR). Affinity was measured in bispecific IgG format, having just one arm specific for PD-L1. To determine the kinetics of binding of anti-PD-L1 Fab arms to the antigen, Surface Plasmon Resonance (SPR) using a BIAcore T100 was used. Recombinant, purified, Fc-tagged human PD-L1 (R&D Systems, cat. nr. 156-B7-100) was coupled to flow cell (FC) 2 of a CM5 sensor chip (FC1 served as blank for subtraction and was activated, then inactivated directly using ethanolamine) at to a level of approximately 200 resonance units (RU) using NHS/EDC chemistry at pH5.0 (NaAc buffer), 2µg/mL antigen concentration and 10µL/min flow rate. Bispecific IgG composed of an anti-PD-L1 Fab arm and an irrelevant Fab arm were then run over the surfaces of FC1 and 2 at different concentrations (100 nM and serial 2-fold dilutions in HBS, 6 dilutions) in a kinetic run at 30 µL/min. Regeneration was performed using a pulse of 50 mM HCl in water (15µL at a flow rate of 10 µL/min). Obtained sensorgrams were evaluated using the BIAevaluation software and kinetic association- and dissociation rate constants were determined. Several measurements were performed on different surfaces of different sizes on several days. Different measurements gave very similar results, underscoring their validity. All measurements were carried out at 25°C.

The binding affinities are presented in Table 2.

IgG comprising:	Binding affinity (nM)
SEQ ID NO: 21	2.5
SEQ ID NO: 22	5.5
SEQ ID NO: 23	0.6

Table 2.

Bispecific IgG antibodies were generated by transient co-transfection of two plasmid vectors: one encoding an IgG heavy chain with a LAG-3 binding VH region and the other encoding an IgG heavy chain with a PD-L1 binding VH region. CH3 engineering technology as described in WO 2013/157954 and WO 2013/157953 was employed to ensure efficient hetero-dimerization and formation of bispecific antibodies. Both vectors further encode a common light chain comprising the IGKV1-39/Jk1 light chain variable region. Cell transfection, cell culture, and the harvesting and purification of antibodies was performed by methods known in the art.

Example 2 – Screening of LAG-3 x PD-L1 bispecific antibodies

Reference and control antibodies

Bispecific antibodies were compared with an analog of anti-LAG-3 antibody relatlimab, which comprises two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28 (relatlimab analog), and an analog of anti-PD-L1 antibody atezolizumab, which comprises two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ: 26 (atezolizumab analog), or a combination thereof.

An Fc-silenced anti-RSV antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 29 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 30 was used as a negative control antibody (RSV control antibody).

A number of bispecific antibodies were selected for further screening, including bispecific antibodies comprising the following combination of heavy chain variable regions:

LAG-3 VH	PD-L1 VH
SEQ ID NO: 1	SEQ ID NO: 23
SEQ ID NO: 3	SEQ ID NO: 23
SEQ ID NO: 5	SEQ ID NO: 23
SEQ ID NO: 6	SEQ ID NO: 23
SEQ ID NO: 15	SEQ ID NO: 23
SEQ ID NO: 16	SEQ ID NO: 23

The bispecific antibodies were produced in Fc-silenced IgG1 format, and purified by protein A and gel filtration. Potential homodimer impurities were removed by CIEX. LAG-3 homodimer formation was mitigated by use of CH3 engineering technology to abridge potential impact in functional assays. Monospecific parental antibodies were included in the screening assays to compare the activity of bispecific antibodies to their parental IgG and to determine the sensitivity of the functional assays for PD-L1 and LAG-3 single targeting agents. The monospecific parental antibodies were produced and characterized in a similar fashion as the bispecific antibodies.

Antigen binding

Binding of the bispecific antibodies to LAG-3 and PD-L1 was analyzed by FACS using a 293FF cell line stably transfected with human and rhesus LAG-3 and a CHO-K1 cell line stably transfected with human and rhesus PD-L1.

The bispecific antibodies and parental antibodies were analyzed in an 8-step, 5-fold titration starting at 50 µg/mL. A goat-anti-human PE antibody (Invitrogen, H10104) was used as secondary antibody at a concentration of 3 µg/mL. In all plates containing cells expressing LAG-3, the relatlimab analog was used as a positive control, whereas the atezolizumab analog was used as a positive control for plates containing PD-L1 expressing cells. A 6-step, 5-fold titration starting at 50 µg/mL of the RSV control antibody was included on all plates as a negative control. Two wells were used for secondary antibody only and unstained cells, as additional

controls. As a negative control, cells not expressing the target, 293FF and CHO-K1 cells, were included where the IgG's were only tested at the two highest concentrations (50 and 10 µg/mL).

Results for LAG-3 binding are shown in Figure 1A. EC50 values were calculated using GraphPad Prism software version 7.02 (nonlinear regression, 3-parameter dose-response curve). Each of the bispecific antibodies is plotted together with the positive control antibody, the negative control antibody and its parental LAG-3 binding antibody.

The positive control antibody relatlimab analog showed inconsistent binding to human LAG-3 across the three plates used in this assay: the degree of binding on the plate with the LAG-3 arm comprising SEQ ID NO: 16 was much lower than that observed on the other plates. EC50 values were higher for the bispecific antibodies (monovalent for LAG-3) than for the monospecific parental antibodies (bivalent for LAG-3). The LAG-3 arms comprising SEQ ID NO: 3 and 5 showed the highest degree of binding to human LAG-3. An overview of the EC50 values is shown in Table 3.

Format	**LAG-3**	**PD-L1**	**EC50 (nM) human LAG-3**
Monovalent for LAG-3	SEQ ID NO:1	SEQ ID NO:23	52.13
Bivalent for LAG-3	SEQ ID NO:1	NA	0.54
Monovalent for LAG-3	SEQ ID NO:3	SEQ ID NO:23	9.45
Bivalent	SEQ ID NO:3	NA	0.40
Monovalent for LAG-3	SEQ ID NO:5	SEQ ID NO:23	8.64
Bivalent for LAG-3	SEQ ID NO:5	NA	1.88
Monovalent for LAG-3	SEQ ID NO:6	SEQ ID NO:23	23.92
Bivalent for LAG-3	SEQ ID NO:6	NA	0.80
Monovalent for LAG-3	SEQ ID NO:15	SEQ ID NO:23	113.16
Bivalent for LAG-3	SEQ ID NO:15	NA	0.94
Monovalent for LAG-3	SEQ ID NO:16	SEQ ID NO:23	24.05

Bivalent for LAG-3	SEQ ID NO:16	NA	13.27

Table 3. EC50 values.

Results for PD-L1 binding are shown in Figure 1B. EC50 values were calculated using GraphPad Prism software version 7.02 (nonlinear regression, 3-parameter dose-response curve). The bispecific antibodies are plotted together with the positive control antibody, the negative control antibody and the parental PD-L1 binding antibody.

All bispecific antibodies showed binding to CHO cells expressing huPD-L1. The maximal effect at the highest drug concentration (Emax) was higher for the bispecific antibody comprising SEQ ID NO: 23, monovalent for PD-L1, than for the bivalent monospecific parental antibody. A number of bispecific antibodies comprising the PD-L1 arm having SEQ ID NO: 23 showed better binding than, or comparable binding to, the atezolizumab analog. An overview of the EC50 values is shown in Table 4.

Format	**LAG-3**	**PD-L1**	**EC50 (nM) human PD-L1**
Monovalent for PD-L1	SEQ ID NO:1	SEQ ID NO:23	0.74
Monovalent for PD-L1	SEQ ID NO:3	SEQ ID NO:23	3.02
Monovalent for PD-L1	SEQ ID NO:5	SEQ ID NO:23	1.21
Monovalent for PD-L1	SEQ ID NO:6	SEQ ID NO:23	1.21
Monovalent for PD-L1	SEQ ID NO:15	SEQ ID NO:23	2.41
Monovalent for PD-L1	SEQ ID NO:16	SEQ ID NO:23	1.01
Bivalent for PD-L1	NA	SEQ ID NO:23	0.54
Bivalent for PD-L1	NA	SEQ ID NO: 25	1.12

Table 4. EC50 values.

PD-1/LAG-3 reporter assay

A PD-1/LAG-3 reporter assay was performed using PD-1 and LAG-3 expressing Jurkat T cells as effector cells and PD-L1 expressing Raji cells as target cells. The PD-1 and LAG-3 effector cells were prepared and plated at 100,000 cells per well. Antibody solution was added followed by the Raji cells (25,000 per well). The T cells were activated by the addition of partially purified Staphylococcal enterotoxin D (ppSED, final concentration of 16.6 ng/mL). After 6 hours incubation at 37°C, luciferase reporter gene activity was determined by adding Bio-Glo reagent and measuring luminescence on an EnVision plate reader.

The bispecific IgG's were tested in a 6-step semi-log titration starting at 100 µg/mL (final concentration). IgG dilutions were prepared at 3x final concentration in assay medium. As a positive control, a 6-step semi-log titration of a combination of atezolizumab analog and relatlimab analog, with a highest concentration of 50 µg/mL + 50 µg/mL, were included on each plate. Atezolizumab analog and relatlimab analog were also tested as single agents at 100 µg/mL starting concentration. As a negative control on each plate a 4-step semi-log titration of the RSV control antibody was used starting at 100 µg/mL. Two wells were left without IgG as a control for the basal level of activity.

Results are shown in Figure 2. The bispecific antibodies were compared with each other and with the atezolizumab analog, the relatlimab analog, as well as a combination of the relatlimab and atezolizumab analogs. The area under the curve (AUC) of the antibody response was determined using GraphPad Prism software version 7.02. The AUCs were expressed relative to the AUC of the positive control.

An overview of the AUC is shown in Table 5.

LAG-3	**PD-L1**	**AUC compared to control**
SEQ ID NO:5	SEQ ID NO:23	83.9
SEQ ID NO:3	SEQ ID NO:23	76.6
SEQ ID NO:6	SEQ ID NO:23	71.5
SEQ ID NO:15	SEQ ID NO:23	71.0
SEQ ID NO:16	SEQ ID NO:23	58.3
SEQ ID NO:1	SEQ ID NO:23	54.8

Table 5. AUC values.

SEB assay

The bispecific antibodies and parental antibodies were analyzed in a SEB assay using cells from two donors: PBMC donor1 and PBMC donor2. First, PBMCs from these donors were shown to respond to the anti-LAG-3 reference antibody relatlimab analog and the anti-PD-L1 antibody atezolizumab analog (data not shown). In short, a dilution series of the IgG's were added to $2x10^5$ PBMC cells, followed by the addition of 2 µg/mL SEB (final concentration). IgG's were analyzed in a 6-step 7-fold dilution series starting at 50 µg/mL (final concentration). As a positive control, a 5-fold titration of a combination of the atezolizumab analog and relatlimab analog, starting at 25 µg/mL + 25 µg/mL, was included on each plate. As a negative control on each plate a 4-step semi-log titration of the RSV-control antibody was used starting at 50 µg/mL. Two wells were left without IgG as a control for the basal level of activity. PBMCs were cultured for three days after which IL-2 and TNFα levels were measured in the supernatant by Luminex.

Results are shown in Figure 3. The AUCs of the antibody response were determined using GraphPad Prism software version 7.02.

The standard curves for the cytokine measurements by Luminex were as expected, and the MFI values of all samples were in the range of the standard curves for IL-2 and TNFα (data not shown). The IL-2 data from the SEB assay are shown in Figure 3A1 (donor1) and Figure 3B1 (donor2). The data for TNFα is provided in Figure 3A2 (donor1) and Figure 3B2 (donor2).

In the first assay (PBMC donor1), the positive and negative controls were as expected for both the IL-2 and TNFα read-outs. The activity of the combination of atezolizumab and relatlimab analogs was higher than that for the atezolizumab analog alone for the IL-2 read-out. For both IL-2 and TNFα read-outs, the LAG-3xPD-L1 bispecific antibodies were at least as potent as the combination of atezolizumab and relatlimab analogs.

In the second assay (PBMC donor2), the positive and negative controls were as expected for IL-2. However, the degree of TNFα induction for the positive control was rather low. Again, the activity of the combination of atezolizumab and relatlimab analogs was higher than that for the atezolizumab analog alone for the IL-2 read-out. For both read-outs, the LAG-3xPD-L1 bispecific antibodies were at least as potent as the combination of atezolizumab and relatlimab analogs. The activity of the LAG-3xPD-L1 bispecific antibodies correlated well between the two donors. The bispecific antibodies with the LAG-3 arms having an amino acid sequence as set

forth in SEQ ID NO: 5, SEQ ID NO: 15 and SEQ ID NO: 16 showed similar activity to one another and were at least as potent as the combination of atezolizumab and relatlimab analogs.

Example 3 – Binding affinity of bispecific antibodies comprising further LAG-3 and PD-L1 heavy chain variable regions

Binding affinity of bispecific antibodies comprising a LAG-3 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 5 and a PD-L1 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20, and a bispecific antibody comprising a LAG-3 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and a PD-L1 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24, was determined by SPR technology using a BIAcore T200.

Bispecific antibody binding to four recombinant protein antigens sourced from Sino Biological (human LAG-3-His, Cat nr. 16498-H08H; cynomolgus monkey LAG-3-His, Cat nr. 90841-C08H; human PD-L1-His, Cat nr. 10084-H08H; cynomolgus monkey PD-L1-His, Cat nr. 90251-C08H) was determined in separate experiments. In these assays, anti-huIgG Fcγ (JIR; Cat nr. 109-005-098) is covalently coupled to the surface of a CM5 sensor chip using free amine chemistry: the capturing antibody is diluted in a kAc buffer to 40 µg/mL and coupled to a surface that is activated with NHS/EDC (according to the manufacturer's recommendations). Next, bispecific antibodies are injected at concentrations up to 20 nM at 30 µL/min for 2 minutes in the flow cell. Subsequently, antigen (0.6-20 nM) in 0.01 M HEPES, 0.5 M NaCl, 0.003 M EDTA and 0.05% v/v Surfactant P20 buffer is flowed over the surface of the CM5 sensor chip at 30 µL/min for 2 minutes. Sensorgrams of the association and dissociation phases for the different antigens are thus obtained. Using the BIA evaluation software and curve-fitting employing a 1: 1 interaction model (for monovalent interaction), the affinities of the individual Fab arms are determined.

Results are shown in Figure 4. A bispecific antibody comprising a LAG-3 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 5 and a PD-L1 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 20, and a bispecific antibody comprising a LAG-3 binding

domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17 and a PD-L1 binding domain with a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24, have a lower binding affinity for human LAG-3 and a higher binding affinity for cynomolgus LAG-3 as compared to the relatlimab analog. The bispecific antibodies have a similar binding affinity for human PD-L1 and a higher binding affinity for cynomolgus PD-L1 as compared to the atezolizumab analog.

Both bispecific antibodies bind to human LAG-3 and human PD-L1 simultaneously (data not shown).

These antibodies were screened in binding, PD-1/LAG-3 reporter, and SEB assays as described in Example 2 to confirm their properties. Results are shown in Figure 5. Both bispecific antibodies bind human and rhesus LAG-3 (Figure 5A and B) and human and rhesus PD-L1 (Figure 5C and D). Both bispecific antibodies show comparable activity to a combination of relatlimab and atezolizumab analogs in the reporter assay (Figure 5E) and SEB assay (Figure 5F). EC50 values are provided in Tables 6 and 7.

LAG-3	PD-L1	EC50 (nM)
SEQ ID NO: 17	SEQ ID NO: 24	14.80
SEQ ID NO: 5	SEQ ID: NO 20	10.43

Table 6. EC50 values from the PD-1/LAG-3 reporter assay.

LAG-3	PD-L1	EC50 ± SD (nM)
SEQ ID NO: 17	SEQ ID NO: 24	0.34 ± 0.29
SEQ ID NO: 5	SEQ ID: NO 20	0.27 ± 0.19

Table 7. EC50 values from the SEB assay.

Example 4 – *In vivo* study

Anti-tumor efficacy of bispecific antibodies in comparison with relatlimab and atezolizumab analogs were evaluated in a human stem cell humanized NSG mouse model bearing orthotopic MDA-MB-231 tumors.

Female hu-CD34 NSG™ mice (JAX stock # 705557) that have been engrafted with human CD34+ cells and have >25% human CD45+ cells in the peripheral blood 14 weeks post engraftment but not later than 24 weeks were used. Cohorts of hu-CD34 NSG™ mice engrafted with $CD34^+$ cells from three independent donors were used.

120 HSC-NSG mice (72 + overage) were engrafted with $5x10^6$ MDA-MB-231 human breast adenocarcinoma cells, re-suspended in PBS with matrigel in a 1:1 ratio, implanted into the mammary fat pad. HSC-NSG mice are immuno-deficient NOD.Cg-Prkdc^{scid} 1l2rg^{tm1Wjl}/SzJ (NSG^{TM}) mice engrafted with human $CD34^+$ hematopoietic stem cells (HSC) from cord blood, which undergo multilineage differentiation into all major immune cell types.

72 mice were enrolled 15 days post tumor-inoculation, when tumor volume (TV) was between 50-150mm^3. Tumor volume for enrollment was measured the previous day (Day -1). Dosing was initiated on the day of enrollment, designated Day 0 of treatment. Each treatment arm (Table 1) had mice from 3 HSC donors, 4 mice per donor (N=12). Tumor size and body weight were measured twice weekly.

Group	N	Treatment	Dose level (mg/kg)	Dose Route	Dosing Frequency
1	12 (4X3 donors)	Vehicle- PBS	-	*i.p*	q5dX9
2	12 (4X3 donors)	relatlimab*	5	*i.p*	q5dX9
3	12 (4X3 donors)	atezolizumab*	5	*i.p*	q5dX9
4	12 (4X3 donors)	relatlimab*	5	*i.p*	q5dX9
		atezolizumab*	5	*i.p*	q5dX9
5	12 (4X3 donors)	SEQ ID NO: 5 x SEQ ID NO: 20	10	*i.p*	q5dX9
6	12 (4X3 donors)	SEQ ID NO: 17 x SEQ ID NO: 24	10	*i.p*	q5dX9

Table 8. Study Design. * Analog antibody

Terminal tumors were isolated at 24 hours post final dose for flow cytometry analysis of $CD4^+$ and $CD8^+$ T cell and regulatory T cell (Treg) populations in MDA-MB-231 tumor samples harvested on the day of termination.

Results are shown in Figure 6. Single and combination treatment of reference anti-LAG-3 antibody relatlimab analog and anti-PD-L1 antibody atezolizumab analog were not effective. Decreased tumor size in mice treated with bispecific antibody comprising a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 17, a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 24, and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 30, is significant when data from all donors are combined (Figure 6A).

Tumor growth profile is presented in Table 9.

	Vehicle	**relatlimab* 5mg/kg**	**atezolizumab* 5mg/kg**	**relatlimab* 5mg/kg + atezolizumab* 5mg/kg**	**SEQ ID NO: 5 x SEQ ID NO: 20 10mg/kg**	**SEQ ID NO: 17 x SEQ ID NO: 24 10mg/kg**
PROGRESSIVE	11	10	8	10	9	7
STABLE	1	2	2	2	3	3
REGRESSING	0	0	1	0	0	1
Complete regression (TV=0)	0	0	1	0	0	1
Total	12	12	12	12	12	12
% progressive	**92**	**83**	**67**	**83**	**75**	**58**

Table 9. Tumor growth profile. * Analog antibody

Figure 6B4 shows that PD-L1 and LAG-3xPD-L1 treatment increases the percentage of proliferating $CD8^+$. LAG-3, PD-L1, and LAG-3xPD-L1 treatment increases the percentage of proliferating $CD4^+$ T cells (Figure 6B5). Figure 6B3 shows that treatment with the bispecific antibodies results in a lower percentage of Tregs than treatment with a combination of relatlimab and atezolizumab analogs.

Example 5: Screening of further LAG-3xPD-L1 bispecific antibodies

The bispecific antibodies described in Table 10 were screened essentially as described in Example 2.

Bispecific antibody	**LAG-3 binding domain**					**PD-L1 binding domain**			
	VH	**CH1**	**CH2**	**CH3**		**VH**	**CH1**	**CH2**	**CH3**

SEQ ID NO: 5 x SEQ ID NO :20	SEQ ID NO: 5	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50		SEQ ID NO :20	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51
SEQ ID NO: 52 x SEQ ID NO :20	SEQ ID NO: 52	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50		SEQ ID NO :20	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51
SEQ ID NO: 17 x SEQ ID NO :24	SEQ ID NO: 17	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 53 x SEQ ID NO :24	SEQ ID NO: 53	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 54 x SEQ ID NO :24	SEQ ID NO: 54	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 55 x SEQ ID NO :24	SEQ ID NO: 55	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 56 x SEQ ID NO :24	SEQ ID NO: 56	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 57 x SEQ ID NO :24	SEQ ID NO: 57	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 58 x SEQ ID NO :24	SEQ ID NO: 58	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50
SEQ ID NO: 59 x SEQ ID NO :24	SEQ ID NO: 59	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 51		SEQ ID NO :24	SEQ ID NO: 42	SEQ ID NO: 45	SEQ ID NO: 50

Table 10. Overview of further LAG-3xPD-L1 bispecific antibodies.

Antigen Binding

Binding of the bispecific antibodies to LAG-3 and PD-L1 was analyzed by FACS using a 293FF cell line stably transfected with human and rhesus LAG-3 and a CHO-K1 cell line stably transfected with human and rhesus PD-L1, as in Example 2.

The bispecific antibodies were analyzed in an 8-step, 4-fold titration starting at 100 µg/mL on 293FF-huLAG-3 and 293FF-reLAG-3 cells and 25 µg/mL on CHO-K1-huPD-L1 cells. A goat-anti-human PE antibody (Invitrogen, H10104) was used as secondary antibody at a concentration of 3 µg/mL. RSV control antibody was included on all plates as a negative control, in an 8-step, 4-fold dilution, starting at 100 µg/mL on 293FF-huLAG-3 and 293FF-reLAG-3 cells, and starting at 25 µg/mL on CHO-K1-huPD-L1 cells. Two wells were used for secondary antibody only and unstained cells, as additional controls. As a negative control, cells not expressing the target, 293FF and CHO-K1 cells, were included where the IgG's were tested at the three highest concentrations: 100, 25 and 6.3 µg/mL on 293FF cells and 25, 6.3 and 1.6 µg/mL on CHO-K1 cells.

Results for human and rhesus LAG-3 binding are shown in Figure 7A and 7B. Results for PD-L1 binding are shown in Figure 7C. Fold induction was obtained by normalizing mean MFI values with respect to that of wells without antibody and plotted as a function of the log of antibody concentration. EC50 values were calculated using GraphPad Prism software version 7.02 (nonlinear regression, 3-parameter dose-response curve). Each of the bispecific antibodies is plotted together with the negative control antibody.

All bispecific antibodies showed binding to human and rhesus LAG-3. All bispecific antibodies showed binding to CHO cells expressing huPD-L1. The EC50 values are provided in Table 11.

		293FF - Human LAG-3	293FF - Rhesus LAG-3	CHO-K1 Human PD-L1
LAG-3	**PD-L1**	**EC50 (µg/mL)**	**EC50 (µg/mL)**	**EC50 (µg/mL)**
SEQ ID NO: 5	SEQ ID NO :20	1.06	2.88	0.0135
SEQ ID NO: 52	SEQ ID NO :20	1.25	3.22	0.009
SEQ ID NO: 17	SEQ ID NO :24	0.27	0.98	0.0097
SEQ ID NO: 53	SEQ ID NO :24	0.35	1.09	0.0091
SEQ ID NO: 54	SEQ ID NO :24	0.63	1.13	0.0093
SEQ ID NO: 55	SEQ ID NO :24	0.23	0.72	0.0117
SEQ ID NO: 56	SEQ ID NO :24	0.24	0.57	0.0103
SEQ ID NO: 57	SEQ ID NO :24	0.4	0.86	0.0098
SEQ ID NO: 58	SEQ ID NO :24	0.24	0.67	0.0086
SEQ ID NO: 59	SEQ ID NO :24	0.52	0.54	0.0064

Table 11. EC50 and AUC values of the binding of the bispecific antibodies to human and rhesus LAG-3 and human PD-L1.

PD-1/LAG-3 reporter assay

A PD-1/LAG-3 reporter assay was performed essentially as described in Example 2. The Staphylococcal enterotoxin D (ppSED) was validated to be used at a final concentration of 150 ng/mL.

The bispecific IgG's were tested in a 6-step semi-log titration starting at 100 µg/mL (final concentration). IgG dilutions were prepared at 3x final concentration in assay medium. As a positive control, a 6-step semi-log titration of a combination of atezolizumab analog and

relatlimab analog, with a highest concentration of 50 µg/mL + 50 µg/mL, was included on each plate. As a negative control on each plate a 4-step semi-log titration of the RSV control antibody was used starting at 100 µg/mL. Two wells were left without IgG as a control for the basal level of activity.

Results are shown in Figure 8. All LAG-3xPD-L1 bispecific antibodies show activity as compared to a combination of relatlimab and atezolizumab analogs. EC50 and area under the curve (AUC) of the antibody response was determined using GraphPad Prism software version 7.02. The AUCs were expressed relative to the AUC of the combination of relatlimab and atezolizumab analogs.

LAG-3	PD-L1	EC50 µg/mL)	AUC (% of control)
SEQ ID NO: 52	SEQ ID NO: 20	1.154	96.93
SEQ ID NO: 5	SEQ ID NO: 20	1.132	86.25
SEQ ID NO: 59	SEQ ID NO: 24	0.5736	77.11
SEQ ID NO: 58	SEQ ID NO: 24	0.6303	85.47
SEQ ID NO: 57	SEQ ID NO: 24	0.481	75.11
SEQ ID NO: 56	SEQ ID NO: 24	0.9666	79.11
SEQ ID NO: 55	SEQ ID NO: 24	0.6529	86.97
SEQ ID NO: 54	SEQ ID NO: 24	0.5695	73.64
SEQ ID NO: 53	SEQ ID NO: 24	0.6613	77.11
SEQ ID NO: 17	SEQ ID NO: 24	0.815	76.53

Table 12. EC50 and AUC values of the bispecific antibodies as determined in a PD-1/LAG-3 reporter assay.

SEQUENCES

SEQ ID NO: 1

QVQLQESGPGLVRPSETLSLTCTVSGGSIS**SYSWS**WIRQPPGKGLEWIG**YIDYSGSTNYN PSLKS**RVTISVDTSKTQFSLKLSSVSAADTAVYYCAK**DLLYKWNYVEGFDI**WGQGTTV TVSS

SEQ ID NO: 2

QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYSWS**WIRQPPGKGLEWIG**YIDYSGTTNFN PSLKS**RVTISVDTSKTQFSLKLSSVSAADTAVYYCAK**DLLYKWNYVEGFDI**WGQGTM VTVSS

SEQ ID NO: 3

EVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN KYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAMYYCAR**ERGWDVFDI**WGQGTL VTVSS

SEQ ID NO: 4

QVQLVQSGAEVKKPGSSVKVSCKASGGTFS**KYVVS**WVRQAPGQGFDWMG**GIIPMFGT ANYAQMFQG**RVTITADKSTSTVNMELSSLRSEDTAVYYCVR**DKAVAGLYYFDS**WGQ GTLVTVSS

SEQ ID NO: 5

QVQLQESGPGLVKPSETLSLTCTVSDDSIS**DYYWS**WIRQPPGKGLEWIG**YIYYSGNTKY NPSLKN**RVTISVDTSKSQFSLKLTSVTAADTAVYYCAR**IPLTGEFDY**WAQGTLVTVSS

SEQ ID NO: 6

EVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYGMH**WVRQAPGKGLEWVA**VISYHGSD KYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DGDNWDVFDI**WGQGT LVTVSS

SEQ ID NO: 7

QVQLVQSGAEVKKPGSSVKVSCKASGDTFS**TYAIN**WIRQAPGQGLEWMG**GIIPIFGTA YYAQEFQD**RVTITADKSTSTGYMEMSSLISEDTAVYYCAR**ERELGALYAFDI**WGQGT MVTVSS

SEQ ID NO: 8

EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**SHAIS**WVRQVPGQGLEWMG**GIIPLFDTA KNAQKFQG**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**DRETGTLYYFDY**WGQGT LVTVSS

SEQ ID NO: 9

EVQLVQSGSELKKPGASVKVSCKASGYTFT**TNALN**WVRQAPGQGLEWMG**WINTHTG NPTYAQGFIG**RFVFSLDTSVSTAYLQIRSLKAEDTAVYYCAR**EPNWGVYFDY**WGQGT LVTVSS

SEQ ID NO: 10

QVQLVQSGAEVKRPGASVKVSCKVSGYTLT**ELSMH**WVRQAPGKGLEWMG**GSDPEHG ETVDAQKFQG**RVTMTEDTSTDTAYMELSSLRSEDTAVYYCTT**GGTYYYGSGSYYTLD F**WGQGTLVTVSS

SEQ ID NO: 11

QVQLVQSGAEVKKPGSSVKVSCKASGGTFS**NFAFS**WVRQAPGQGLEWMG**GIIPMFDT AKYAQKFQG**RVTIIADKSTNTAYMDLNSLRSEDTAVYYCVR**DRAIGTLYYFDY**WGQG TLVTVSS

SEQ ID NO: 12

QVQLVQSGAEVRKPGSSVMVSCKASGGTFN**TYAIN**WVRQAPGQGLEWMG**GIIPIFGTP YYGQRFQG**RVTITADKSTNTVFMELSSLRSEDTAMYFCAR**ERDIGSLYYFDS**WGQGTL VTVSS

SEQ ID NO: 13

QVQLVQSGAEVRKPGSSVMVSCKASGGTFS**TYAIN**WLRQAPGQGLEWMG**GIIPIFGTP YYGQRFQG**RVTITADKSTNTVFMELSSLRSEDTAIYYCAR**DRDSGGLYYFDS**WGQGTL VTVSS

SEQ ID NO: 14

QVQLVQSGAEVKKPGSSVKVSCKTSGGTFS**NYAFS**WVRQAPGQGLEWMG**GIIPIFGST NYAQSFQG**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**DREMGTLYFFDQ**WGQGT TVTVSS

SEQ ID NO: 15

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYGIS**WVRQAPGQGLEWMG**WISAYSGN TNYAQKLQG**RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**DGSGWDDFDY**WGQG TLVTVSS

SEQ ID NO: 16

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**SYGIS**WVRQAPGQGLEWMG**WISAYSGN**
TNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR**GSILAAQMWGDI**WGQ
GTLVTVSS

SEQ ID NO: 17

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**ERGWDVFDI**WGQGTT
VTVSS

SEQ ID NO: 18

EVQLVESGGGLVQPGGSLRLSCAASGFTFS**SYAMS**WVRQAPGKGLEWVS**SISGGGVST**
FYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAI**VPAAATPSGTYYWIFDL**
WGRGTLVTVSS

SEQ ID NO: 19

EVQLVESGGGLVQPGGSLRLSCAASGFTFS**SYAMN**WVRQAPGKGLEWVS**TISGSGVST**
YYADSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCAK**DRGYDYSGSYHNWFDP**
WGQGTLVTVSS

SEQ ID NO: 20

QVQLVQSGAEVKKPGSSVKVSCKASGGTFS**TYAIS**WVRQAPGQGLEWMG**WIIPIFGTG**
NYAQKFQGRVTITADKSTSTAYMELRSLRSEDTAVHYCAR**HDYTNTVDAFDI**WGQGT
MVTVSS

SEQ ID NO: 21

QVQLVQSGAEVKKPGSSVKVSCKASGDTFR**SYGIT**WVRQAPGQGLEWMG**GIIPIFGTT**
NYAQKFQGRVTITADKSTSTVYMELSSLRSEDTAVYYCAR**RRGYSNPHWLDP**WGQG
TLVTVSS

SEQ ID NO: 22

QVQLVQSGAEVKKPGSSVKVSCKASGGTFS**TYGIL**WVRQAPGQGLEWMG**GIIPIFGTA**
NYAQKFQGRVTITADISTSTAYMELSSLRSEDTAVYYCAR**GGGNYYEFVY**WGQGTLV
TVSS

SEQ ID NO: 23

EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**TYAIS**WVRQAPGQGLEWMG**WIIPIFDTG**
NYAQKIQGRVTITADKSTSTAYMELTSLRSEDTAVYYCAR**HDYTNTVDAFDI**WGQGT
MVTVSS

SEQ ID NO: 24

EVQLVQSGAEVKKPGSSVKVSCKASGGTFS**TYAIS**WVRQAPGQGLEWMG**WIIPIFDTG**
NYAQKFQGRVTITADKSTSTAYMELTSLRSEDTAVYYCAR**HDYTNTVDAFDI**WGQGT
MVTVSS

SEQ ID NO: 25

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGST
YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVT
VSA

SEQ ID NO: 26

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIK

SEQ ID NO: 27

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKGLEWIGEINHRGSTN
SNPSLKSRVTLSLDTSKNQFSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTLV
TVSS

SEQ ID NO: 28

EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYDASNRATGIPAR
FSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGQGTNLEIK

SEQ ID NO: 29

EVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVISYDGST
KYSADSLKGRFTISRDNSKNTLYLQMNSLRADDTAVYYCAKEGWSFDSSGYRSWFDS
WGQGTLVTVSS

SEQ ID NO: 30 LCDRs indicated according to IMGT

DIQMTQSPSSLSASVGDRVTITCRAS**QSISSY**LNWYQQKPGKAPKLLIY**AAS**SLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPPT**FGQGTKVEIK

SEQ ID NO: 31 Light chain CDR1 IMGT
QSISSY

SEQ ID NO: 32 Light chain CDR2 IMGT
AAS

SEQ ID NO: 33 Light chain CDR3 IMGT

QQSYSTPPT

SEQ ID NO: 34 LCDRs indicated according to IMGT

DIQMTQSPSSLSASVGDRVTITCRAS**QSISSY**LNWYQQKPGKAPKLLIY**AAS**SLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPPIT**FGQGTRLEIK

SEQ ID NO: 35 LCDRs indicated according to IMGT

EIVMTQSPATLSVSPGERATLSCRAS**QSVSSN**LAWYQQKPGQAPRLLIY**GAS**TRATGIPA
RFSGSGSGTEFTLTISSLQSEDFAVYYC**QQYNNWPWT**FGQGTKVEIK

SEQ ID NO: 36 LCDRs indicated according to IMGT

EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPD
RFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSSPWT**FGQGTKVEIK

SEQ ID NO: 37 LCDRs indicated according to IMGT

SYVLTQPPSVSVAPGETARITCGGD**NIGRKS**VYWYQQKSGQAPVLVIY**YDS**DRPSGIPE
RFSGSNSGNTATLTISRVEAGDEADYYC**QVWDGSSDHWV**FGGGTKLTVL

SEQ ID NO: 38

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTP

SEQ ID NO: 39

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPA
RFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWP

SEQ ID NO: 40

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPD
RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSP

SEQ ID NO: 41

SYVLTQPPSVSVAPGETARITCGGDNIGRKSVYWYQQKSGQAPVLVIYYDSDRPSGIPER
FSGSNSGNTATLTISRVEAGDEADYYCQVWDGSSDH

SEQ ID NO: 42

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV

SEQ ID NO: 43

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 44

EPKSCDKTHTCPPCP

SEQ ID NO: 45

APELGRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK

SEQ ID NO: 46

SEQ ID NO: 47
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 48

SEQ ID NO: 49

SEQ ID NO: 50
GQPREPQVYTDPPSREEMTKNQVSLTCEVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 51
GQPREPQVYTKPPSREEMTKNQVSLKCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 52
QVQLQESGPGLVKPSETLSLTCTVSDDSIS**DYYWS**WIRQPPGKGLEWIG**YIYYSGNTKY**
NPSLKNRVTISVDTSKSQFSLKLTSVTAADTAVYYCAR**IPLTGDFDF**WAQGTLVTVSS

SEQ ID NO: 53
QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAK**ERGWDVFDL**WGQGTT
VTVSS

SEQ ID NO: 54
QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAK**ERGWDVFDV**WGQGTT
VTVSS

SEQ ID NO: 55

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**EKGWDVFDL**WGQGTT
VTVSS

SEQ ID NO: 56

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**EKGWDVFDV**WGQGTT
VTVSS

SEQ ID NO: 57

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**ERGWDIFDV**WGQGTT
VTVSS

SEQ ID NO: 58

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**ERGWDLFDL**WGQGTT
VTVSS

SEQ ID NO: 59

QVQLVQSGGGVVQPGRSLRLSCAASGFTFS**SYDTH**WVRQAPGKGLEWVA**VISYDGSN**
KYYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAMYYCAR**ERGWDLFDV**WGQGTT
VTVSS

SEQ ID NO: 60

SYSWS

SEQ ID NO: 61

YIDYSGSTNYNPSLKS

SEQ ID NO: 62
DLLYKWNYVEGFDI

SEQ ID NO: 63
YIDYSGTTNFNPSLKS

SEQ ID NO: 64
SYDTH

SEQ ID NO: 65
VISYDGSNKYYADSVKG

SEQ ID NO: 66
ERGWDVFDI

SEQ ID NO: 67
KYVVS

SEQ ID NO: 68
GIIPMFGTANYAQMFQG

SEQ ID NO: 69
DKAVAGLYYFDS

SEQ ID NO: 70
DYYWS

SEQ ID NO: 71
YIYYSGNTKYNPSLKN

SEQ ID NO: 72

IPLTGEFDY

SEQ ID NO: 73
SYGMH

SEQ ID NO: 74
VISYHGSDKYYADSVKG

SEQ ID NO: 75
DGDNWDVFDI

SEQ ID NO: 76
TYAIN

SEQ ID NO: 77
GIIPIFGTAYYAQEFQD

SEQ ID NO: 78
ERELGALYAFDI

SEQ ID NO: 79
SHAIS

SEQ ID NO: 80
GIIPLFDTAKNAQKFQG

SEQ ID NO: 81
DRETGTLYYFDY

SEQ ID NO: 82
TNALN

SEQ ID NO: 83
WINTHTGNPTYAQGFIG

SEQ ID NO: 84
EPNWGVYFDY

SEQ ID NO: 85
ELSMH

SEQ ID NO: 86
GSDPEHGETVDAQKFQG

SEQ ID NO: 87
GGTYYYGSGSYYTLDF

SEQ ID NO: 88
NFAFS

SEQ ID NO: 89
GIIPMFDTAKYAQKFQG

SEQ ID NO: 90
DRAIGTLYYFDY

SEQ ID NO: 91
GIIPIFGTPYYGQRFQG

SEQ ID NO: 92
ERDIGSLYYFDS

SEQ ID NO: 93
DRDSGGLYYFDS

SEQ ID NO: 94
NYAFS

SEQ ID NO: 95
GIIPIFGSTNYAQSFQG

SEQ ID NO: 96
DREMGTLYFFDQ

SEQ ID NO: 97
SYGIS

SEQ ID NO: 98
WISAYSGNTNYAQKLQG

SEQ ID NO: 99
DGSGWDDFDY

SEQ ID NO: 100
GSILAAQMWGDI

SEQ ID NO: 101
SYAMS

SEQ ID NO: 102
SISGGGVSTFYADSVKG

SEQ ID NO: 103

VPAAATPSGTYYWIFDL

SEQ ID NO: 104
SYAMN

SEQ ID NO: 105
TISGSGVSTYYADSVKG

SEQ ID NO: 106
DRGYDYSGSYHNWFDP

SEQ ID NO: 107
TYAIS

SEQ ID NO: 108
WIIPIFGTGNYAQKFQG

SEQ ID NO: 109
HDYTNTVDAFDI

SEQ ID NO: 110
SYGIT

SEQ ID NO: 111
GIIPIFGTTNYAQKFQG

SEQ ID NO: 112
RRGYSNPHWLDP

SEQ ID NO: 113
TYGIL

SEQ ID NO: 114
GIIPIFGTANYAQKFQG

SEQ ID NO: 115
GGGNYYEFVY

SEQ ID NO: 116
WIIPIFDTGNYAQKIQG

SEQ ID NO: 117
WIIPIFDTGNYAQKFQG

SEQ ID NO: 118
IPLTGDFDF

SEQ ID NO: 119
ERGWDVFDL

SEQ ID NO: 120
ERGWDVFDV

SEQ ID NO: 121
EKGWDVFDL

SEQ ID NO: 122
EKGWDVFDV

SEQ ID NO: 123
ERGWDIFDV

SEQ ID NO: 124

ERGWDLFDL

SEQ ID NO: 125

ERGWDLFDV

CLAIMS

1. A multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26.

2. The multispecific antibody or variant thereof according to claim 1, wherein the antibody or variant comprises a single binding domain that binds to LAG-3 and/or a single binding domain that binds to PD-L1.

3. The multispecific antibody or variant thereof according to claim 1 or 2, wherein the potency is determined by measuring tumor volume reduction in an *in vivo* mouse study.

4. The multispecific antibody or variant thereof according to claim 3, wherein a comparable potency is a tumor volume reduction within a 5 fold range of the tumor volume reduction of the combination of reference antibodies, and includes a 5 to 2 fold, preferably a 3 to 2 fold, deviation from the tumor volume reduction of the combination of reference antibodies.

5. The multispecific antibody or variant thereof according to claim 1 or 2, wherein the potency is determined by the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1.

6. The multispecific antibody or variant thereof according to claim 5, wherein the potency in blocking ligand binding to LAG-3 and/or PD-L1 is measured in a PD-1/LAG-3 reporter assay.

7. The multispecific antibody or variant thereof according to claim 5 or 6, wherein a comparable potency is a potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, within a 5 fold range of the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1 of the combination of reference antibodies, and includes a 5 to 2 fold, preferably a 3 to 2 fold, deviation from the LAG-3 and/or PD-L1 blocking activity of the combination of reference antibodies.

8. The multispecific antibody or variant thereof according to any one of claims 1-7, wherein the binding domain that binds to LAG-3 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: 1;

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: 2;

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: 3;

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: 4;

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: 5;

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: 6;

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: 7;

h) 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: 8;

i) 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: 9;

j) 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: 10;

k) 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;

l) 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;

m) 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;

n) 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;

o) 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;

p) 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;

q) 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,

r) 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: 52,

s) 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: 53,

t) 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: 54,

u) 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: 55,

v) 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: 56,

w) 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: 57,

x) 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: 58, or

y) 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: 59,

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

9. The multispecific antibody or variant thereof according to any one of claims 1- 8, wherein the LAG-3 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 1-17 or SEQ ID NO: 52-59, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

10. The multispecific antibody or variant thereof according to any one of claims 1-9, wherein the LAG-3 binding domain further comprises a light chain variable region.

11. The multispecific antibody or variant thereof according to any one of claims 1-10, wherein the LAG-3 binding domain further comprises a CH1 and CL region.

12. The multispecific antibody or variant thereof according to any one of claims 1-11, wherein the binding domain that binds to PD-L1 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: 20;

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: 21;

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: 22;

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: 23; or

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: 24,

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

13. The multispecific antibody or variant thereof according to any one of claims 1- 12, wherein the PD-L1 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 20-24 or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

14. The multispecific antibody or variant thereof according to any one of claims 1-13, wherein the PD-L1 binding domain further comprises a light chain variable region.

15. The multispecific antibody or variant thereof according to any one of claims 1-10, wherein the PD-L1 binding domain further comprises a CH1 and CL region.

16. A multispecific antibody, or variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant thereof comprises a binding domain that specifically binds to an extracellular domain of LAG-3 and a binding domain that specifically binds to an extracellular domain of a protein of the B7 family,

wherein the 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: 1;

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: 2;

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: 3;

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: 4;

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: 5;

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: 6;

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: 7;

h) 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: 8;

i) 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: 9;

j) 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: 10;

k) 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;

l) 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;

m) 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;

n) 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;

o) 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;

p) 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;

q) 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,

r) 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: 52,

s) 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: 53,

t) 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: 54,

u) 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: 55,

v) 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: 56,

w) 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: 57,

x) 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: 58, or

y) 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: 59,

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

17. The multispecific antibody or variant thereof according to claim 16, wherein the LAG-3 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 1-17 or SEQ ID NO: 52-59, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

18. The multispecific antibody or variant thereof according to claim 16 or 17, wherein the LAG-3 binding domain further comprises a light chain variable region.

19. The multispecific antibody or variant thereof according to any one of claims 16-18, wherein the LAG-3 binding domain further comprises a CH1 and CL region.

20. The multispecific antibody or variant thereof according to any one of claims 16-19, wherein the antibody or variant is monovalent for binding to LAG-3.

21. The multispecific antibody or variant thereof according to any one of claims 16-20, wherein the protein of the B7 family is selected from the group consisting of PD-L1, PD-L2, CD80, CD86, B7-H4, TNFRSF14, and B7-H7.

22. The multispecific antibody or variant thereof according to any one of claims 16-21, wherein the protein of the B7 family is PD-L1.

23. The multispecific antibody or variant thereof according to any one of claims 16-22, wherein the variable domain that specifically binds to an extracellular domain of a protein of the B7 family blocks the binding of PD-L1 to its receptor.

24. The antibody or variant thereof according to claim 23, wherein the receptor is PD-1 and/or CD80.

25. The multispecific antibody or variant thereof according to any one of claims 16-24, wherein the binding domain that binds to PD-L1 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: 20;

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: 21;

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: 22;

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: 23; or

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: 24,

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

26. The multispecific antibody or variant thereof according to any one of claims 16-25, wherein the PD-L1 binding domain comprises a heavy chain variable region having an amino acid sequence as set forth in any one of SEQ ID NO: 20-24, or having at least 80%, preferably 85%, more preferably 90%, or most preferably 95% sequence identity thereto.

27. The multispecific antibody or variant thereof according to any one of claims 16-26, wherein the PD-L1 binding domain further comprises a light chain variable region.

28. The multispecific antibody or variant thereof according to any one of claims 16-27, wherein the PD-L1 binding domain further comprises a CH1 and CL region.

29. The multispecific antibody or variant thereof according to any one of claims 16-28, wherein the antibody or variant is monovalent for binding to PD-L1.

30. The multispecific antibody or variant thereof according to any one of claims 16-29, wherein the antibody or variant has comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26.

31. The multispecific antibody or variant thereof according to claim 30, wherein the potency is determined by measuring tumor volume reduction in an *in vivo* mouse study.

32. The multispecific antibody or variant thereof according to claim 30 or 31, wherein a comparable potency includes a 5 to 2 fold, preferably a 3 to 2 fold, deviation from the tumor volume reduction of the combination of reference antibodies.

33. The multispecific antibody or variant thereof according to claim 30, wherein the potency is determined by the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1.

34. The multispecific antibody or variant thereof according to claim 33, wherein the potency in blocking ligand binding to LAG-3 and/or PD-L1 is measured in a PD-1/LAG-3 reporter assay.

35. The multispecific antibody or variant thereof according to claim 33 or 34, wherein a comparable potency is a potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1, within a 5 fold range of the potency in blocking ligand or receptor binding to LAG-3 and/or PD-L1 of the combination of reference antibodies, and includes a 5 to 2 fold, preferably 3 to 2 fold, deviation from the LAG-3 and PD-L1 blocking activity of the combination of reference antibodies.

36. The multispecific antibody or variant thereof according to any one of claims 1-35, wherein the antibody or variant is a full length antibody, in particular a full length bispecific antibody.

37. A pharmaceutical composition comprising the multispecific antibody or variant thereof according to any one of claims 1-36 and a pharmaceutical acceptable carrier, diluent or excipient.

38. The multispecific antibody or variant thereof according to any one of claims 1-36, or pharmaceutical composition according to claim 37, for use as a medicament.

39. The multispecific antibody or variant thereof according to any one of claims 1-36, or the pharmaceutical composition as claimed in claim 37, for use in the treatment of a disease associated with a suppressed immune system.

40. The multispecific antibody or variant thereof according to any one of claims 1-36, or the pharmaceutical composition as claimed in claim 37, for use in the treatment of cancer.

41. A method for treating a disease, comprising administering an effective amount of the multispecific antibody or variant thereof as claimed in any one of claims 1-36, or the pharmaceutical composition as claimed in claim 37, to an individual in need thereof.

42. A method for treating a disease associated with a suppressed immune system, in particular cancer, comprising administering an effective amount of the multispecific antibody or variant thereof as claimed in any one of claims 1-36, or the pharmaceutical composition as claimed in claim 37, to an individual in need thereof.

43. A method for treating cancer, comprising administering an effective amount of the multispecific antibody or variant thereof as claimed in any one of claims 1-36, or the pharmaceutical composition as claimed in claim 37, to an individual in need thereof.

44. A vector comprising a nucleic acid sequence encoding the heavy chain variable region of a LAG-3 binding domain as defined in any one of claims 16-20 and a nucleic acid sequence encoding the heavy chain variable region of a PD-L1 binding domain as defined in any one of claims 25-28.

45. The vector according to claim 44, wherein the vector further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.

46. The vector according to claim 44 or 45, further comprising at least one nucleic acid sequence encoding a light chain variable region, and preferably a CL region.

47. The vector according to claim 46, 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.

48. A cell comprising a nucleic acid sequence encoding the heavy chain variable region of a LAG-3 binding domain as defined in any one of claims 16-20 and a nucleic acid sequence encoding the heavy chain variable region of a PD-L1 binding domain as defined in any one of claims 25-28.

49. The cell according to claim 48, wherein the cell further comprises a nucleic acid sequence encoding a CH1 region and preferably a hinge, CH2 and CH3 region.

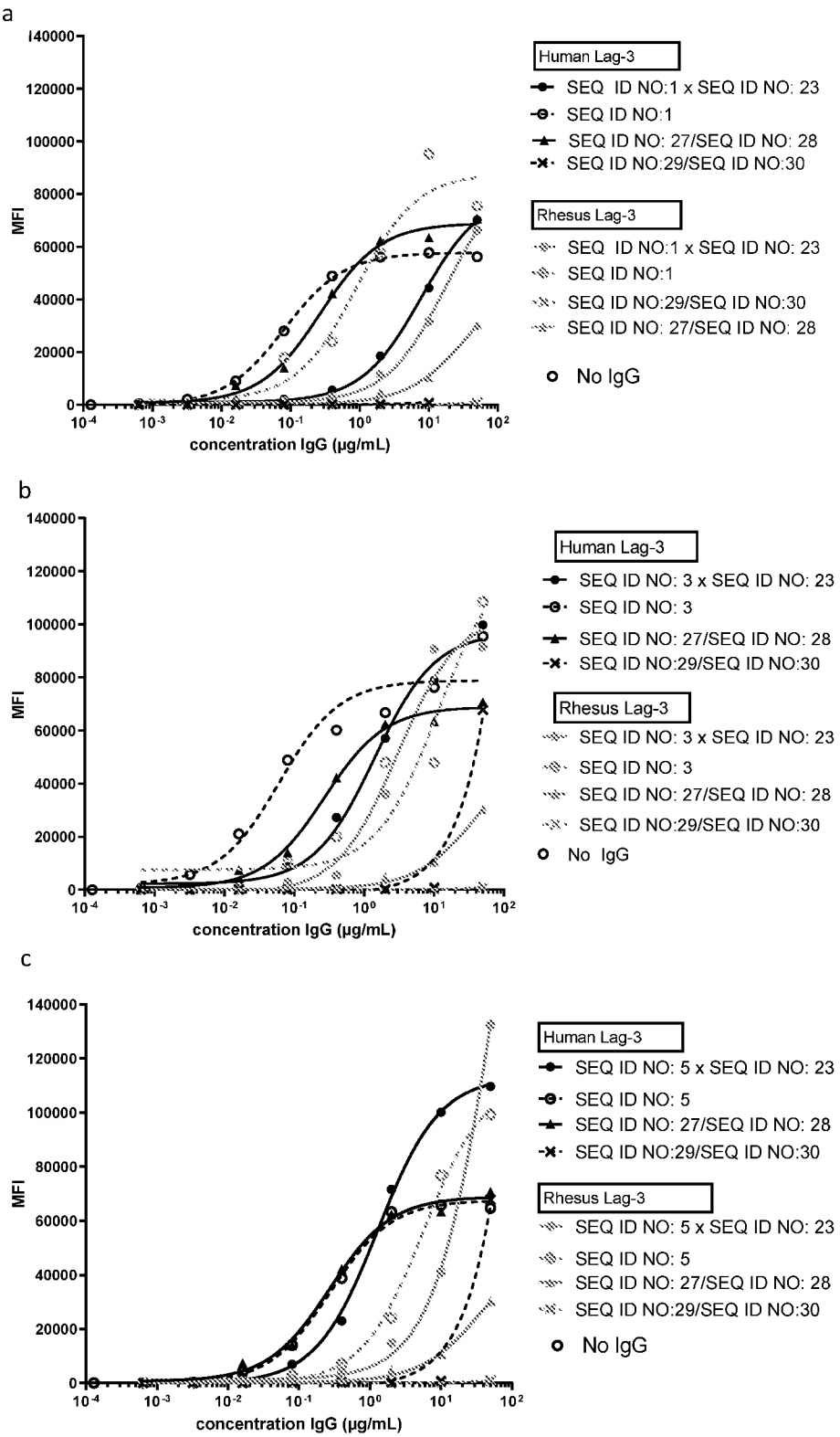
50. The cell according to claim 48 or 49, further comprising at least one nucleic acid sequence encoding a light chain variable region, and preferably a CL region.

51. The cell according to claim 50, 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.

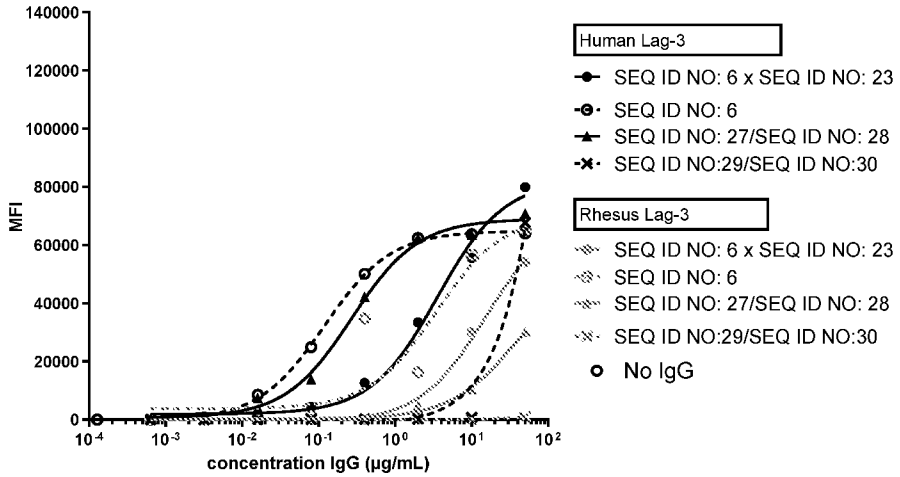
52. A cell producing a multispecific antibody or variant thereof according to any one of claims 1-36.

53. The cell according to claim 52, wherein the cell is a recombinant cell, which has been transformed with a vector as claimed in any one of claims 44-47.

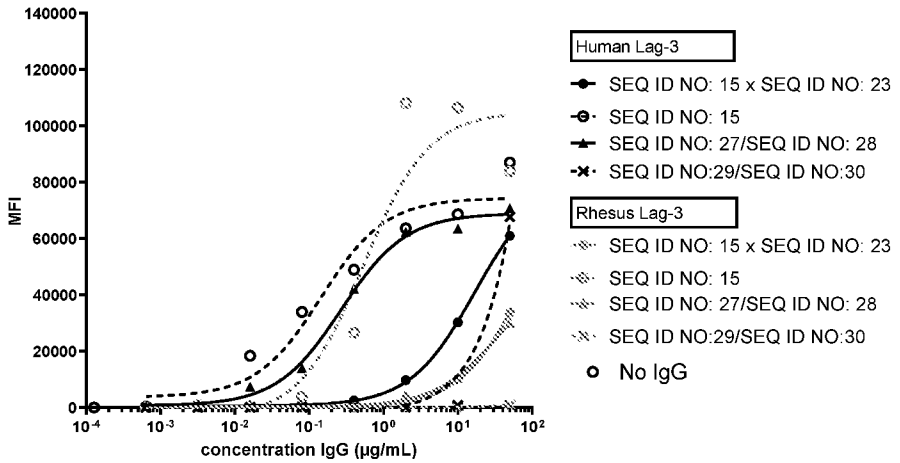
Figure 1A


a
MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO:1 x SEQ ID NO: 23
SEQ ID NO:1
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO:1 x SEQ ID NO: 23
SEQ ID NO:1
SEQ ID NO:29/SEQ ID NO:30
SEQ ID NO: 27/SEQ ID NO: 28
No IgG
b
MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO: 3 x SEQ ID NO: 23
SEQ ID NO: 3
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO: 3 x SEQ ID NO: 23
SEQ ID NO: 3
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
No IgG
c
MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO: 5 x SEQ ID NO: 23
SEQ ID NO: 5
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO: 5 x SEQ ID NO: 23
SEQ ID NO: 5
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
No IgG

d


MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO: 6 x SEQ ID NO: 23
SEQ ID NO: 6
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO: 6 x SEQ ID NO: 23
SEQ ID NO: 6
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
No IgG

e


MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO: 15 x SEQ ID NO: 23
SEQ ID NO: 15
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO: 15 x SEQ ID NO: 23
SEQ ID NO: 15
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
No IgG

f

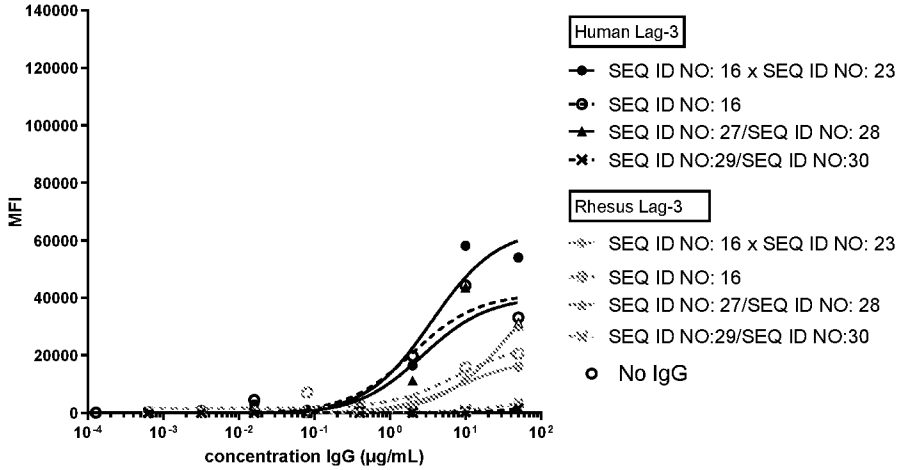

MFI
concentration IgG (µg/mL)
Human Lag-3
SEQ ID NO: 16 x SEQ ID NO: 23
SEQ ID NO: 16
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
Rhesus Lag-3
SEQ ID NO: 16 x SEQ ID NO: 23
SEQ ID NO: 16
SEQ ID NO: 27/SEQ ID NO: 28
SEQ ID NO:29/SEQ ID NO:30
No IgG

Figure 1B

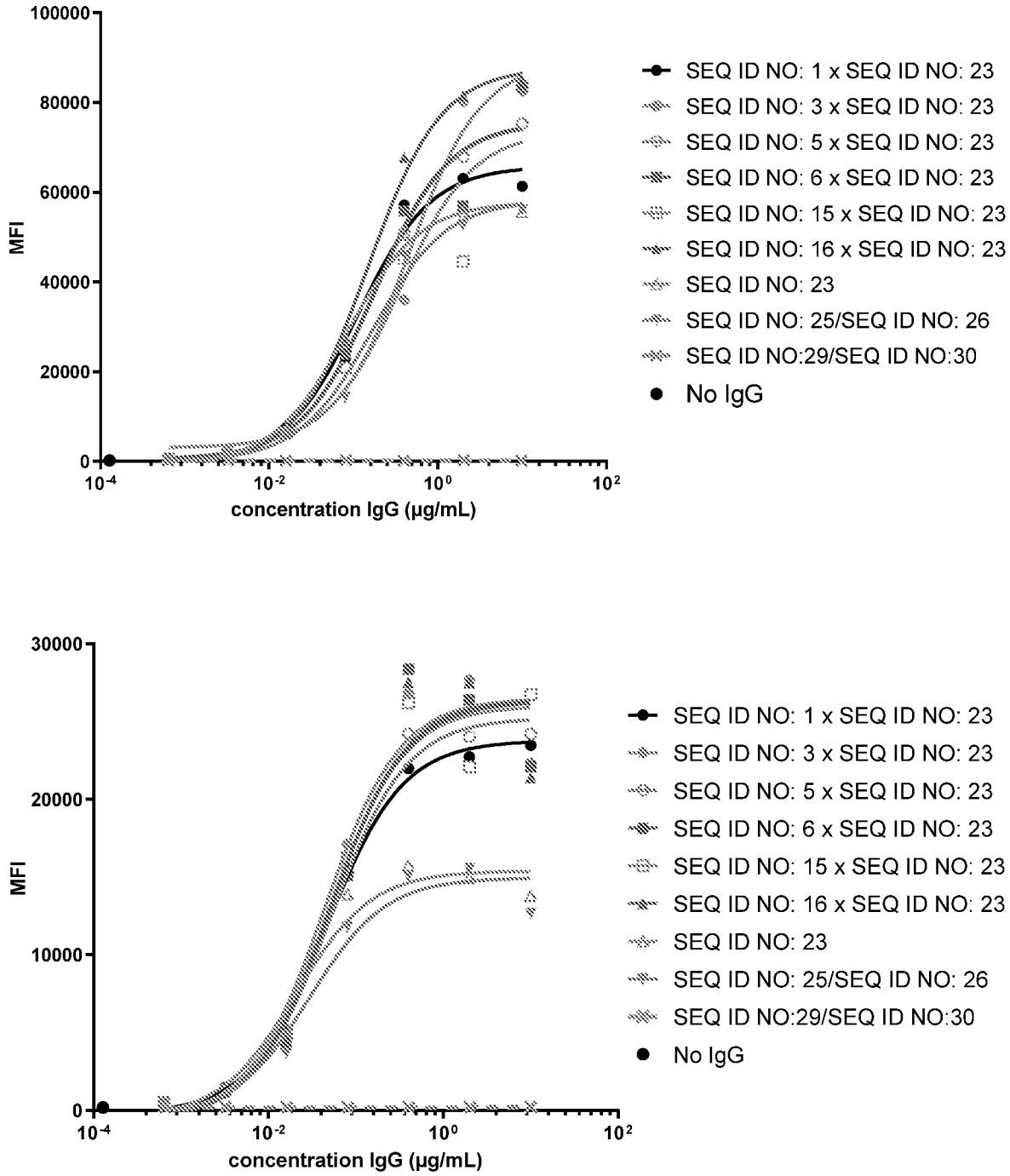
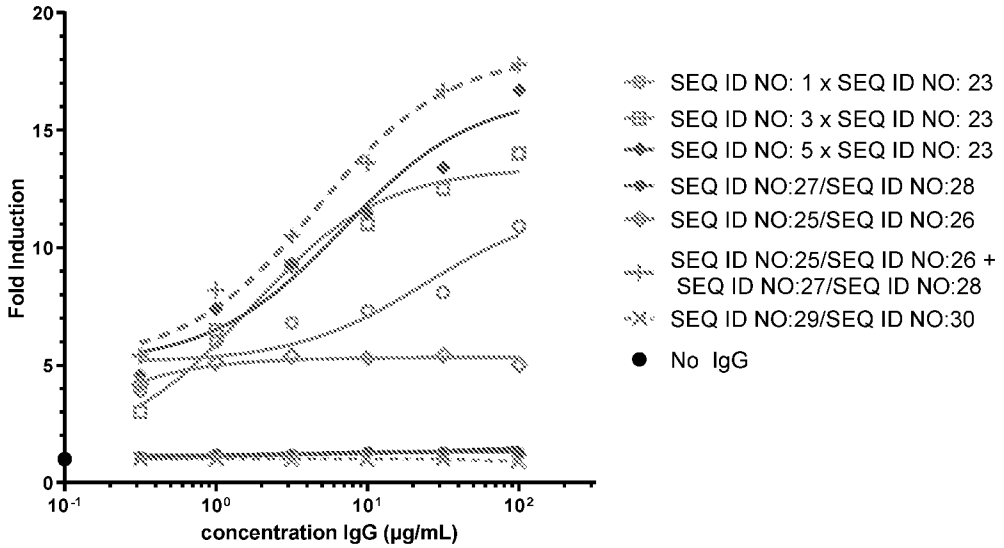

100000
80000
60000
40000
20000
0
MFI
10-4
10-2
100
102
concentration IgG (µg/mL)
SEQ ID NO: 1 x SEQ ID NO: 23
SEQ ID NO: 3 x SEQ ID NO: 23
SEQ ID NO: 5 x SEQ ID NO: 23
SEQ ID NO: 6 x SEQ ID NO: 23
SEQ ID NO: 15 x SEQ ID NO: 23
SEQ ID NO: 16 x SEQ ID NO: 23
SEQ ID NO: 23
SEQ ID NO: 25/SEQ ID NO: 26
SEQ ID NO:29/SEQ ID NO:30
No IgG
30000
20000
10000
0
MFI
10-4
10-2
100
102
concentration IgG (µg/mL)
SEQ ID NO: 1 x SEQ ID NO: 23
SEQ ID NO: 3 x SEQ ID NO: 23
SEQ ID NO: 5 x SEQ ID NO: 23
SEQ ID NO: 6 x SEQ ID NO: 23
SEQ ID NO: 15 x SEQ ID NO: 23
SEQ ID NO: 16 x SEQ ID NO: 23
SEQ ID NO: 23
SEQ ID NO: 25/SEQ ID NO: 26
SEQ ID NO:29/SEQ ID NO:30
No IgG

Figure 2


20
15
10
5
0
Fold Induction
10-1
100
101
102
concentration IgG (µg/mL)
SEQ ID NO: 1 x SEQ ID NO: 23
SEQ ID NO: 3 x SEQ ID NO: 23
SEQ ID NO: 5 x SEQ ID NO: 23
SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:25/SEQ ID NO:26
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
No IgG

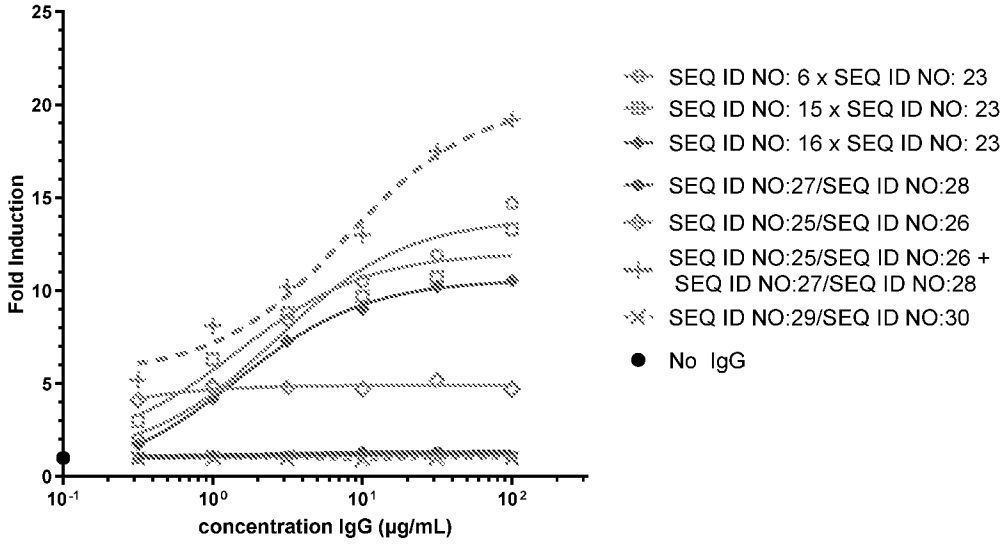

25
20
15
10
5
0
Fold Induction
10-1
100
101
102
concentration IgG (µg/mL)
SEQ ID NO: 6 x SEQ ID NO: 23
SEQ ID NO: 15 x SEQ ID NO: 23
SEQ ID NO: 16 x SEQ ID NO: 23
SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:25/SEQ ID NO:26
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
No IgG

Figure 3A1

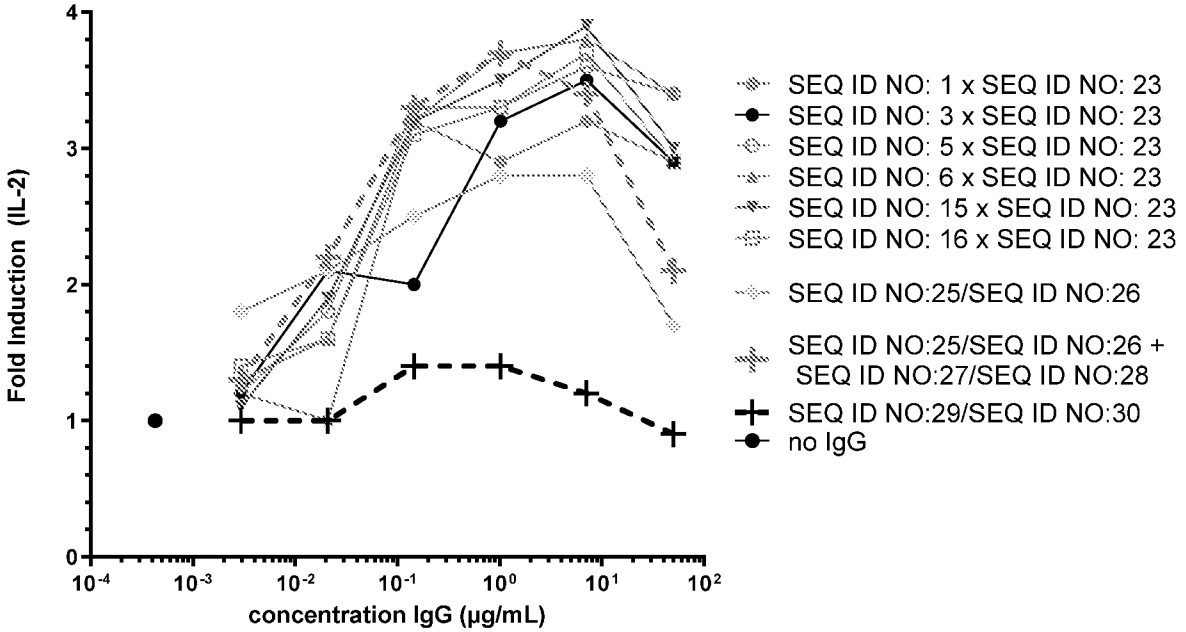


Figure 3A2

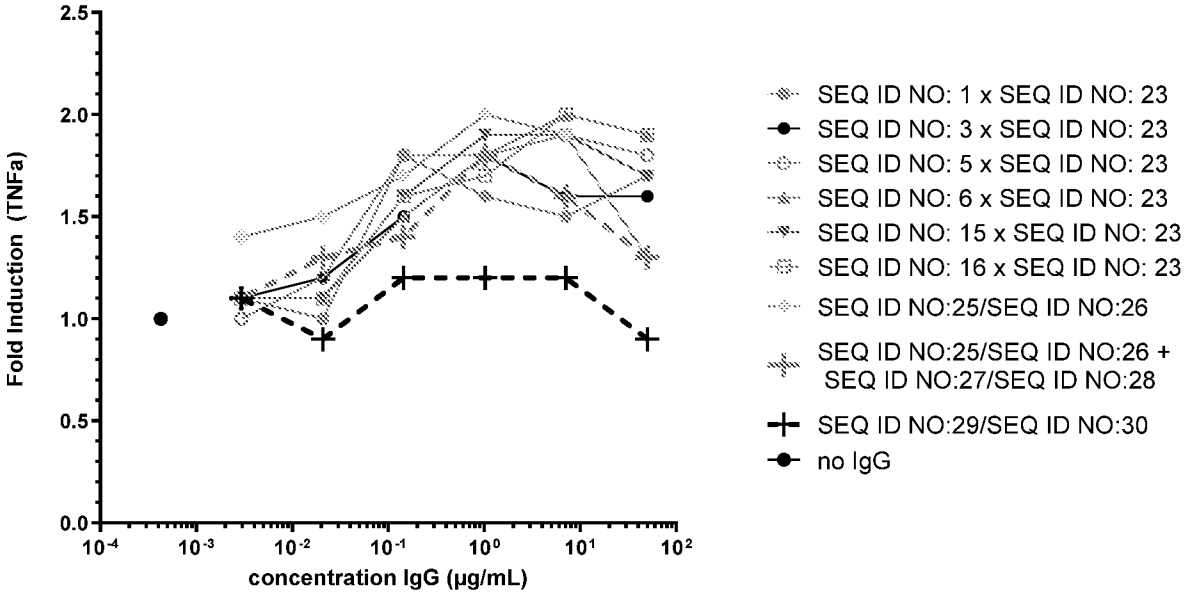


Figure 3B1

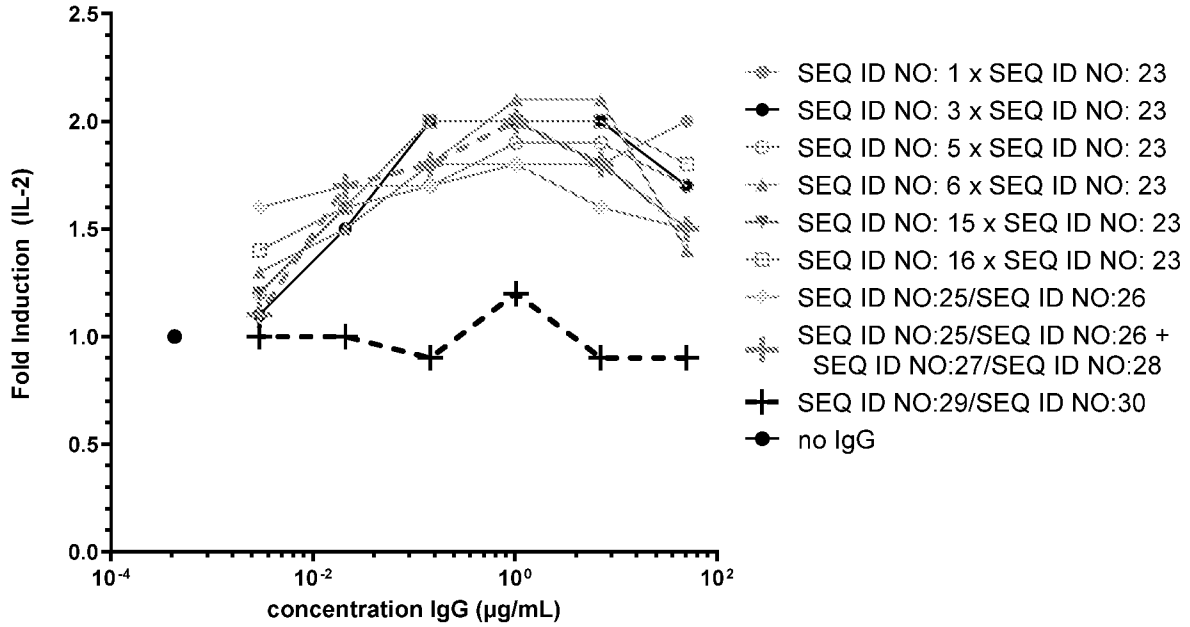


Figure 3B2

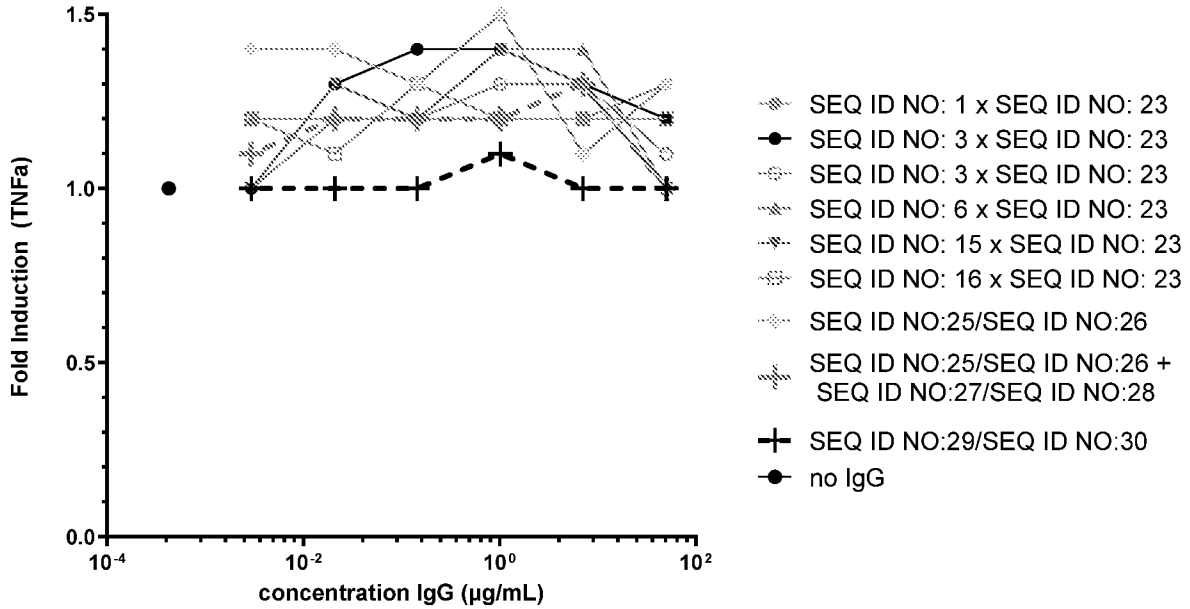


Figure 4

Antigen / Antibody	huLAG-3			cyLAG-3			huPD-L1			cyPD-L1		
	Kon (1/Ms)	Koff (1/s)	KD (nM)	Kon (1/Ms)	Koff (1/s)	KD (nM)	Kon (1/Ms)	Koff (1/s)	KD (nM)	Kon (1/Ms)	Koff (1/s)	KD (nM)
SEQ ID NO:17 x SEQ ID NO:24	2.38E+06	4.58E-03	1.93	3.42E+06	1.40E-03	0.41	1.28E+06	5.21E-04	0.41	1.39E+06	4.75E-04	0.34
SEQ ID NO:5 x SEQ ID NO:20	5.28E+05	7.66E-04	1.45	1.24E+06	1.42E-03	1.15	1.49E+06	2.52E-04	0.17	1.65E+06	2.44E-04	0.15
SEQ ID NO:27/ SEQ ID NO:28	2.28E+06	5.63E-04	0.25	6.08E+06	6.97E-02	11.50	-	-	-	-	-	-
SEQ ID NO:25/ SEQ ID NO:26	-	-	-	-	-	-	7.27E+05	1.34E-04	0.18	7.49E+05	4.43E-03	5.92

Figure 5A

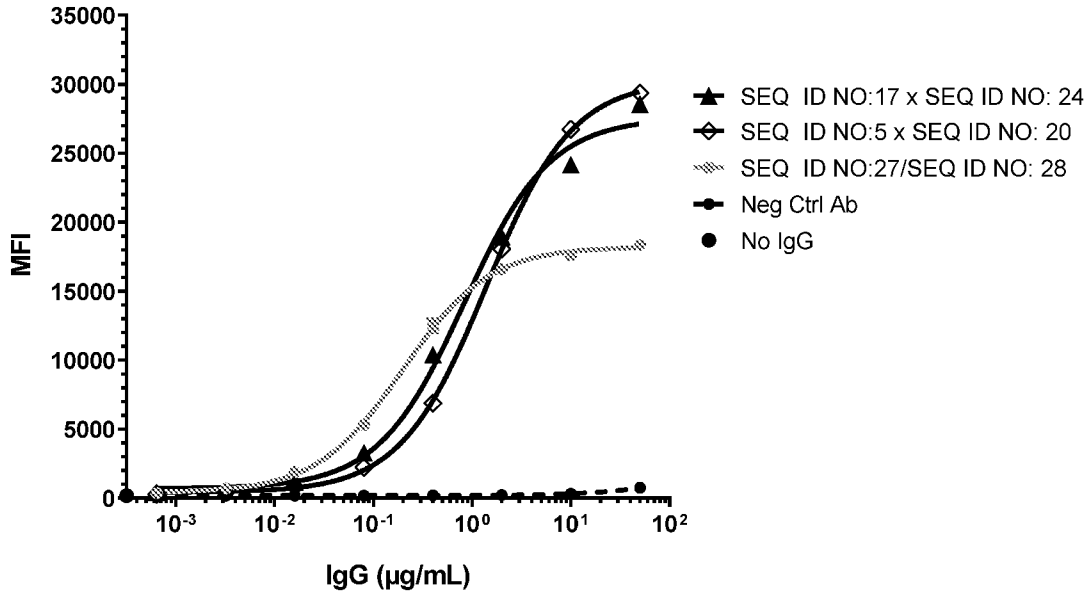


Figure 5B

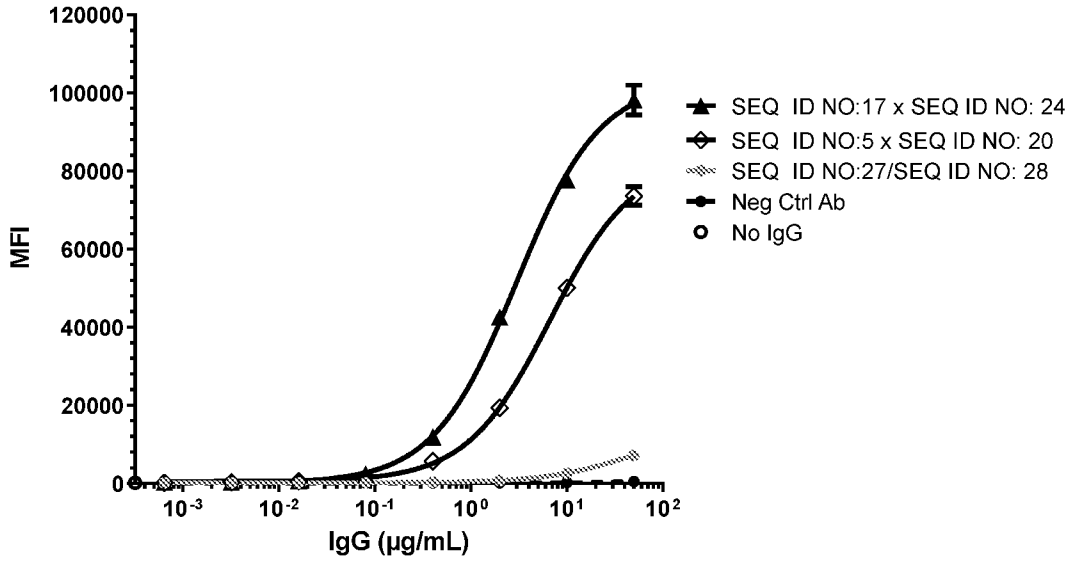


Figure 5C

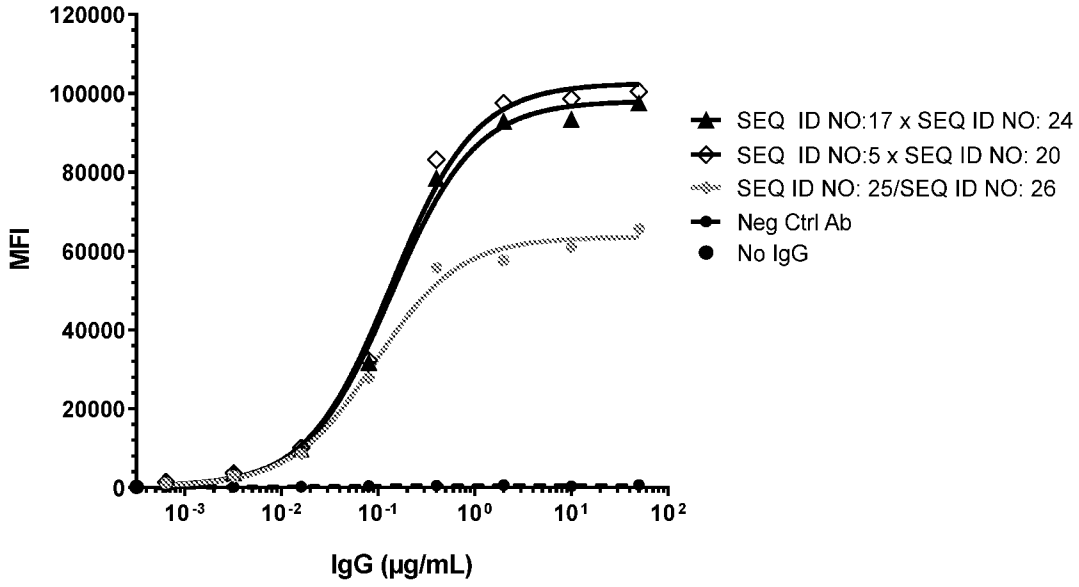


Figure 5D

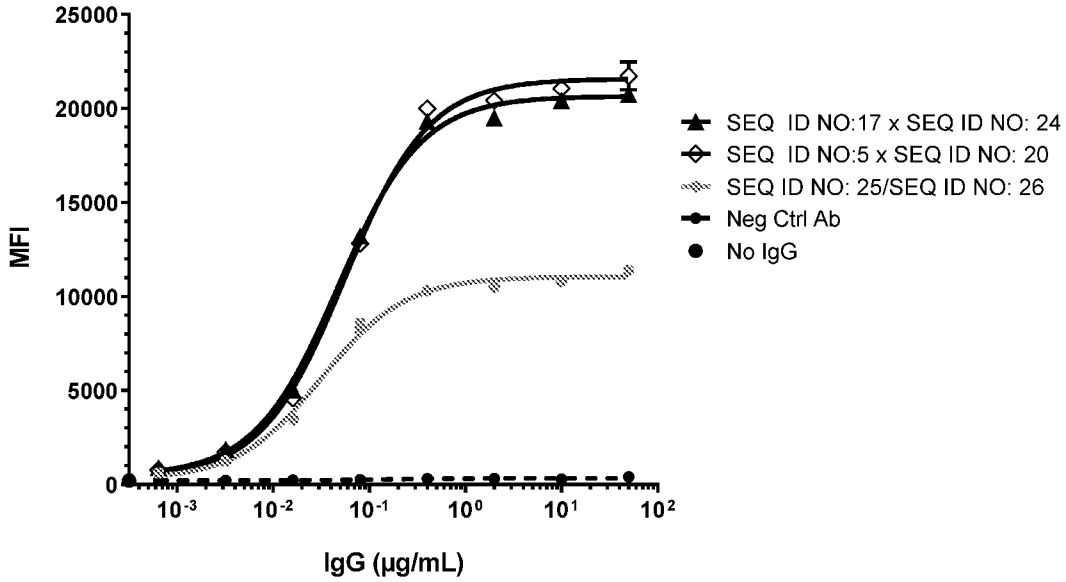


Figure 5E

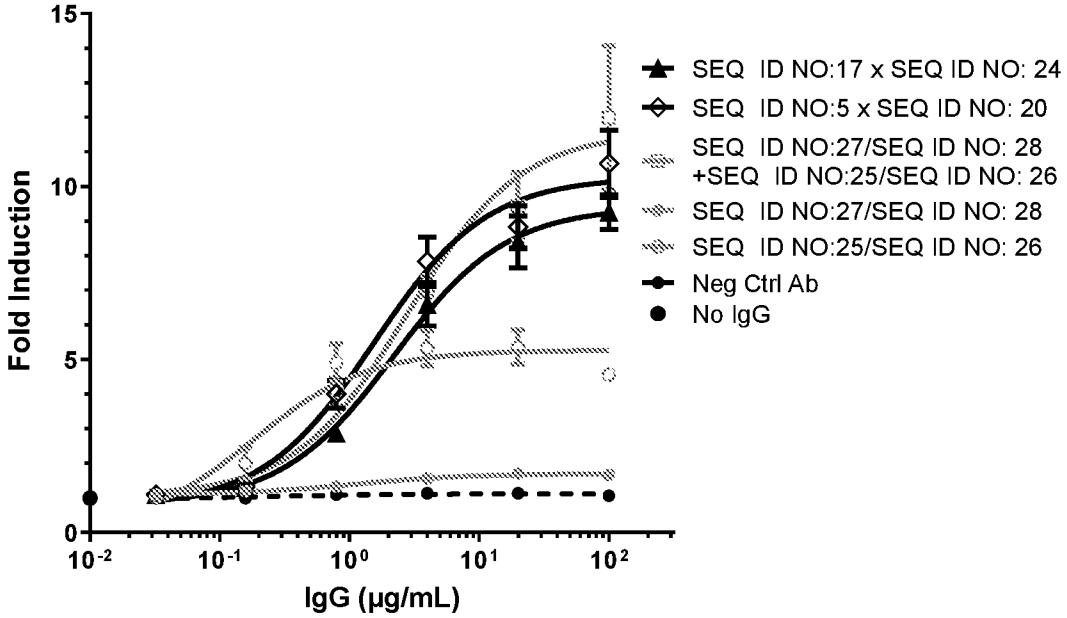
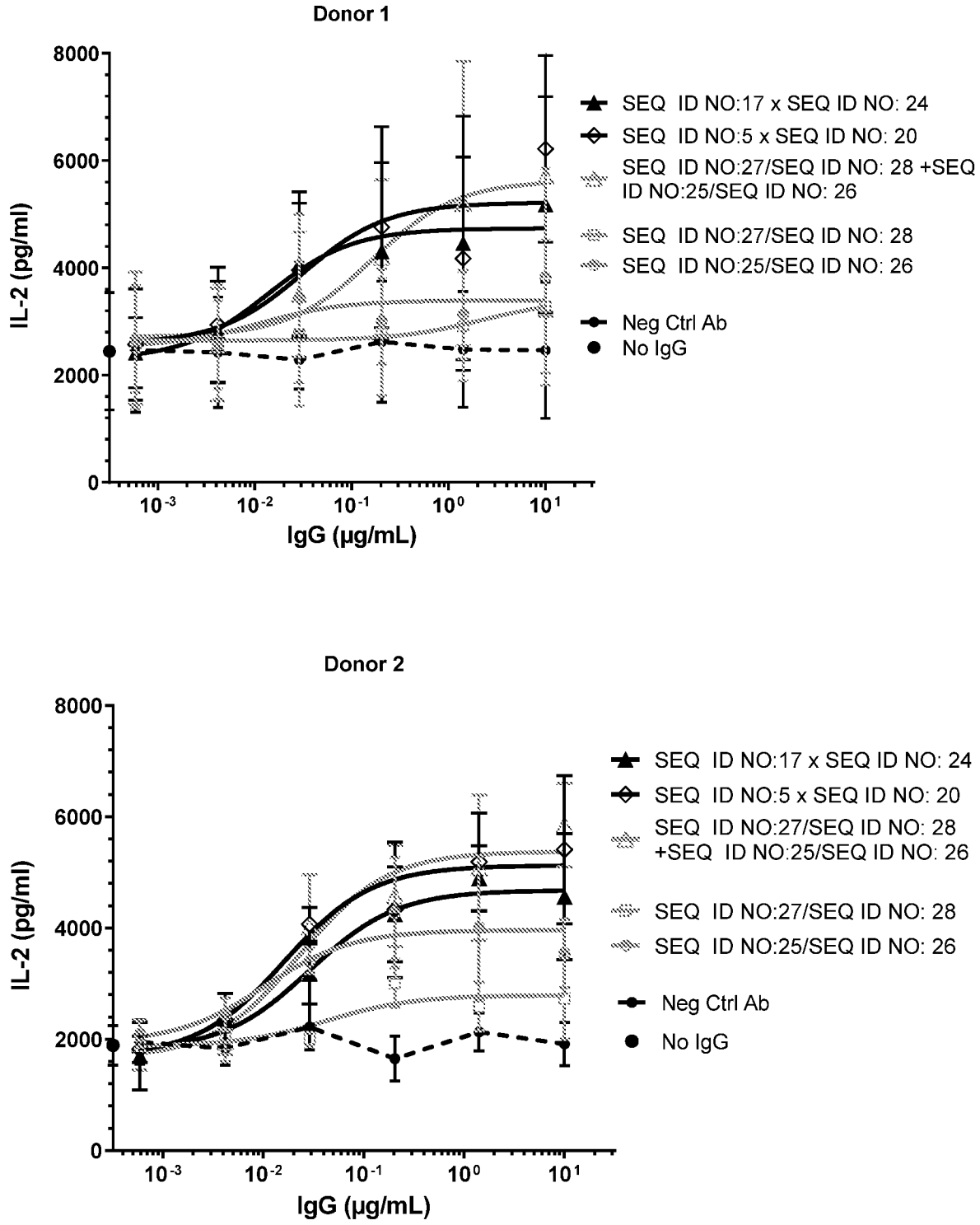
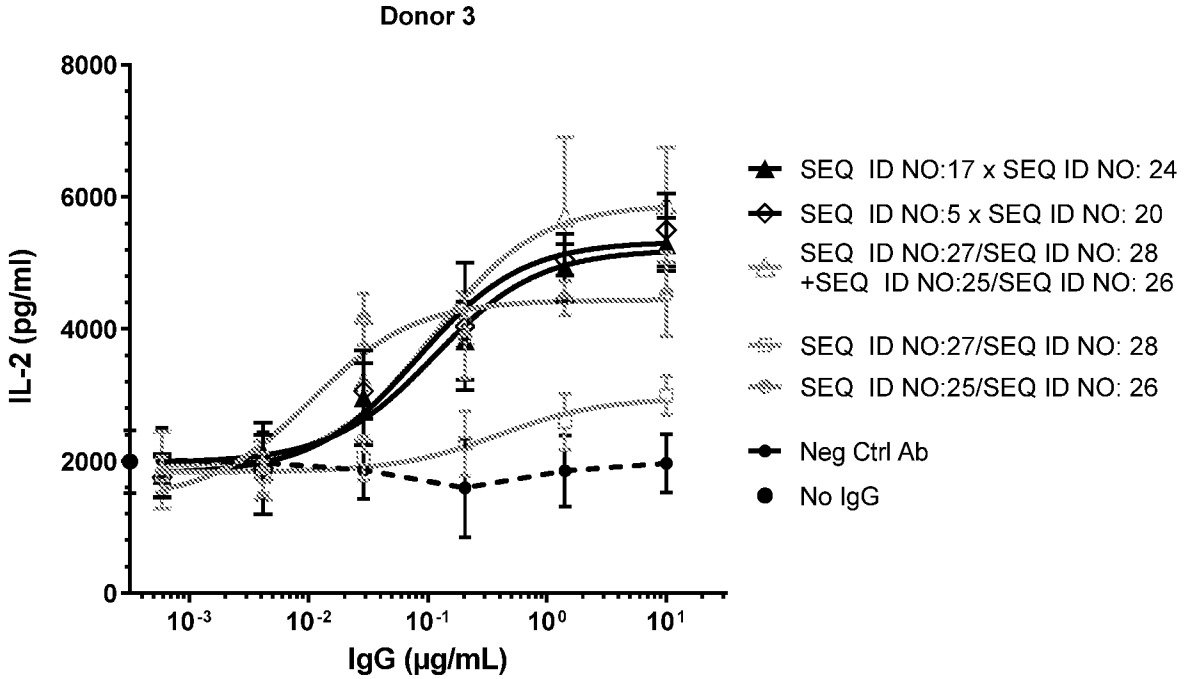

15
10
5
0
Fold Induction
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO: 24
SEQ ID NO:5 x SEQ ID NO: 20
SEQ ID NO:27/SEQ ID NO: 28 +SEQ ID NO:25/SEQ ID NO: 26
SEQ ID NO:27/SEQ ID NO: 28
SEQ ID NO:25/SEQ ID NO: 26
Neg Ctrl Ab
No IgG

Figure 5F


Donor 1
IL-2 (pg/ml)
8000
6000
4000
2000
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO: 24
SEQ ID NO:5 x SEQ ID NO: 20
SEQ ID NO:27/SEQ ID NO: 28 +SEQ ID NO:25/SEQ ID NO: 26
SEQ ID NO:27/SEQ ID NO: 28
SEQ ID NO:25/SEQ ID NO: 26
Neg Ctrl Ab
No IgG
Donor 2
IL-2 (pg/ml)
8000
6000
4000
2000
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO: 24
SEQ ID NO:5 x SEQ ID NO: 20
SEQ ID NO:27/SEQ ID NO: 28 +SEQ ID NO:25/SEQ ID NO: 26
SEQ ID NO:27/SEQ ID NO: 28
SEQ ID NO:25/SEQ ID NO: 26
Neg Ctrl Ab
No IgG


Donor 3
8000
6000
4000
2000
0
IL-2 (pg/ml)
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO: 24
SEQ ID NO:5 x SEQ ID NO: 20
SEQ ID NO:27/SEQ ID NO: 28 +SEQ ID NO:25/SEQ ID NO: 26
SEQ ID NO:27/SEQ ID NO: 28
SEQ ID NO:25/SEQ ID NO: 26
Neg Ctrl Ab
No IgG

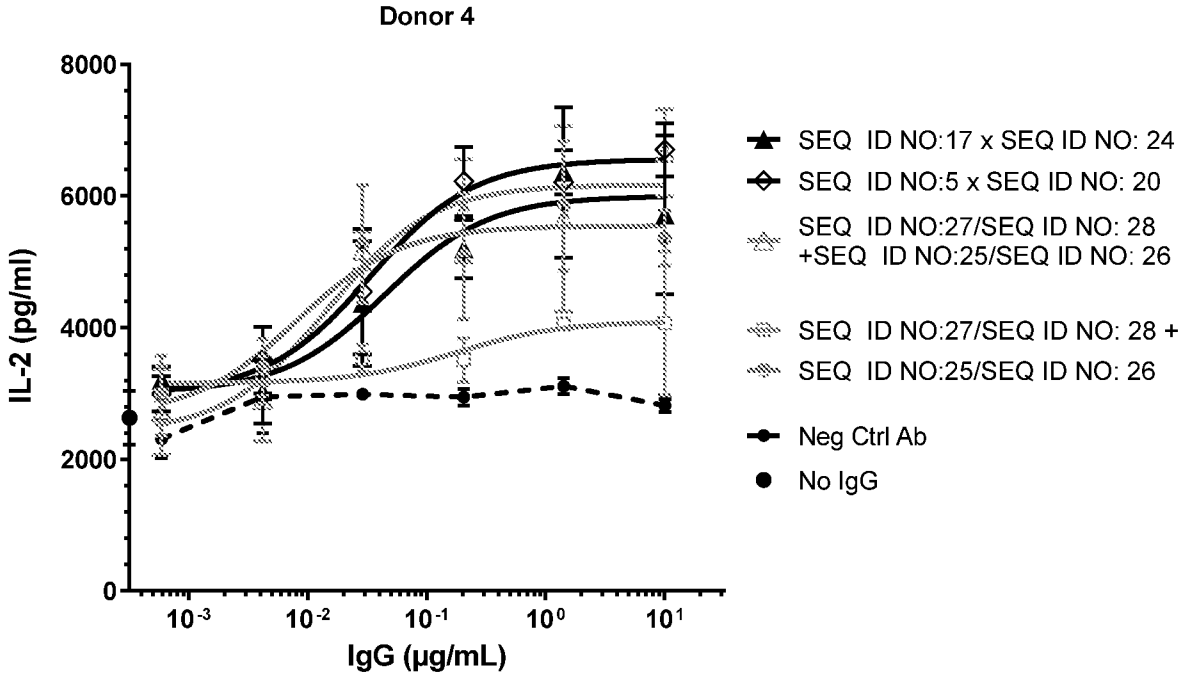

Donor 4
8000
6000
4000
2000
0
IL-2 (pg/ml)
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO: 24
SEQ ID NO:5 x SEQ ID NO: 20
SEQ ID NO:27/SEQ ID NO: 28 +SEQ ID NO:25/SEQ ID NO: 26
SEQ ID NO:27/SEQ ID NO: 28 +
SEQ ID NO:25/SEQ ID NO: 26
Neg Ctrl Ab
No IgG

Figure 6A1

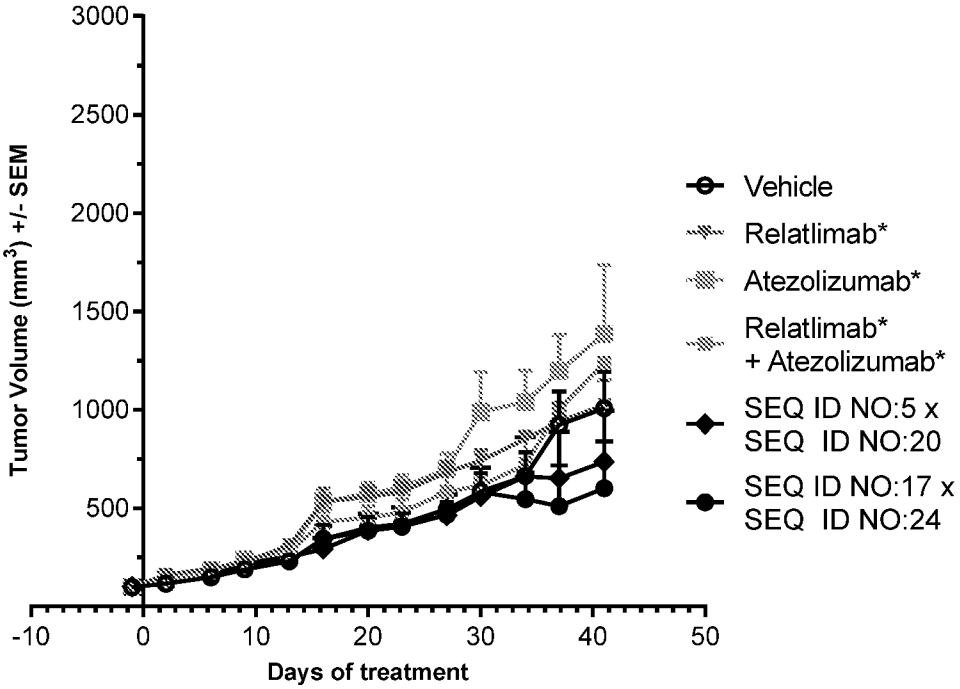


Figure 6A2

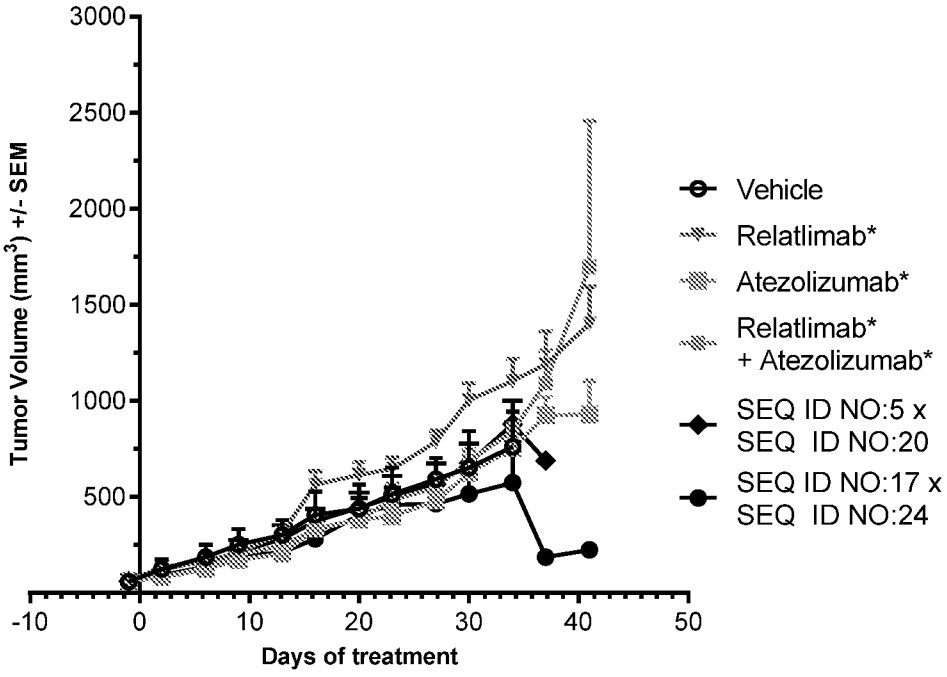


Figure 6A3

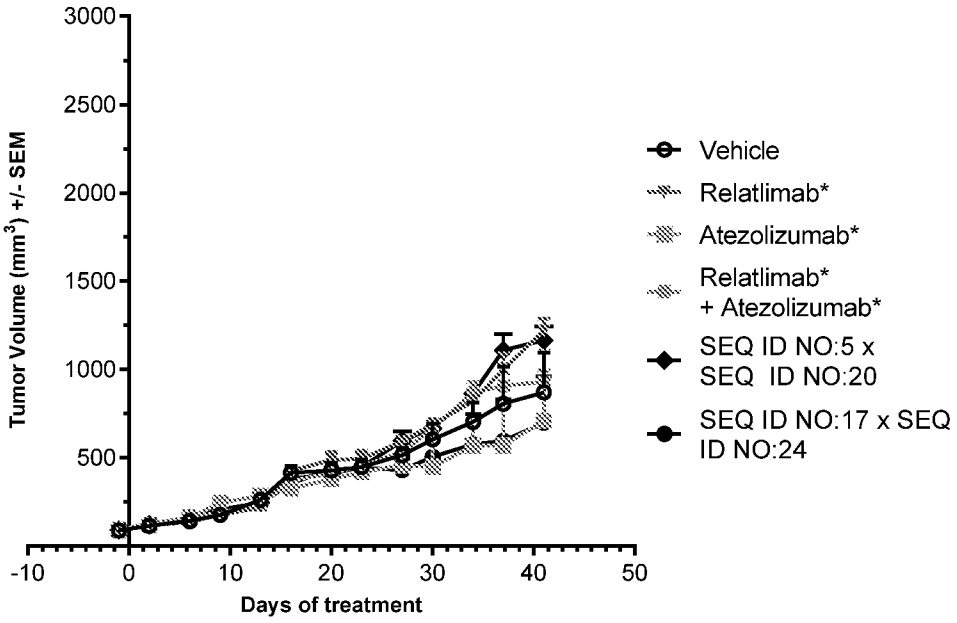


Figure 6A4

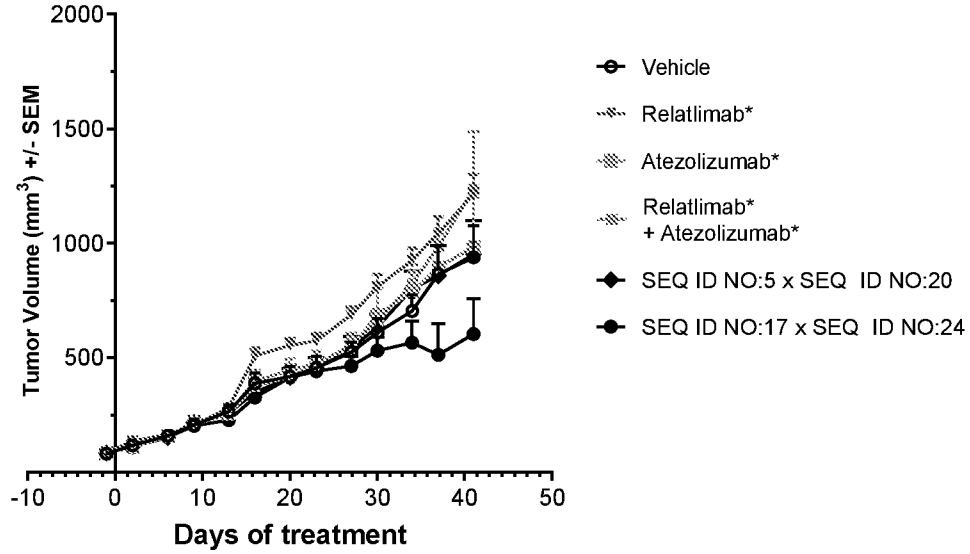


Figure 6B1

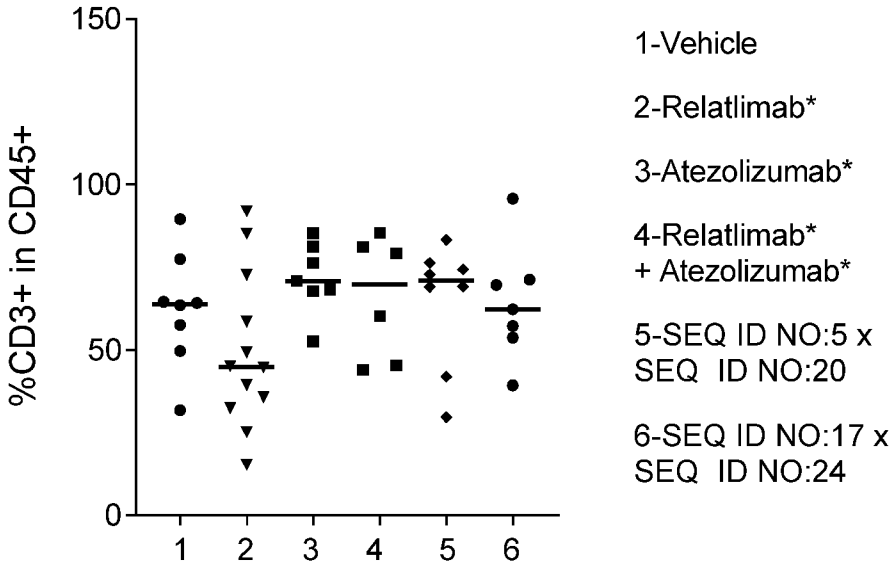


Figure 6B2

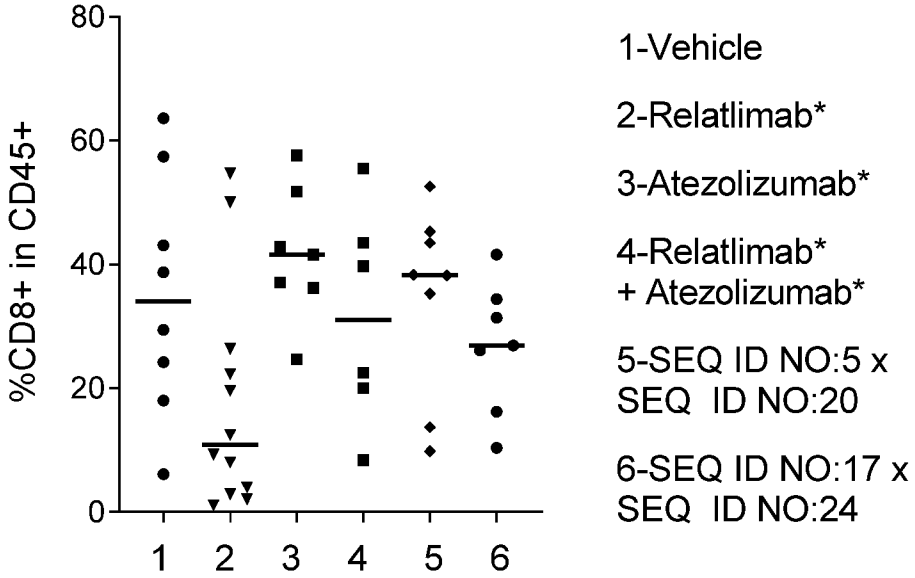


Figure 6B3

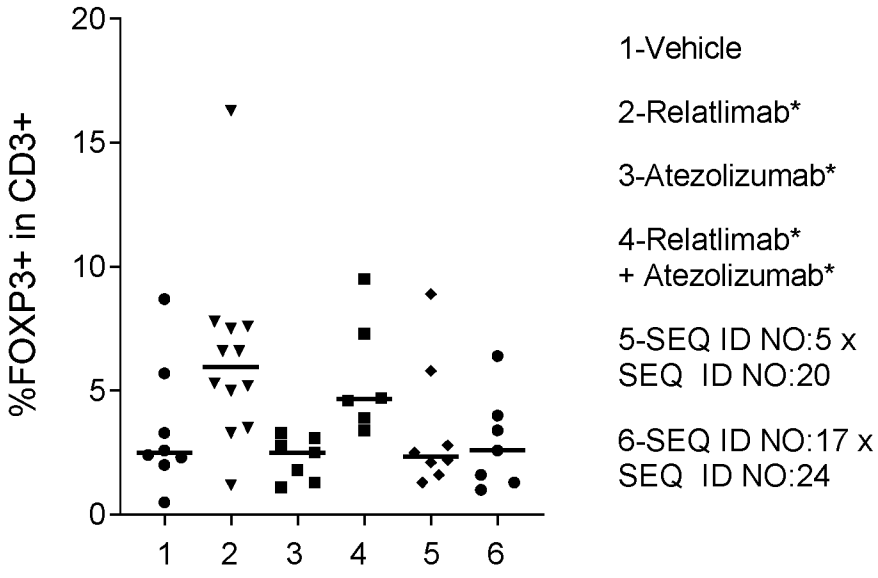


Figure 6B4

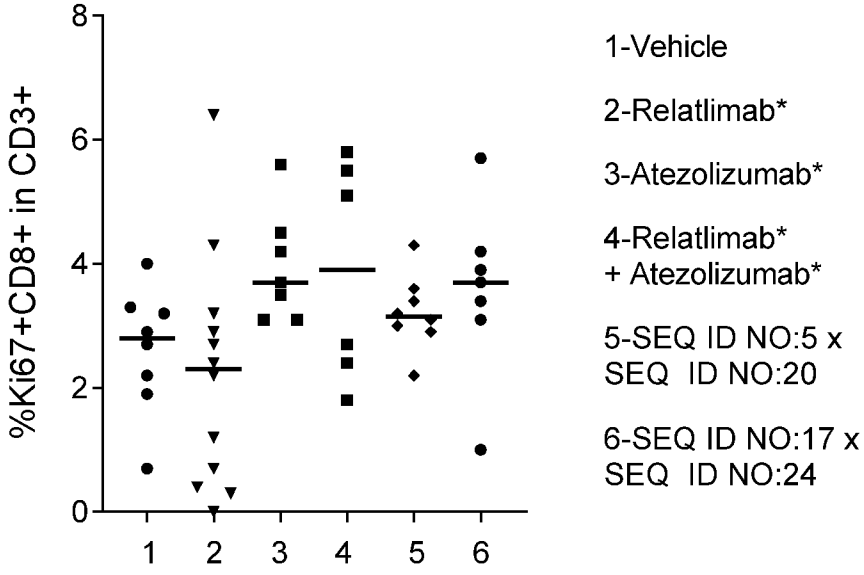


Figure 6B5

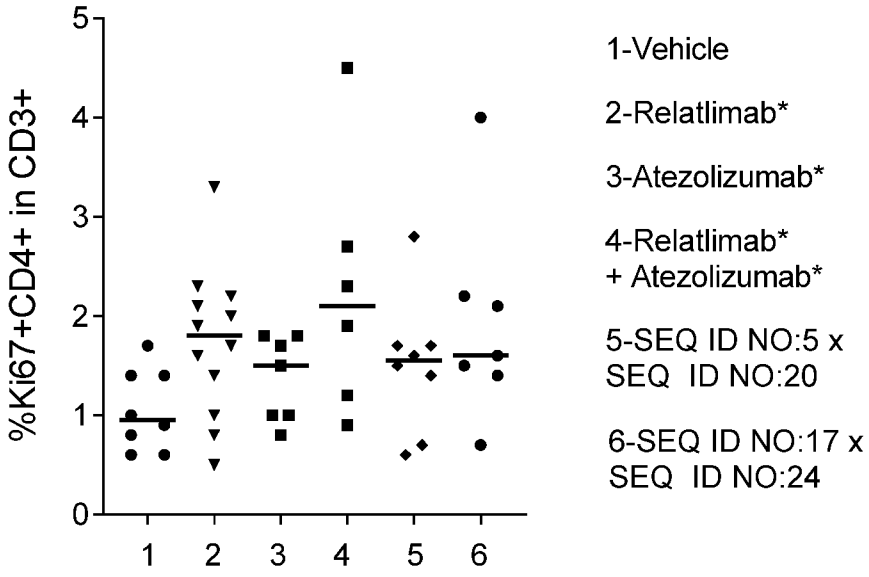
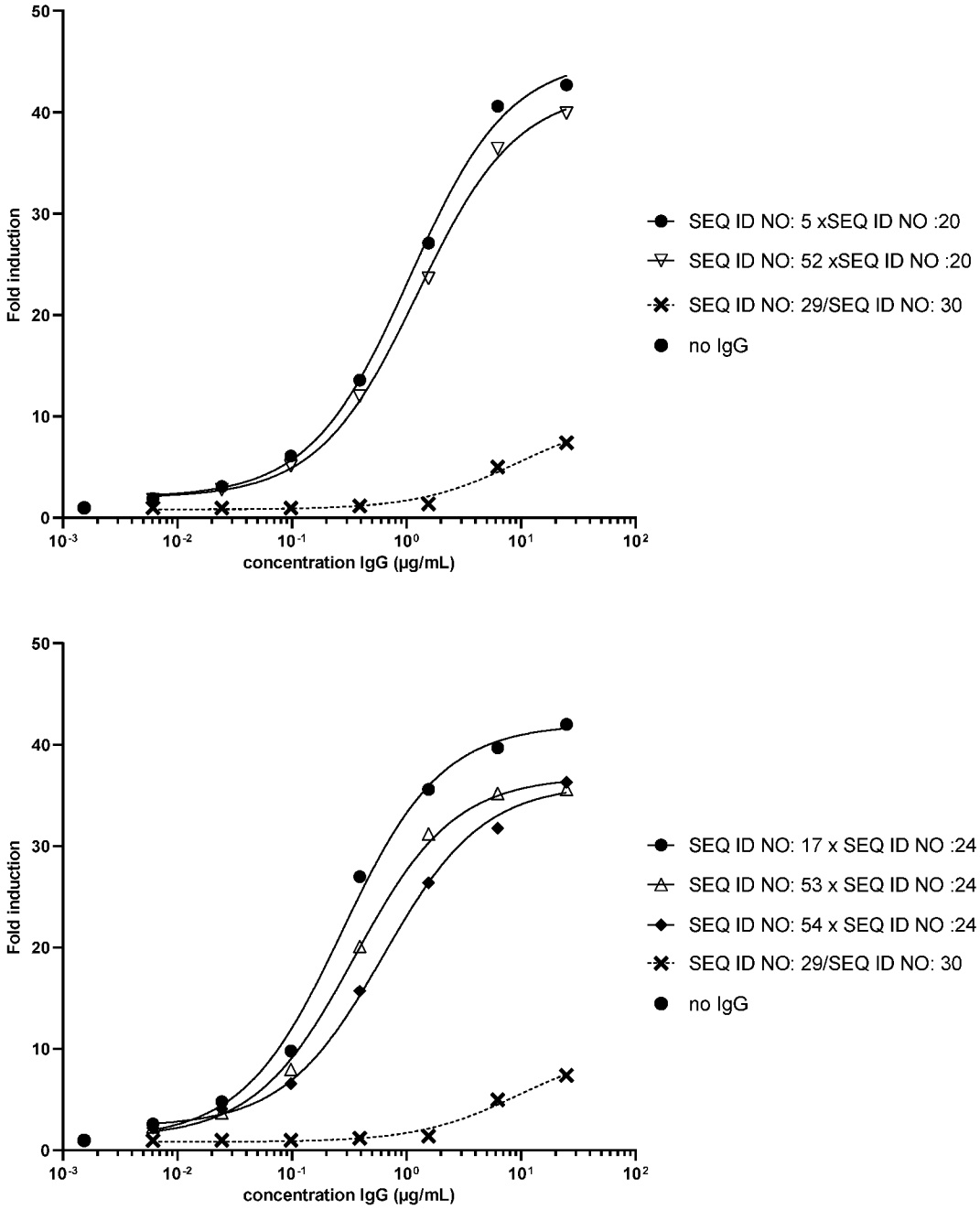
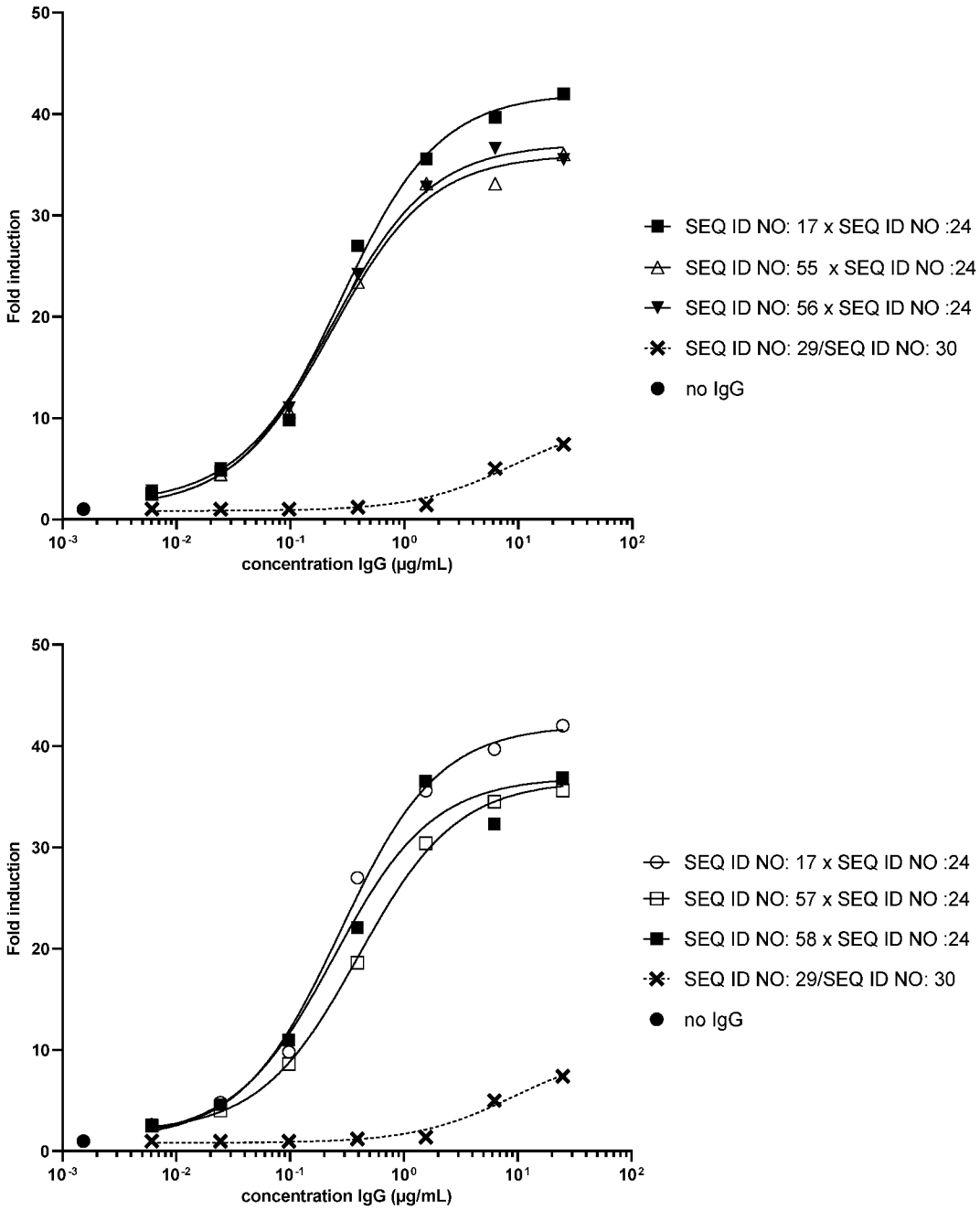

%Ki67+CD4+ in CD3+
0
1
2
3
4
5
1
2
3
4
5
6
1-Vehicle
2-Relatlimab*
3-Atezolizumab*
4-Relatlimab*
+ Atezolizumab*
5-SEQ ID NO:5 x
SEQ ID NO:20
6-SEQ ID NO:17 x
SEQ ID NO:24

Figure 7A


Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 5 xSEQ ID NO :20
SEQ ID NO: 52 xSEQ ID NO :20
SEQ ID NO: 29/SEQ ID NO: 30
no IgG
Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 53 x SEQ ID NO :24
SEQ ID NO: 54 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 55 x SEQ ID NO :24
SEQ ID NO: 56 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG
Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 57 x SEQ ID NO :24
SEQ ID NO: 58 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

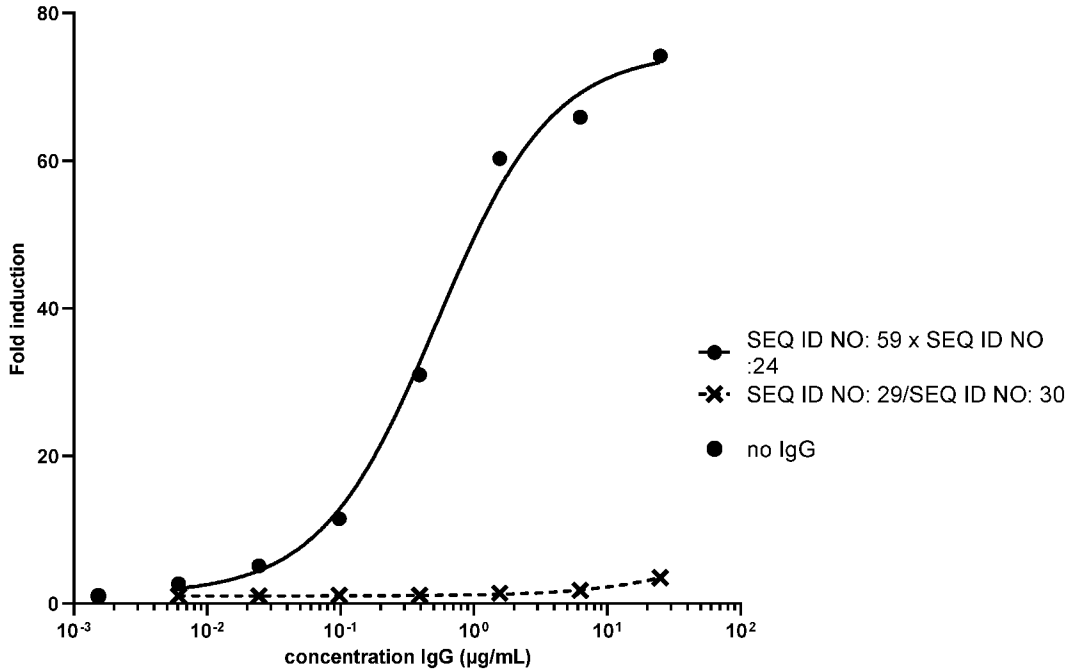
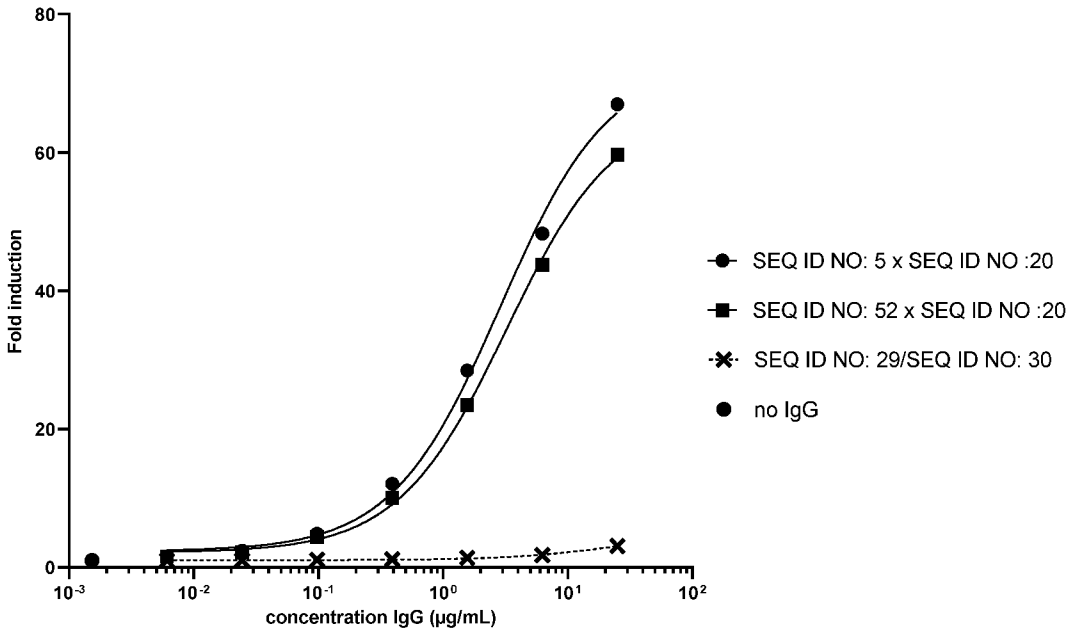
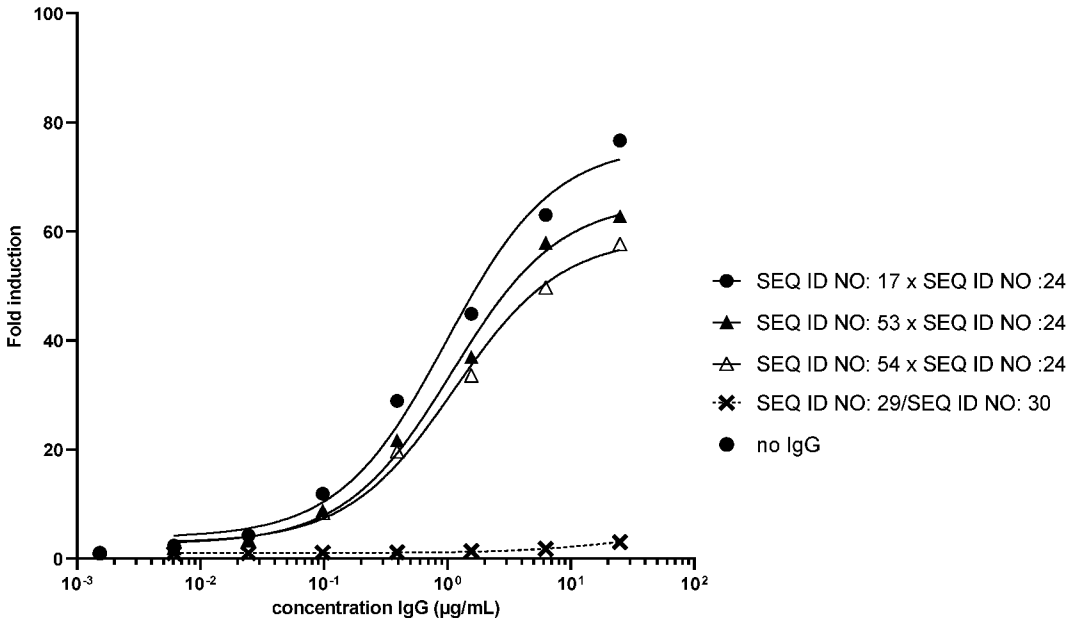
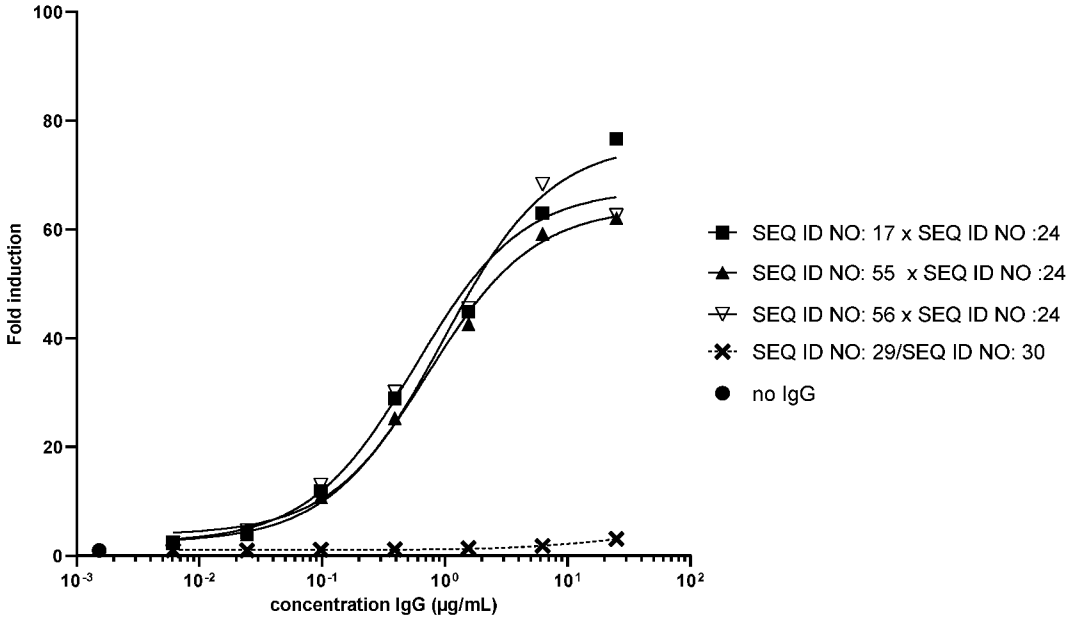
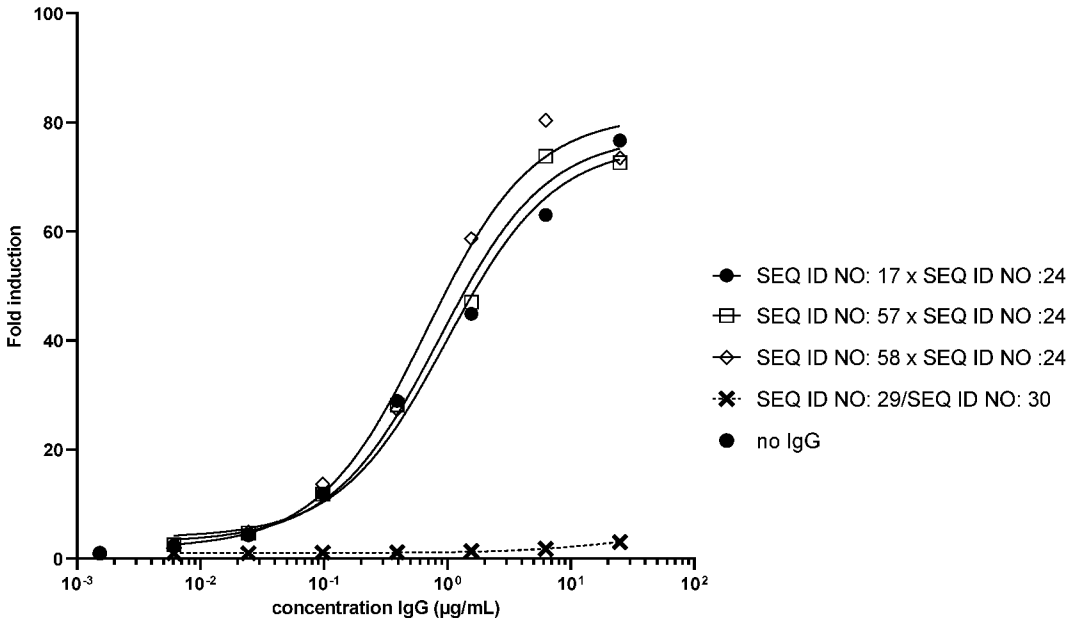

80
60
40
20
0
Fold induction
10-3
10-2
10-1
100
101
102
concentration IgG (µg/mL)
SEQ ID NO: 59 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

Figure 7B


80
60
40
20
0
Fold induction
10-3
10-2
10-1
100
101
102
concentration IgG (µg/mL)
SEQ ID NO: 5 x SEQ ID NO :20
SEQ ID NO: 52 x SEQ ID NO :20
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


Fold induction
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 53 x SEQ ID NO :24
SEQ ID NO: 54 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


Fold induction
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 55 x SEQ ID NO :24
SEQ ID NO: 56 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


Fold induction
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 57 x SEQ ID NO :24
SEQ ID NO: 58 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

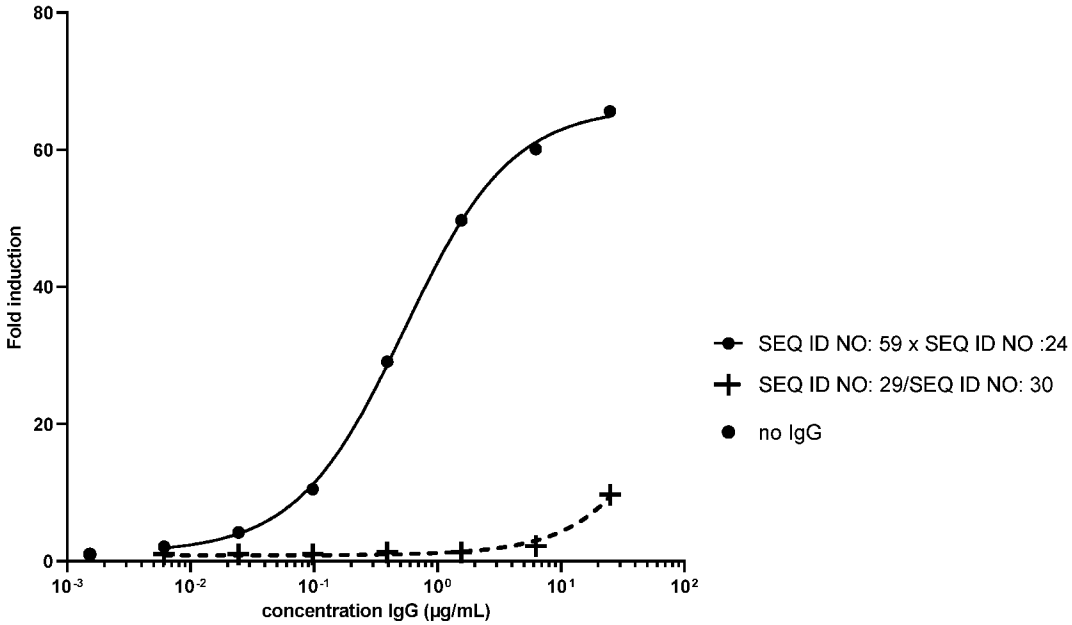
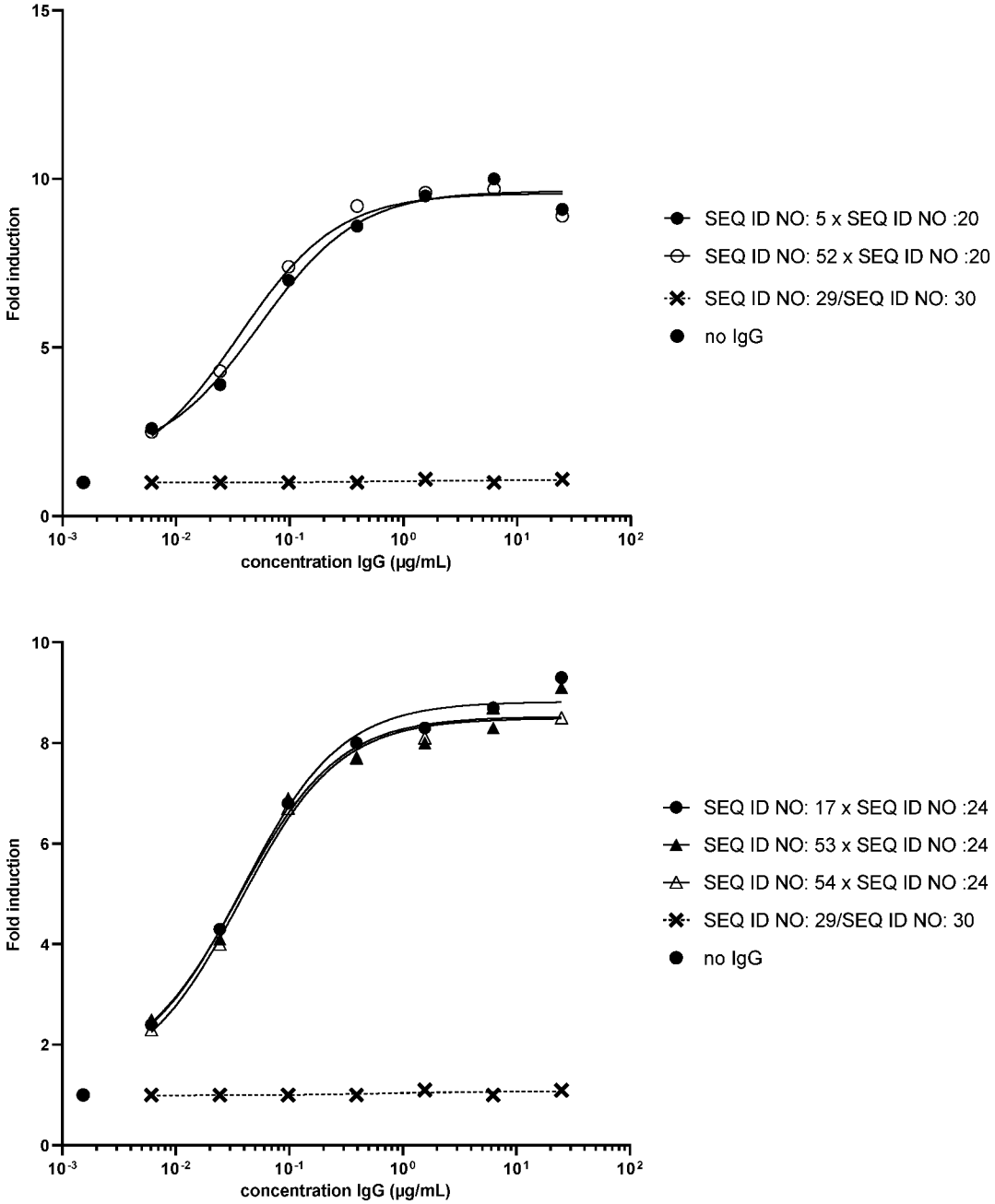
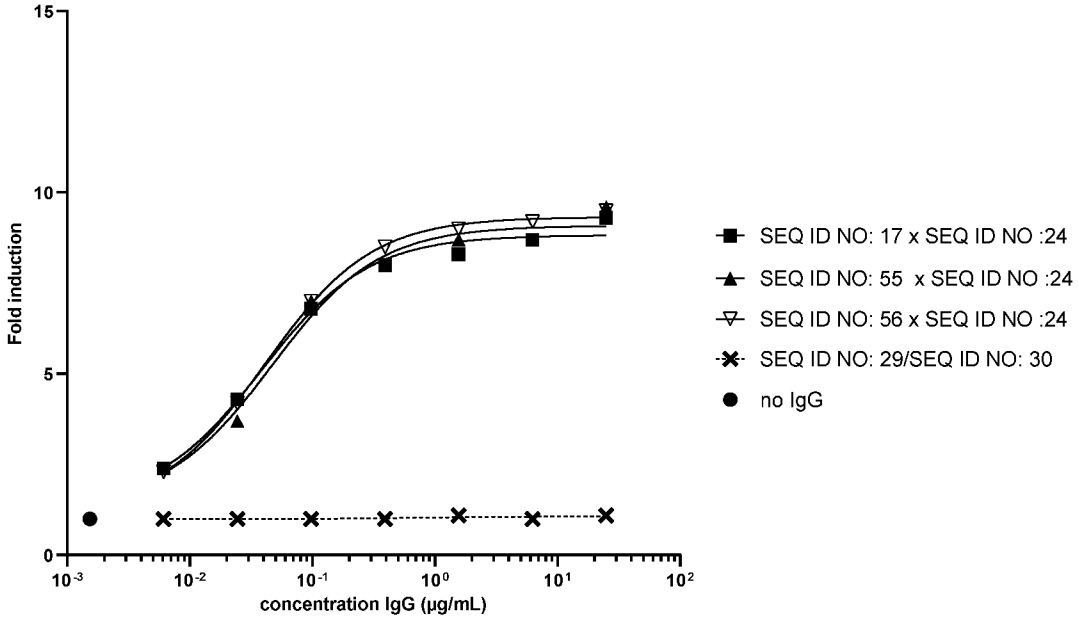
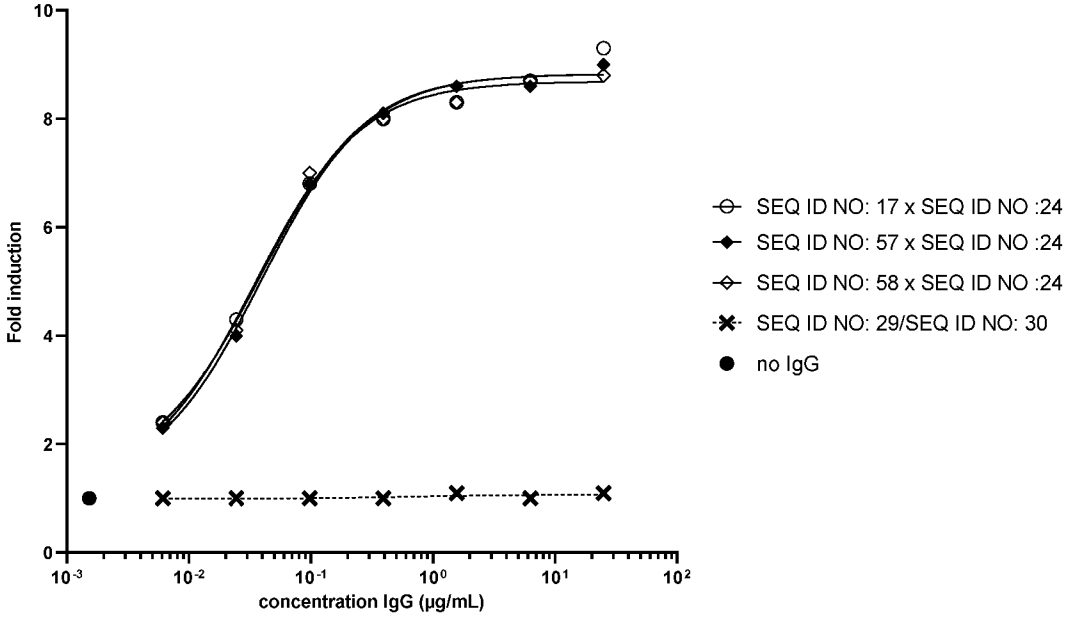

Fold induction
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 59 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

Figure 7C


Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 5 x SEQ ID NO :20
SEQ ID NO: 52 x SEQ ID NO :20
SEQ ID NO: 29/SEQ ID NO: 30
no IgG
Fold induction
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 53 x SEQ ID NO :24
SEQ ID NO: 54 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


15
10
5
0
Fold induction
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 55 x SEQ ID NO :24
SEQ ID NO: 56 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG


10
8
6
4
2
0
Fold induction
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 17 x SEQ ID NO :24
SEQ ID NO: 57 x SEQ ID NO :24
SEQ ID NO: 58 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

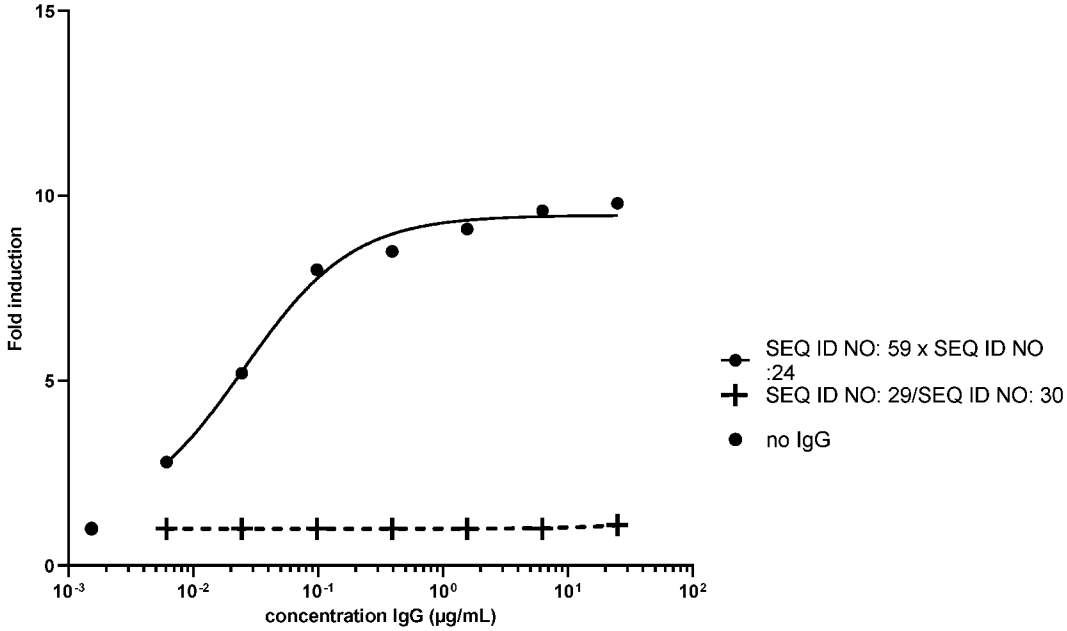
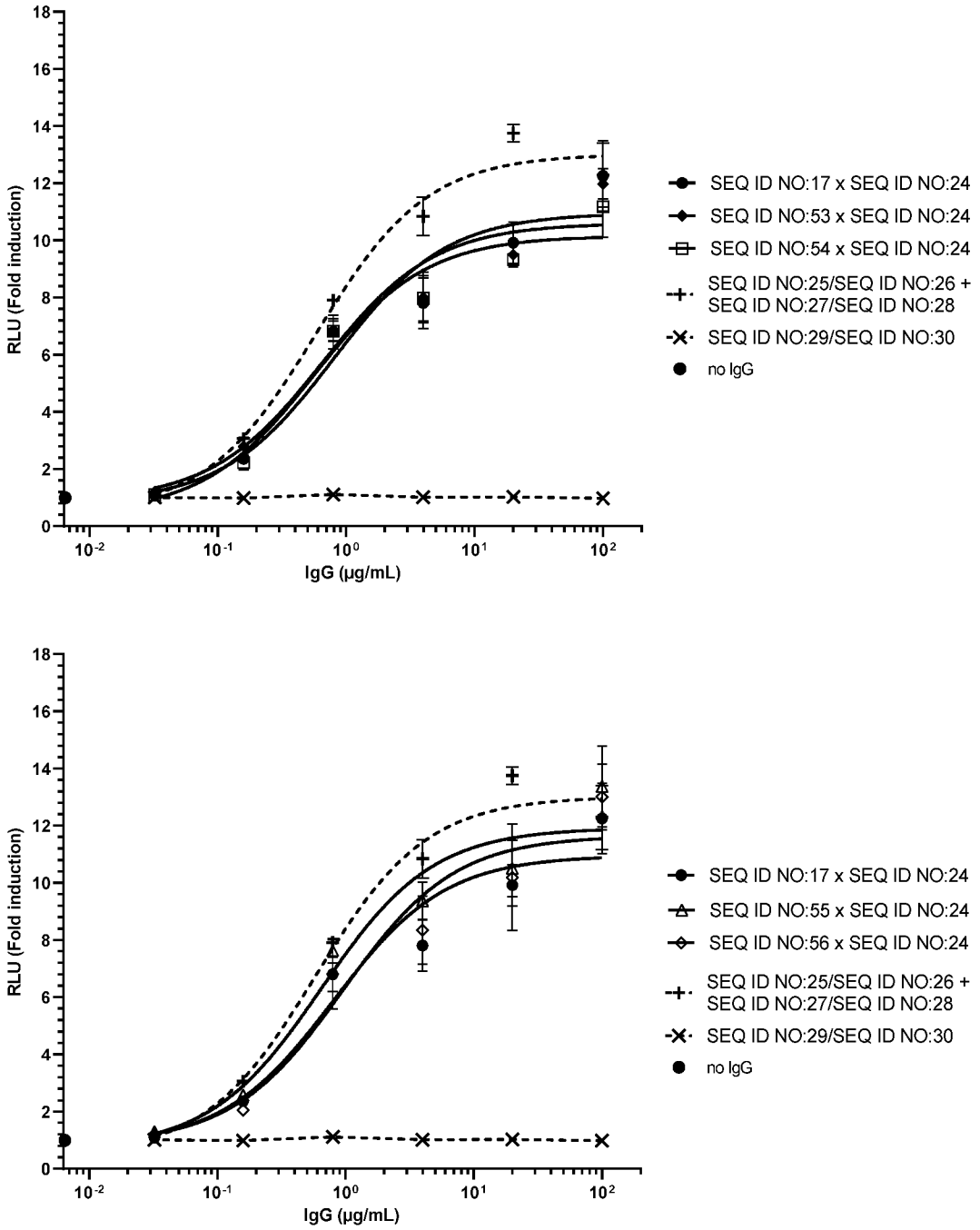
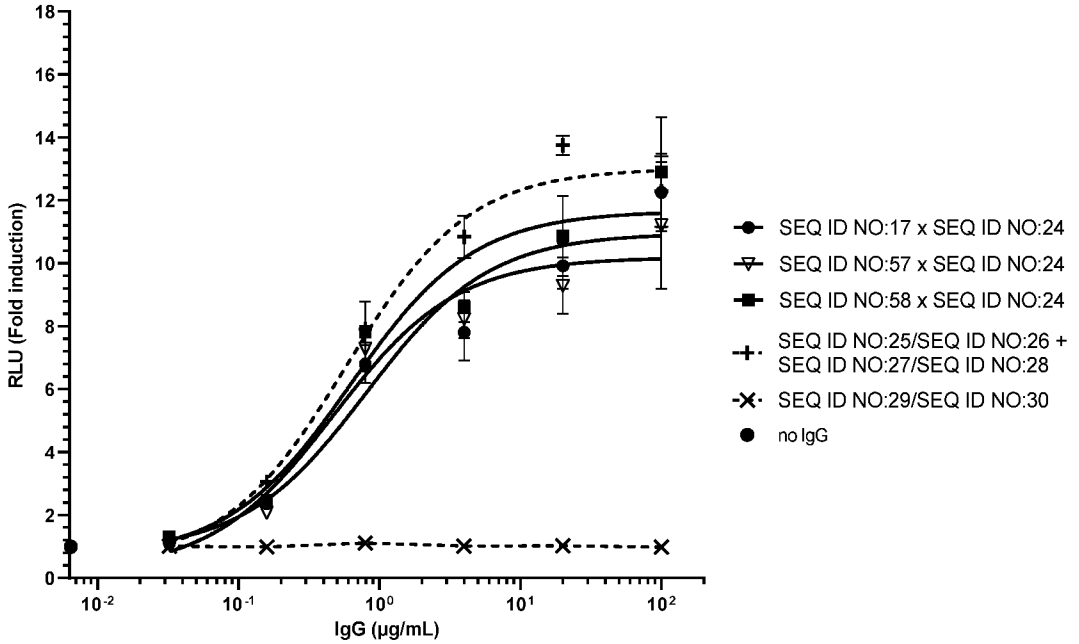
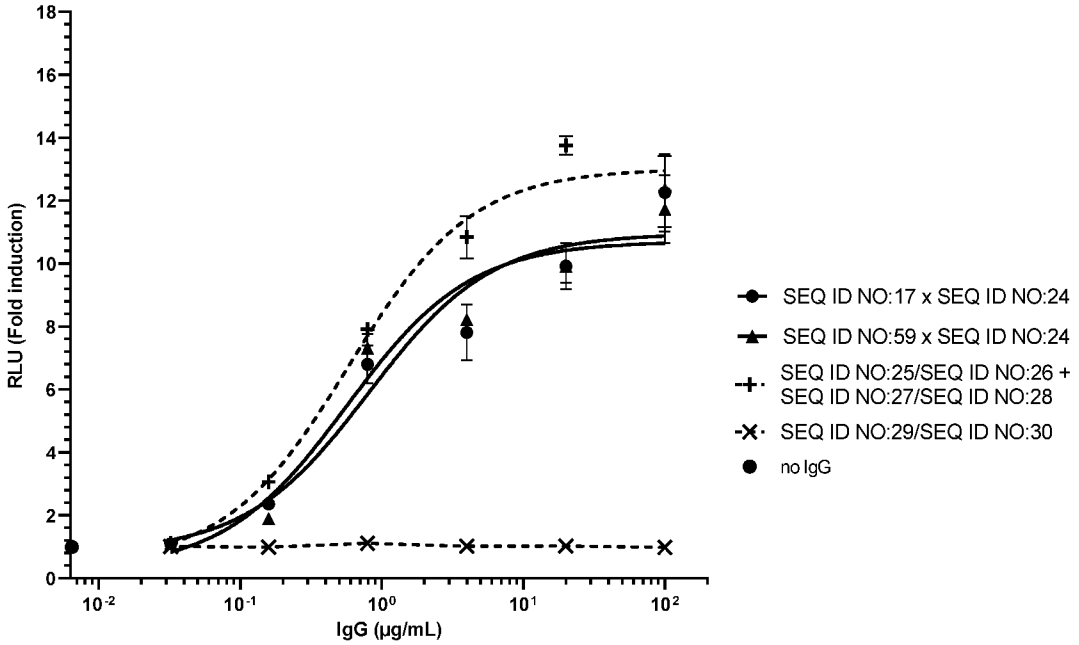
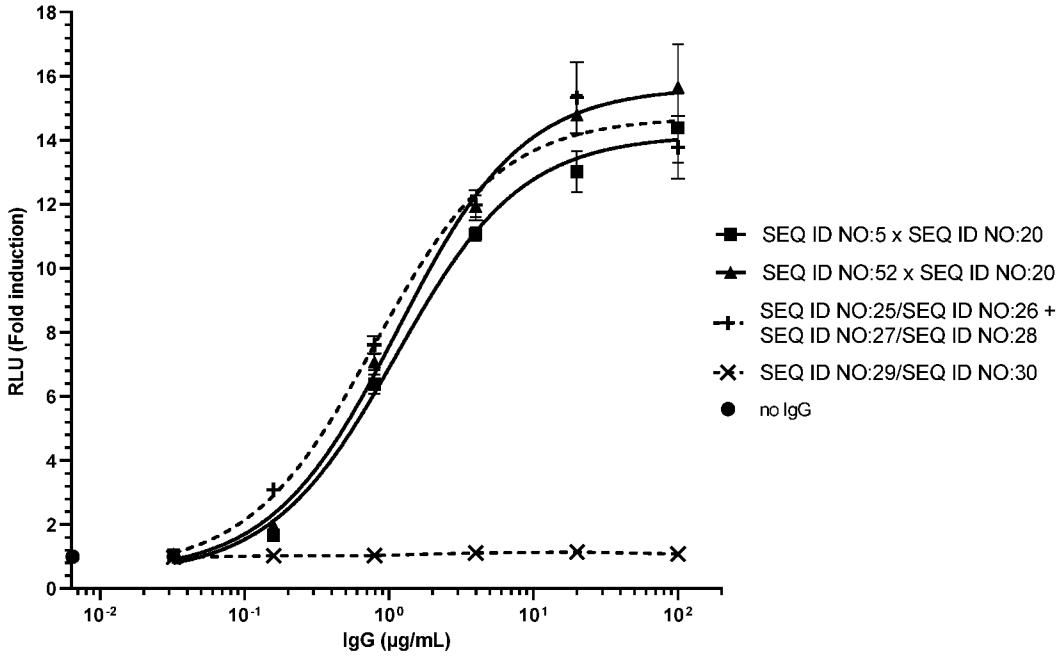

15
10
5
0
Fold induction
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
concentration IgG (µg/mL)
SEQ ID NO: 59 x SEQ ID NO :24
SEQ ID NO: 29/SEQ ID NO: 30
no IgG

Figure 8


RLU (Fold induction)
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO:24
SEQ ID NO:53 x SEQ ID NO:24
SEQ ID NO:54 x SEQ ID NO:24
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
no IgG
RLU (Fold induction)
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO:24
SEQ ID NO:55 x SEQ ID NO:24
SEQ ID NO:56 x SEQ ID NO:24
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
no IgG


RLU (Fold induction)
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO:24
SEQ ID NO:57 x SEQ ID NO:24
SEQ ID NO:58 x SEQ ID NO:24
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
no IgG


RLU (Fold induction)
IgG (µg/mL)
SEQ ID NO:17 x SEQ ID NO:24
SEQ ID NO:59 x SEQ ID NO:24
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
no IgG


RLU (Fold induction)
IgG (µg/mL)
SEQ ID NO:5 x SEQ ID NO:20
SEQ ID NO:52 x SEQ ID NO:20
SEQ ID NO:25/SEQ ID NO:26 + SEQ ID NO:27/SEQ ID NO:28
SEQ ID NO:29/SEQ ID NO:30
no IgG

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2022/050174

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/038397 A1 (I MAB; ABL BIO INC [KR]) 27 February 2020 (2020-02-27) page 2, line 24 - page 6, line 2 page 7, line 20 - line 28; figures 1-47; examples 1-6	1-53
X	WO 2020/249071 A1 (NANJING GENSCRIPT BIOTECH CO LTD [CN]) 17 December 2020 (2020-12-17) paragraphs [0001] - [0025], [0031] - [0043]; figures 1-13; examples 1,2	1-53
X	WO 2020/229626 A1 (F STAR DELTA LTD [GB]) 19 November 2020 (2020-11-19) the whole document	1-53

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2022	26/09/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stein, Annette

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/009728 A1 (MERUS NV [NL]) 10 January 2019 (2019-01-10) cited in the application the whole document sequences 74, 58-60, 73, 81, 30	1-53
A	WO 2019/009726 A1 (MERUS NV [NL]) 10 January 2019 (2019-01-10) cited in the application the whole document sequences 25, 7	1-53
X	WO 2016/200782 A1 (MACROGENICS INC) 15 December 2016 (2016-12-15) paragraphs [0013] - [0020], [0023] - [0025], [0080] - [0133], [0168], [0169]; examples 1-4	16-21, 30-43,52
A	WANG MIAO ET AL: "LAG3 and its emerging role in cancer immunotherapy", CLINICAL AND TRANSLATIONAL MEDICINE, vol. 11, no. 3, 18 March 2021 (2021-03-18), XP055961068, SE ISSN: 2001-1326, DOI: 10.1002/ctm2.365 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7989707/pdf/CTM2-11-e365.pdf> the whole document, in particular page 2, left-hand column	1-53
T	ZHANG WEI ET AL: "B7 Family Members in Lymphoma: Promising Novel Targets for Tumor Immunotherapy?", FRONT. ONCOL., vol. 11, no. Article 647526, 31 March 2021 (2021-03-31), pages 1-11, XP055961111, DOI: 10.3389/fonc.2021.647526 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL2022/050174

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL2022/050174

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-53 (partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-53 (partially)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-53(partially)

Multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has at least comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26; and wherein the LAG-3 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of the heavy chain variable region having an amino acid sequence as set forth in SEQ ID NOs: 1, and wherein the PD-L1 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of the heavy chain variable region having an amino acid sequence as set forth in SEQ ID NOs: 20; and related subject-matter.

2-4. claims: 1-53(partially)

Multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has at least comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26; and wherein the LAG-3 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of one of the heavy chain variable regions having an amino acid sequences as set forth in SEQ ID NOs: 1, and wherein the PD-L1 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

(HCDR3), of one of the heavy chain variable regions having an amino acid sequences as set forth in SEQ ID NOs: 21-24; wherein each combination identifies one independent invention, and related subject-matter.

5-125. claims: 1-53(partially)

Multispecific antibody comprising a binding domain that binds to LAG-3 and a binding domain that binds to PD-L1, or a variant thereof that maintains the binding specificity of the antibody, wherein the antibody or variant has at least comparable, or equal or higher, potency than a combination of reference antibodies, wherein the combination of reference antibodies comprises a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 27 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 28, and a reference antibody comprising two heavy chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 25 and two light chain variable regions having an amino acid sequence as set forth in SEQ ID NO: 26; and wherein the LAG-3 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of one of the heavy chain variable regions having an amino acid sequences as set forth in SEQ ID NOs: 2-17 and SEQ ID NOs: 52-59, and wherein the PD-L1 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of one of the heavy chain variable regions having an amino acid sequences as set forth in SEQ ID NOs: 20-24; wherein each combination identifies one independent invention, and related subject-matter.

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126. claims: 16-21, 30-43, 52(all partially)

Multispecific antibody comprising a binding domain that binds to an extracellular domain of LAG-3 and a binding domain that binds to an extracellular domain of a B7 family member other than PD-L1; wherein the LAG-3 binding domain comprises a heavy chain variable region comprising heavy chain CDR1 (HCDR1), heavy chain CDR2 (HCDR2), and heavy chain CDR3 (HCDR3), of one of the heavy chain variable regions having an amino acid sequences as set forth in SEQ ID NOs: 1-17 and SEQ ID NOs: 52-59, and related subject-matter.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-53(partially)

Present claims 1-36 relate to an extremely large number of possible antibodies. Further, claims 1-7, 23, 24 and 30-35 attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.
Support and
disclosure in the sense of Article 6 and 5 PCT is to be found for only a very small proportion of the antibodies encompassed by present claims 1-36, see the antibodies defined by their specific VH sequences disclosed in table 1 on pages 53-55 and table 10 on pages 102-103. CDR sequences of the antibodies are defined in the present application on, e.g. page 59, line 26- page 60, line 4, however, the corresponding VH sequences are not indicated. Thus, antibodies defined by referring to CDR sequences or combinations of CDRs of different antibodies is not supported or disclosed by the present application. Nevertheless, it is considered that support and disclosure can be found for antibodies comprising the specific CDR sequences derivable (i.e. in bold) from the VH sequences of SEQ ID NOs: 1-17, 20-24, 52-59 on pages 106-110 and 114-115 in combination with the teaching of tables 1 and 10. In view of all the antibodies encompassed by present claims 1-36, however, the non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of these claims (PCT Guidelines 9.19 and 9.23). The search of said claims (as well as all other claims due to dependencies thereon) has to be restricted to those claimed antibodies which appear to be supported (see sequences of VH in tables 1 and 10 and the common light chain of SEQ ID NO: 30) as well as to antibodies comprising the specific CDR sequences derivable (i.e. in bold) from the VH sequences of SEQ ID NOs: 1-17, 20-24, 52-59 on pages 106-110 and 114-115 in combination with the teaching of tables 1 and 10 (see also objection as to lack of unity).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

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PCT/NL2022/050174

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