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(71) Applicants: **SYSTIMMUNE, INC.** [US/US]; 15318 NE 95th St, Redmond, Washington 98052 (US). **SICHUAN BAILI PHARMACEUTICAL CO. LTD.** [CN/CN]; 161 Baili Road, Wenjiang District, Chengdu, Sichuan (CN).

(72) Inventors: **KOVACEVICH, Brian**; 13916 233rd St. SE, Snohomish, Washington 98296 (US). **XIA, Dong**; 17401 NE 97th Way, Redmond, Washington 98052 (US). **JANSEN, Anne**; 16524, 14th Dr. SE, Mill Creek, Washington 98012 (US). **FALLEN, Jon**; 95 W. Squantum St. #1112, Quincy, Massachusetts 02171 (US). **RENSHAW, Blair**; 16210 SE 166th Ct, Renton, Washington 98058 (US). **ADAMO, Jeffrey B.**; 528 18th Ave. E, Seattle, Washington 98112 (US). **TAN, Phil**; 8704 200th St. SW, Edmonds, Washington 98026 (US). **GAO, Zeren**; 9816 229th LN NE, Redmond, Washington 98053 (US). **ZHU, Yi**; 8-24, Building 6, No. 6, Lidu Road, Wuhou District, Chengdu, Sichuan (CN).

(74) Agent: **HAN, Zhihua**; EpiMED LLC, 10398 NE 17th St. Unit 306, Bellevue, Washington 98004 (US).

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(54) Title: ANTI-PD-1 ANTIBODIES AND METHODS OF MAKING AND USING THEREOF

(57) Abstract:

ANTI-PD-1 ANTIBODIES AND METHODS OF MAKING AND USING THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 62545603 filed August 15, 2017, U.S. Provisional Patent Application No. 62524553 filed June 25, 2017, U.S. Provisional Patent Application No. 62524554 filed June 25, 2017, U.S. Provisional Patent Application No. 62524557 filed June 25, 2017, and U.S. Provisional Patent Application No. 62524558 filed June 25, 2017, which application is expressly incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present application generally relates to the technical field of antibodies, and more particularly relates to making and using anti-PD-1 antibodies.

BACKGROUND

Cancer is a major health problem across the world. In the United States alone it is estimated that in 2016 there were 1,685,210 new cases of cancer diagnosed and 595,690 deaths from the disease (http://www.cancer.gov). As such, any pharmaceutical agent that can reduce the severity or mortality rate from cancer is desirable.

Cancerous tumours can adopt a variety of mechanisms to avoid detection and/or destruction by the host immune system. One method utilized by a variety of tumours is to suppress the immune T-cell response by the expression of PD-1 on the surface of tumour cells. When the PD-1 engages its receptor PD-1 on the surface of T-cells, a negative co-stimulatory signal is sent into the T-cell that results in the suppression of the T-cell. In this manner tumour cells are able to avoid a T-cell mediated response of the host immune system.

Pharmaceutical agents that are able to bind to PD-1 and block the negative co-stimulatory signal from suppressing the T-cell response have been shown to increase the host immune response to cancerous tumours and have resulted in a beneficial response for cancer patients (see Iwai et al. J. Biomed. Sci. 24:26 (2017)).

In the immune system, resting T-cells can be activated to respond to antigen through a primary signal delivered through the T-cell receptor (TCR) by foreign antigen peptides presented by antigen-presenting cells (APCs). In addition to this primary signal, there are secondary positive and negative co-stimulatory signals that further influence the response of the T-cells. A secondary positive signal is required for full T-cell activation ((Lafferty et al., Ausl. J. Exp. Biol. Med. Sci. 53: 27-42 (1975)). Negative secondary signals can result in T-cell suppression and tolerance.

Programmed death 1 (PD-1) is a member of the CD28 family of receptors and is expressed on T-cells and other cell types. PD-1 is one of the routes used by to transmit negative secondary signals into T-cells. PD-1 is a cell-surface ligand glycoprotein for PD-1 that was shown to downregulate T-cell activation upon binding to PD-1 (Freeman et al. J. Exp. Med. 192: 1027-34 (2000)). PD-1, also known as B7-H1 or CD274,

is a 40kDa type 1 transmembrane protein that has been shown to be expressed in several human cancers and is associated with increased tumour aggressiveness and an increased risk of death (Thomson et al. PNAS 101: 17174-9 (2004)). PD-1 expression in cancers is thought to supress the immune response to tumours via suppression of T-cells via its interaction with PD-1 (Dong et al. Nat. Med. 8: 793-800 (2002)). Consequently, several PD-1 inhibitors are currently being developed or have been developed to enhance T-cell activity against tumours for the treatment of cancer.

While pharmaceutical agents that are able to bind to PD-1 and block the negative co-stimulatory signal from suppressing the T-cell response have been shown to increase the host immune response to cancerous tumours and have resulted in a beneficial response for cancer patients (see Iwai et al. J. Biomed. Sci. 24:26 (2017)), it remains unclear what is the optimal PD-1 binding site(s) and relevant affinity for developing the most effective and tumour cell-specific anti-PD-1 antibodies for cancer treatment.

SUMMARY

In one aspect, the application provides anti-PD-1 monoclonal antibodies, antigen binding portions thereof, therapeutic compositions thereof and/or nucleic acid encoding the same, and their use to upregulate the function of T-cells to enhance cell-mediated immune responses in the treatment of cancer and other T-cell dysfunctional disorders.

In one embodiment, an isolated monoclonal antibody (mAb) or antigen-binding fragment thereof that binds specifically to human PD-1 is provided. In one embodiment, the isolated mAb or antigen-binding fragment comprises an amino acid sequence having a percentage homology with SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, or SEQ ID NO:80. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, the isolated mAb or antigen-binding fragment has a binding affinity to human PD-1 with a Kd not greater than 3-nM, 40nM, 50nM, 60nM, 70nM, 80nM, 90nM, or 100nM.

In one embodiment, the isolated mAb or antigen-binding fragment may exhibit one or more functional properties including without limitation high affinity binding to human PD-1, inhibiting binding of human PD-L1 to PD-1, enhancing T cell activation, stimulating antibody response, reversing the suppressive function of an immunosuppressive cell, or a combination thereof. In one embodiment, the immunosuppressive cell comprises a regulatory cell. In one embodiment, the isolated mAb or antigen-binding fragment may enhance T-cell activation via mechanisms or pathways including T-cell proliferation, IFN-γ and/or IL-2 secretion, or a combination thereof.

In one embodiment, the isolated mAb or antigen-binding fragment comprises a human framework region. In one embodiment, the isolated mAb or antigen-binding fragment is a humanized antibody, a chimeric antibody, or a recombinant antibody.

In one embodiment, the isolated mAb or antigen-binding fragment is an IgG. In one embodiment, the antigen-binding fragment is a Fv, a Fab, a F(ab')2, a scFV or a scFV2 fragment. In one embodiment, the isolated mAb is a bispecific antibody, tri-specific antibody, or multi-specific antibody.

In one embodiment, the application provides an isolated mAb or antigen-binding fragment that has an IgG1 heavy chain with an amino acid sequence having a percentage homology with SEQ ID NO:7, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:55, SEQ ID NO:63, SEQ ID NO:71, or SEQ ID NO:79. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, the application provides an isolated mAb or antigen-binding fragment that has a kappa light chain having an amino acid sequence having a percentage homology SEQ ID NO:3, SEQ ID NO:11, SEQ ID NO:19, SEQ ID NO:27, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:51, SEQ ID NO:59, SEQ ID NO:67, or SEQ ID NO:75. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, the application provides an isolated mAb or antigen-binding fragment that has a variable light chain having an amino acid sequence having a percentage homology with SEQ ID NO:4, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:36, SEQ ID NO:44, SEQ ID NO:52, SEQ ID NO:60, SEQ ID NO: 68, or SEQ ID NO:76. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, the application provides an isolated mAb or antigen-binding fragment that has a variable heavy chain having an amino acid sequence having a percentage homology with SEQ ID NO:8, SEQ ID NO:16, SEQ ID NO:24, SEQ ID NO:32, SEQ ID NO:40, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:64, SEQ ID NO:72, or SEQ ID NO:80. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, isolated nucleic acids are provided that encode at least a portion of the isolated mAb or antigen-binding fragment disclosed herein. In some embodiments, the isolated nucleic acid encodes an amino acid having a percentage homology with: 1) the IgG1 heavy chain having the sequence of SEQ ID NO:7, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:55, SEQ ID NO:63, SEQ ID NO:71, or SEQ ID NO:79; 2) the kappa light chain having the sequence of SEQ ID NO:3, SEQ ID NO:11, SEQ ID NO:19, SEQ ID NO:27, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:51, SEQ ID NO:59, SEQ ID NO:67, or SEQ ID NO:75; 3) the variable light chain having the sequence of SEQ ID NO:4, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:36, SEQ ID NO:44, SEQ ID NO:52, SEQ ID NO:60, SEQ ID NO: 68, or SEQ ID NO:76; and 4) the variable heavy chain having a sequence of SEQ ID NO:8, SEQ ID NO:16, SEQ ID NO:24, SEQ ID NO:32, SEQ ID NO:40, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:64, SEQ ID NO:72, or SEQ ID NO:80. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, an expression vector is provided comprising the isolated nucleic acid that encodes an amino acid sequence disclosed herein. In one embodiment, the expression vector is expressible in a cell.

In one embodiment, the application provides a host cell comprising nucleic acids that encode an amino acid sequence disclosed herein. In one embodiment, the application provides a host cell comprising the expression vector that comprises one or more of nucleic acids that encode an amino acid sequence disclosed herein. In one embodiment, the host cell can be a prokaryotic cell or a eukaryotic cell.

In another aspect, the application provides methods for producing an antibody. In one embodiment, the method comprises the step of using the host cell described above. The method includes the steps of providing a host cell that contains an expression vector expressible in the host cell, the expression vector comprises nucleic acids encoding at least at portion of the isolated mAb or antigen-binding fragment, or peptides disclosed herein, to produce an antibody by the expression of the nucleic acids.

The application further provides immuno-conjugates including a drug unit or an imaging agent linked to the mAb or antigen-binding fragments disclosed herein. The immuno-conjugate may include a drug unit and an isolated mAb or antigen-binding fragment disclosed herein.

The linker may be cleavable or non-cleavable. In one embodiment, the linker comprises an ester bond, an ether bond, an amine bond, an amide bond, a disulphide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, a hydrazone bond or a combination thereof. In one embodiment, the linker comprises a hydrophobic poly(ethylene glycol) linker.

In one embodiment, the drug unit in the immuno-conjugate is a chemotherapeutic agent, a growth inhibitory agent, a toxin, or a radioactive isotope. In one embodiment, the drug unit comprises a cytotoxic agent from class of calicheamicin, an antimitotic agent, or a combination thereof. In one embodiment, the drug unit comprises, ozogamicin, monomethyl auristatin E, emtansine, a derivative or a combination thereof.

In one embodiment, the drug unit is selected from a cytotoxic agent, an immune regulatory reagent, an imaging agent or a combination thereof. In one embodiment, the cytotoxic agent is selected from a growth inhibitory agent or a chemotherapeutic agent from a class of tubulin binders, DNA intercalators, DNA alkylators, enzyme inhibitors, immune modulators, antimetabolite agents, radioactive isotopes, or a combination thereof. In one embodiment, the cytotoxic agent is selected from a calicheamicin, ozogamicin, monomethyl auristatin E, emtansine, a derivative or a combination thereof. In one embodiment, the immune regulatory reagents activate or suppress immune cells, T cell, NK cell, B cell, macrophage, or dendritic cell.

In one embodiment, the imaging agent may be radionuclide, a florescent agent, a quantum dots, or a combination thereof.

The application further provides pharmaceutical compositions. In one embodiment, the pharmaceutical composition includes the isolated mAb or antigen-binding fragment disclosed herein and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition provides the immuno-conjugate disclosed herein and pharmaceutically acceptable carrier.

In one embodiment, the pharmaceutical composition further comprises a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, a therapeutic agent, or a combination thereof. In one embodiment, the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, or a combination thereof. In one embodiment, the therapeutic agent comprises an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof.

In one embodiment, a method of treating a subject with a cancer is provided, comprising administering to the subject an effective amount of the isolated mAb or antigen-binding fragment disclosed herein. In one embodiment, the method includes directly injecting into the tumour site an effective amount of the monoclonal antibodies, the antigen-binding fragment thereof, and the immuno-conjugates and disclosed herein.

In one embodiment, the cancer has cells that express PD-1. In one embodiment, the cancer may be breast cancer, colorectal cancer, pancreatic cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, non-small lung cell cancer, glioma, esophageal cancer, nasopharyngeal cancer, anal cancer, rectal cancer, gastric cancer, bladder cancer, cervical cancer, or brain cancer.

In one embodiment, the method of treating a subject with a cancer may further include co-administering an effective amount of a therapeutic agent. In one embodiment, the therapeutic agent comprises an antibody, an enzyme, or a combination thereof. In one embodiment, the therapeutic agent can include a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a radioactive isotope, a toxin, or a combination thereof. In one embodiment, the therapeutic agent comprises an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof. In one embodiment, the therapeutic agent comprises a check point inhibitor.

In one embodiment, the therapeutic agent may include capecitabine, cisplatin, Cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, Mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, Epirubicin, pemetrexed, folinic acid, gemicitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, , fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lafatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, Everolimus, temsirolimus, Dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, Bortezomib, tofacitinib, trastuzumab, a derivative or a combination thereof.

In some embodiments, the subject receiving treatment is a human. In one embodiment, a solution is provided that comprises an effective concentration of the isolated mAb or an antigen-binding fragment disclosed herein, wherein the solution is blood plasma in a subject.

Still other embodiments will become readily apparent to those skilled in the art from the following detailed description, wherein are described embodiments by way of illustrating the best mode contemplated. As will be realized, other and different embodiments are possible and the embodiments' several details are capable of modifications in various obvious respects, all without departing from their spirit and the scope. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments according to the present application may now be described with reference to the FIGUREs, in which like reference numerals denote like elements.

FIGURE 1 shows an example of the PD-1 binding ELISA performed on the supernatants from a B cell culture plate. Shaded wells indicate wells that were identified as positive for anti-PD-1 antibodies.

FIGURE 2 is an example of bio-layer interferometry analysis of the ability of an antibody supernatant to block the association between PD-1 to PD-1. The black trace utilizes a blocking antibody supernatant whereas the gray trace is with a non-blocking antibody supernatant

FIGURE 3 shows bio-layer interferometry analysis of the ability of antibodies AB6 – AB10 to block the association between PD-1 to PD-1. Shown starting from PD-1 binding followed by baseline followed by PD-1 binding. Neg. Control is an anti-PD-1 antibody which can bind to PD-1 but does not block the association between PD-1 to PD-1.

FIGURE 4 is an example of binding kinetics data for two anti-PD-1 antibodies binding to PD-1. The data shown is for the 5 minute association followed by the 15 minute dissociation for various concentrations of PD-1.

FIGURE 5 shows humanized antibodies binding to cell-surface expressed PD-1. Data points show the median fluorescence intensity (MFI) on the AF647 channel after gating on live cells. Nonlinear regression methods were used to fit curves to each data set, and error bars represent the standard deviation of duplicate samples.

FIGURE 6 shows an antibody-mediated blocking of huPD-1/huPD-1 interactions. The ability of the humanized anti-PD-1 antibodies to block PD-1 binding to Jurkat/huPD-1 cell line by FACS. Data show the median fluorescence intensity (MFI) on the APC channel after gating on live cells. Error bars represent the standard deviation of duplicate samples.

FIGURE 7 shows antibody-mediated blocking of huPD-1/huPD-L2 interactions. The ability of the humanized anti-PD-1 antibodies to block PD-L2 binding to Jurkat/huPD-1 cell line by FACS. Data show the median fluorescence intensity (MFI) on the APC channel after gating on live cells. Error bars represent the standard deviation of duplicate samples.

FIGURE 8 shows effect of humanized PD-1 antibodies on T cell activation. IL-2 production from human PBMC cells in response to staphylococcal enterotoxin B in the presence of humanized anti-PD-1 antibodies or control human IgG.

DETAILED DESCRIPTION

The application provides, among others, isolated antibodies, their antigen-binding fragments, methods of making such antibodies or fragments, bispecific or multi-specific molecules, antibody-drug conjugates and/or immuno-conjugates composed from such antibodies or antigen binding fragments, pharmaceutical compositions containing the antibodies, bispecific or multi-specific molecules, antibody-drug conjugates and/or immuno-conjugates and methods for treating cancers using the mAbs and their antigen-binding fragments disclosed herein.

In one aspect, the application provides isolated monoclonal antibodies or their antigen-binding fragments having a binding specificity to human PD-1. The antibodies or their antigen-binding fragments may exhibit one or more desirable functional properties, such as high affinity binding to PD-1, the ability to inhibit binding of PD-1 to PD-L1, the ability to enhance T cell activation including proliferation, IFN-γ and/or IL-2 secretion, the ability to stimulate antibody responses and/or the ability to reverse the suppressive function of immunosuppressive cells, such as T regulatory cells. In one embodiment, the antibodies or their antigen-binding fragments may be derived from specific heavy and light chain amino acid sequences and/or structural features such as complementarity determining regions (CDRs) composed of specific amino acid sequences.

The term “antibody” is used in the broadest sense and specifically covers single monoclonal antibodies (including agonist and antagonist antibodies), antibody compositions with polyepitopic specificity, as well as antibody fragments (e.g., Fab, $F(ab')_2$, and Fv), so long as they exhibit the desired biological activity. In some embodiments, the antibody may be monoclonal, polyclonal, chimeric, single chain, bispecific or bi-effective, human and humanized antibodies as well as active fragments thereof. Examples of active fragments of molecules that bind to known antigens include Fab, $F(ab')_2$, scFv and Fv fragments, including the products of a Fab immunoglobulin expression library and epitope-binding fragments of any of the antibodies and fragments mentioned above. In some embodiments, antibody may include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e. molecules that contain a binding site with the immunological binding specificity to an antigen. The immunoglobulin can be of any type (IgG, IgM, IgD, IgE, IgA and IgY) or class (IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclasses of immunoglobulin molecule. In one embodiment, the antibody may be whole antibodies and any antigen-binding fragment derived from the whole antibodies. A typical antibody refers to heterotetrameric protein comprising typically of two heavy (H) chains and two light (L) chains. Each heavy chain is comprised of a heavy chain variable domain (abbreviated as VH) and a heavy chain constant domain. Each light chain is comprised of a light chain variable domain (abbreviated as VL) and a light chain constant domain. The VH and VL regions can be further subdivided into domains of hypervariable complementarity determining regions (CDR), and more conserved regions called framework regions (FR). Each variable domain (either VH or VL) is typically composed of three CDRs and four FRs, arranged in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 from amino-terminus to

carboxy-terminus. Within the variable regions of the light and heavy chains there are binding regions that interacts with the antigen.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present application may be made by the hybridoma method first described by Kohler & Milstein, *Nature,* 256:495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567).

In one embodiment, the monoclonal antibodies herein may include “chimeric” antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA,* 81:6851-6855 [1984]).

Monoclonal antibodies can be produced using various methods including mouse hybridoma or phage display (see Siegel. Transfus. Clin. Biol. 9:15-22 (2002) for a review) or from molecular cloning of antibodies directly from primary B cells (see Tiller. New Biotechnol. 28:453-7 (2011). In the present application, antibodies were created by the immunization of rabbits with both human PD-1 protein and cells transiently expressing human PD-1 on the cell surface. Rabbits are known to create antibodies of high affinity, diversity and specificity (Weber et al. Exp. Mol. Med. 49:e305). B cells from immunized animals were cultured in vitro and screened for the production of anti-PD-1 antibodies. The antibody variable genes were isolated using recombinant DNA techniques and the resulting antibodies were expressed recombinantly and further screened for desired features such as ability to inhibit the binding of PD-1 to PD-1, the ability to bind to non-human primate PD-1 and the ability to enhance human T-cell activation. This general method of antibody discovery is similar to that described in Seeber et al. PLOS One. 9:e86184 (2014).

The term “antigen-or epitope-binding portion or fragment” refers to fragments of an antibody that are capable of binding to an antigen (PD-1 in this case). These fragments may be capable of the antigen-binding function and additional functions of the intact antibody. Examples of binding fragments include, but are not limited to a single-chain Fv fragment (scFv) consisting of the VL and VH domains of a single

arm of an antibody connected in a single polypeptide chain by a synthetic linker or a Fab fragment which is a monovalent fragment consisting of the VL, constant light (CL), VH and constant heavy 1 (CH1) domains. Antibody fragments can be even smaller sub-fragments and can consist of domains as small as a single CDR domain, in particular the CDR3 regions from either the VL and/or VH domains (for example see Beiboer et al., J. Mol. Biol. 296:833-49 (2000)). Antibody fragments are produced using conventional methods known to those skilled in the art. The antibody fragments are can be screened for utility using the same techniques employed with intact antibodies.

The "antigen-or epitope-binding fragments" can be derived from an antibody of the present application by a number of art-known techniques. For example, purified monoclonal antibodies can be cleaved with an enzyme, such as pepsin, and subjected to HPLC gel filtration. The appropriate fraction containing Fab fragments can then be collected and concentrated by membrane filtration and the like. For further description of general techniques for the isolation of active fragments of antibodies, see for example, Khaw, B. A. et al. J. Nucl. Med. 23:1011-1019 (1982); Rousseaux et al. Methods Enzymology, 121:663-69, Academic Press, 1986.

Papain digestion of antibodies produces two identical antigen binding fragments, called "Fab" fragments, each with a single antigen binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen combining sites and is still capable of cross-linking antigen.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other, chemical couplings of antibody fragments are also known.

"Fv" is the minimum antibody fragment which contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG-1, IgG-2, IgG-3,

and IgG-4; IgA-1 and IgA-2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, delta, epsilon, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

A "humanized antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity. Methods to obtain "humanized antibodies" are well known to those skilled in the art. (see, e.g., Queen et al., Proc. Natl Acad Sci USA, 86:10029-10032 (1989), Hodgson et al., Bio/Technology, 9:421 (1991)). A "humanized antibody" may also be obtained by a novel genetic engineering approach that enables production of affinity-matured humanlike polyclonal antibodies in large animals such as, for example, rabbits (see, e.g. U.S. Pat. No. 7,129,084).

The terms "polypeptide", "peptide", and "protein", as used herein, are interchangeable and are defined to mean a biomolecule composed of amino acids linked by a peptide bond.

The terms "a", "an" and "the" as used herein are defined to mean "one or more" and include the plural unless the context is inappropriate.

By "isolated" is meant a biological molecule free from at least some of the components with which it naturally occurs. "Isolated," when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a cell or cell culture from which it was expressed. Ordinarily, an isolated polypeptide will be prepared by at least one purification step. An "isolated antibody," refers to an antibody which is substantially free of other antibodies having different antigenic specificities.

"Recombinant" means the antibodies are generated using recombinant nucleic acid techniques in exogeneous host cells.

The term "antigen" refers to an entity or fragment thereof which can induce an immune response in an organism, particularly an animal, more particularly a mammal including a human. The term includes immunogens and regions thereof responsible for antigenicity or antigenic determinants.

Also as used herein, the term "immunogenic" refers to substances which elicit or enhance the production of antibodies, T-cells or other reactive immune cells directed against an immunogenic agent and contribute to an immune response in humans or animals. An immune response occurs when an individual produces sufficient antibodies, T-cells and other reactive immune cells against administered immunogenic compositions of the present application to moderate or alleviate the disorder to be treated.

"Specific binding" or "specifically binds to" or is "specific for" a particular antigen or an epitope means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which

generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target.

Specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KD for an antigen or epitope of at least about 10^{-4} M, at least about 10^{-5} M, at least about 10^{-6} M, at least about 10^{-7} M, at least about 10^{-8} M, at least about 10^{-9}, alternatively at least about 10^{-10} M, at least about 10^{-11} M, at least about 10^{-12} M, or greater, where KD refers to a dissociation rate of a particular antibody-antigen interaction. In some embodiments, an antibody that specifically binds an antigen will have a KD that is 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for a control molecule relative to the antigen or epitope.

Also, specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KA or Ka for an antigen or epitope of at least 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for the epitope relative to a control, where KA or Ka refers to an association rate of a particular antibody-antigen interaction.

“Homology” between two sequences is determined by sequence identity. If two sequences which are to be compared with each other differ in length, sequence identity preferably relates to the percentage of the nucleotide residues of the shorter sequence which are identical with the nucleotide residues of the longer sequence. Sequence identity can be determined conventionally with the use of computer programs. The deviations appearing in the comparison between a given sequence and the above-described sequences of the application may be caused for instance by addition, deletion, substitution, insertion or recombination.

In another aspect, the application provides pharmaceutical compositions including the antibodies, the antigen-binding fragments, and the immuno-conjugates thereof. Formulation of the pharmaceutical composition can be accomplished according to standard methodology know to those of ordinary skill in the art.

The antibodies according to the application can be prepared in a physiologically acceptable formulation and may comprise a pharmaceutically acceptable carrier, diluent and/or excipient using known techniques. For example, the antibody according to the application and as described herein including any functionally equivalent antibody or functional parts thereof, in particular, the monoclonal antibody including any functionally equivalent antibody or functional parts thereof thereof is combined with a pharmaceutically acceptable carrier, diluent and/or excipient to form a therapeutic composition.

With respect to the formulation of suitable compositions for administration to a subject such as a human patient in need of treatment, the antibodies disclosed herein may be mixed or combined with pharmaceutically acceptable carriers known in the art dependent upon the chosen route of administration. There are no particular limitations to the modes of application of the antibodies disclosed herein, and the choice of suitable administration routes and suitable compositions are known in the art without undue experimentation.

Suitable pharmaceutical carriers, diluents and/or excipients are well known in the art and include, for example, phosphate buffered saline solutions, water, emulsions such as oil/water emulsions.

"Pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use contact with the tissues of human beings or animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Formulation of the pharmaceutical composition according to the application can be accomplished according to standard methodology know to those of ordinary skill in the art.

In another aspect, the application provides methods for treating a subject using anti-PD-1 antibodies or other molecules disclosed herein. In one embodiment, the method may be used to inhibit growth of tumor cells. In one embodiment, the method may be used to stimulate a protective autoimmune response, to modify an immune response or to stimulate antigen-specific immune responses. In one embodiment, the method includes the step of administering to a subject in need of such treatment an effective amount of the mAB, the antigen-binding fragments, or composition disclosed herein.

The compositions may be administered to a subject in the form of a solid, liquid or aerosol at a suitable, pharmaceutically effective dose. Examples of solid compositions include pills, creams, and implantable dosage units. Pills may be administered orally. Therapeutic creams may be administered topically. Implantable dosage units may be administered locally, for example, at a tumor site, or may be implanted for systematic release of the therapeutic composition, for example, subcutaneously. Examples of liquid compositions include formulations adapted for injection intramuscularly, subcutaneously, intravenously, intra-arterially, and formulations for topical and intraocular administration. Examples of aerosol formulations include inhaler formulations for administration to the lungs.

The compositions may be administered by standard routes of administration. In general, the composition may be administered by topical, oral, rectal, nasal, interdermal, intraperitoneal, or parenteral (for example, intravenous, subcutaneous, or intramuscular) routes. In one embodiment, the administration may be parenterally, e.g. intravenously. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Non-aqueous solvents include without being limited to it, propylene glycol, polyethylene glycol, vegetable oil such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous solvents may be chosen from the group consisting of water, alcohol/aqueous solutions, emulsions or suspensions including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose) and others. Preservatives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, inert gases, etc.

In one embodiment, the composition may be incorporated into sustained release matrices such as biodegradable polymers, the polymers being implanted in the vicinity of where delivery is desired, for example, at the site of a tumor. The method includes administration of a single dose, administration of

repeated doses at predetermined time intervals, and sustained administration for a predetermined period of time.

A sustained release matrix, as used herein, is a matrix made of materials, usually polymers which are degradable by enzymatic or acid/base hydrolysis or by dissolution. Once inserted into the body, the matrix is acted upon by enzymes and body fluids. The sustained release matrix desirably is chosen by biocompatible materials such as liposomes, polylactides (polylactide acid), polyglycolide (polymer of glycolic acid), polylactide co-glycolide (copolymers of lactic acid and glycolic acid), polyanhydrides, poly(ortho)esters, polypeptides, hyaluronic acid, collagen, chondroitin sulfate, carboxylic acids, fatty acids, phospholipids, polysaccharides, nucleic acids, polyamino acids, amino acids such phenylalanine, tyrosine, isoleucine, polynucleotides, polyvinyl propylene, polyvinylpyrrolidone and silicone. A preferred biodegradable matrix is a matrix of one of either polylactide, polyglycolide, or polylactide co-glycolide (co-polymers of lactic acid and glycolic acid).

It is well known to those of ordinary skill in the art that the dosage of the composition will depend on various factors such as, for example, the condition of being treated, the particular composition used, and other clinical factors such as weight, size, sex and general health condition of the patient, body surface area, the particular compound or composition to be administered, other drugs being administered concurrently, and the route of administration.

The term “therapeutically effective amount” refers to the amount of antibody which, when administered to a human or animal, elicits a response which is sufficient to result in a therapeutic effect in said human or animal. The effective amount is readily determined by one of ordinary skill in the art following routine procedures.

The composition may be administered in combination with other compositions comprising a biologically active substance or compound. Example biologically active substances or compounds include without limitation compounds against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepin and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), secretase activators, β- and γ-secretase inhibitors, tau proteins, neurotransmitter, β-sheet breakers, anti-inflammatory molecules, “atypical antipsychotics” such as, for example clozapine, ziprasidone, risperidone, aripiprazole or olanzapine or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine and other drugs and nutritive supplements such as, for example, vitamin B12, cysteine, a precursor of acetylcholine, lecithin, choline, Ginkgo biloba, acyetyl-L-carnitine, idebenone, propentofylline, or a xanthine derivative, together with an antibody according to the present application and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient and instructions for the treatment of diseases.

The pharmaceutical composition may further comprise proteinaceous carriers such as, for example, serum albumin or immunoglobulin, particularly of human origin. Further biologically active agents may be present in the pharmaceutical composition of the application dependent on the intended use. Proteinaceous pharmaceutically active matter may be present in amounts between 1 ng and 10 mg per dose. Generally, the regime of administration should be in the range of between 0.1 µg and 10 mg of the

antibody according to the application, particularly in a range 1.0 µg to 1.0 mg, and more particularly in a range of between 1.0 µg and 100 µg, with all individual numbers falling within these ranges also being part of the application. If the administration occurs through continuous infusion a more proper dosage may be in the range of between 0.01 µg and 10 mg units per kilogram of body weight per hour with all individual numbers falling within these ranges also being part of the application.

The present application may be understood more readily by reference to the following detailed description of specific embodiments included herein. Although the present application has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the application.

EXAMPLES

Example 1: Generation of Anti-PD-1 Antibodies

Monoclonal antibodies against human PD-1 were developed by immunizing New Zealand white rabbits. The initial immunizations were with 100 µg of recombinant human PD-1 extracellular domain mixed 1:1 v/v with Complete Freund's Adjuvant performed by subcutaneous injection. Subsequent boosts were performed at weeks 3, 6, and 8 with 50 µg of antigen in Incomplete Freund's Adjuvant. In addition to antigen, on weeks 3, 6 and 8 the animals were also boosted with 1 x 10^6 HEK-293 cells which were transiently transfected to express full-length human PD-1.

On week 8 the serum from the animals was tested for anti-PD-1 titer by ELISA. 96-well plates were coated overnight by passive adsorption at 4°C with goat anti-rabbit IgG antibody (Jackson ImmunoResearch). The coated wells were washed and blocked with 1% milk for 1 hour at room temperature followed by a 1 hour room temperature incubation with human PD-1 extracellular domain human Fc domain fusion protein. After washing, undiluted serum is added to the wells and serially diluted 1:10 across the plate over a total of 7 wells each. After a 1 hour incubation at room temperature the plates were washed and then incubated with a goat anti-human IgG Fc-specific horseradish peroxidase-conjugated antibody (Jackson ImmunoResearch). The plates were washed and then incubated with Ultra TMB Substrate (Fisher Scientific) for 30 minutes at room temperature. The signal in the wells was detected by an absorbance plate reader at 450 nm wave length to generate a titer curve. The anti-PD-1 titer is compared to an ELISA performed with serum from the same animal that was obtained prior to immunization.

On week 9, Rabbits with significant anti-PD-1 titers were selected for harvest and the generation of monoclonal antibodies.

B-cells from anti-PD-1 positive rabbits were harvested from the spleen and lymph nodes at week 12 following the initial immunization. The B cells were cultured for one week in 96-well plates to allow their differentiation into plasma cells and for secretion of antibodies. The supernatants from these plasma cell cultures were screened by ELISA as described above for the presence of PD-1-specific antibodies as shown in FIGURE 1.

B cells secreting anti-PD-1 antibodies were isolated from positive wells using a magnetic capture method. Briefly, streptavidin magnetic beads (ThermoFisher Scientific) were coated with biotin-conjugated human PD-1 extracellular domain protein. The coated beads were incubated with the cells from an anti-PD-1 positive well. The bead cell complexes were washed using a magnet to remove any non-specific cells and the bead cell complexes were added directly to a tube containing an RT-PCR master mix.

The light and heavy chain variable sequences were amplified by multiplex RT-PCR using degenerate primers designed to anneal to leader sequences and the constant regions of rabbit IgG and rabbit kappa sequences. Secondary PCR was performed separately for the light and heavy chains using nested primers containing restriction sites. Amplicons from the variable heavy chain PCR were cloned into an expression vector containing human IgG1. Light chain amplicons were cloned into an expression vector containing human IgK. Resulting clones were sequenced and analyzed.

The heavy and light chain expression plasmids generated from each well were transiently co-transfected into HEK-293 cells to produce rabbit/human chimeric antibodies. The resulting supernatants containing the recombinant antibodies were clarified by centrifugation.

Recombinant antibody supernatants were confirmed to contain anti-PD-1 antibodies using bio-layer interferometry analysis on a ForteBio Octet Red 96 instrument. Anti-human Fc biosensors (Pall ForteBio) were used to capture antibodies in the supernatants. Association to PD-1 was observed by real-time interferometry by placing the biosensors in wells containing recombinant human PD-1 extracellular domain protein. Dissociation was measured after transfer of the biosensors into wells containing 10X kinetics buffer (Pall ForteBio). The software provided by the manufacturer was used to analyze the interferometry data.

Humanized forms for anti-PD-1 antibodies AB1 – AB5 were produced and are indicated by an appended “HU” following their original designation. For example AB1HU is the humanized form of antibody AB1.

Example 2: Binding Affinities of anti-PD-1 Antibodies

The binding kinetics of selected anti-PD-1 antibodies AB1 – AB5 and AB1HU – AB5HU was determined by bio-layer interferometry analysis on a ForteBio Octet Red 96 instrument. First, purified antibodies were produced by protein A chromatography using HEK-293 transiently-transfected antibody supernatants. This assay was performed by immobilizing the purified antibodies to anti-human Fc biosensors. PD-1 binding to and dissociation from the biosensors was then observed at various concentrations of PD-1. Specifically, eight anti-human Fc biosensors were placed into wells containing the same purified antibody for 5 minutes. Biosensors were equilibrated in kinetics buffer (Pall ForteBio) for 1 minute to establish a baseline. Association of PD-1 was observed by placing the biosensors into wells containing various concentrations of human PD-1 extracellular domain for 5 minutes. Dissociation was measured after transfer of the biosensors into kinetics buffer and monitoring the interferometry signals for 15 minutes. All steps of the assay were performed at 30° C with shaking at 1000 RPM. The on and off rates (kon and koff) and the equilibrium binding constant KD were determined using the software provided by

the manufacturer and were fit using a 1:1 binding global fit model comprising several of the concentrations tested. Results of the kinetic studies are presented in TABLE 1.

TABLE 1

Ab	KD [M]	Kon [1/Ms]	Koff [1/s]
AB1	4.80E-09	3.60E+04	1.60E-04
AB1HU	1.60E-08	1.20E+04	2.00E-04
AB2	8.60E-08	6.70E+04	5.70E-03
AB2HU	1.70E-08	8.90E+04	1.50E-03
AB3	9.00E-10	1.30E+05	1.20E-04
AB3HU	1.10E-09	1.30E+05	1.40E-04
AB4	9.20E-09	1.10E+05	1.00E-03
AB4HU	4.30E-09	8.70E+04	3.80E-04
AB5	3.30E-09	7.80E+04	2.60E-04
AB5HU	6.60E-09	6.10E+04	4.00E-04

Example 3: Antibodies Binding to Cell-Surface Expressed PD-1

The human PD-1 gene was subcloned into the pcDNA3.1 mammalian expression vector and transfected into the Jurkat human T cell line. A clonal cell population expressing high levels of huPD-1 was generated by G418 drug selection and single-cell sorting. This Jurkat/huPD-1 clonal cell line was labeled with FVS520 viability dye (BD Biosciences, 1:2000 dilution) for 15 minutes at room temperature. The labeled cells were then diluted in FACS buffer (2% FBS in PBS), added to V-bottom 96-well plates (50,000 cells per well), and stained with 0-25nM anti-huPD1 or isotype control antibody on ice for 30 minutes. Cells were washed to remove excess primary antibody, then labeled with Alexa luor 647-conjugated goat anti-human Fc secondary antibody (Jackson Immunoresearch, 1:1600 dilution) on ice for 20 minutes. The labeled cells were then washed with FACS buffer before acquisition on a BD FACSCalibur flow cytometer equipped with the Cytek AMS plate loader system. AB1HU – AB5HU results in this assay are shown in FIGURE 2. Data points show the median fluorescence intensity (MFI) on the AF647 channel after gating on live cells. Nonlinear regression methods were used to fit curves to each data set, and error bars represent the standard deviation of duplicate samples.

Example 4: Antibody-mediated blocking of huPD-1/huPD-L1 interactions

The Jurkat/huPD-1 clonal cell line was labeled with FVS520 viability dye (BD Biosciences, 1:2000 dilution) for 15 minutes at room temperature. The labeled cells were then diluted in FACS buffer (2% FBS in PBS), added to V-bottom 96-well plates (50,000 cells per well), and stained with 0-100nM anti-huPD1 or isotype control antibody on ice for 30 minutes. Cells were washed to remove excess antibody, then labeled with 15ug/ml His-tag purified, monobiotinylated huPD-1 on ice for 30 minutes. Cells were washed again with FACS buffer, then labeled with 0.25ug/ml APC-conjugated streptavidin on ice for 20 minutes. Cells were washed again with before acquisition on a BD FACSCalibur flow cytometer equipped with the Cytek AMS plate loader system. AB1HU – AB5HU results in this assay are shown in FIGURE **3**. and show the median fluorescence intensity (MFI) on the APC channel after gating on live cells. Error bars represent the standard deviation of duplicate samples.

Example 5: Antibody-mediated blocking of huPD-1/huPD-L2 interactions

The Jurkat/huPD-1 clonal cell line was labeled with FVS520 viability dye (BD Biosciences, 1:2000 dilution) for 15 minutes at room temperature. The labeled cells were then diluted in FACS buffer (2% FBS in PBS), added to V-bottom 96-well plates (50,000 cells per well), and stained with 0-100nM anti-huPD1 or isotype control antibody on ice for 30 minutes. Cells were washed to remove excess antibody, then labeled with 15ug/ml His-tag purified, monobiotinylated huPD-L2 on ice for 30 minutes. Cells were washed with FACS buffer, then labeled with 0.25ug/ml APC-conjugated streptavidin on ice for 20 minutes. Cells were washed again with FACS buffer before acquisition on a FACSCalibur flow cytometer equipped with the Cytek AMS plate loader system. AB1HU – AB5HU results in this assay are shown in FIGURE **7**. Data show the median fluorescence intensity (MFI) on the APC channel after gating on live cells. Error bars represent the standard deviation of duplicate samples.

Example 6: Effect of PD-1 antibodies on human T cell activation

Human PBMCs (100,000 cells/well) from a healthy donor were combined with 100ng/ml superantigen (staphylococcal enterotoxin B (SEB), Toxin Technology, Inc.) and 0-100nM anti-huPD1 or isotype control antibody in complete RPMI media in flat-bottom 96-well plates. The assay plates were incubated in a 37oC, 5% CO2 incubator for 3 days, then supernatant samples were tested for the presence of huIL-2 using a commercially available kit (R&D Systems). AB1HU – AB5HU results in this assay are shown in FIGURE 4. Data points represent the huIL-2 values for the antibodies tested, which were interpolated from a standard ELISA curve. Nonlinear regression methods were used to fit curves to each data set, and error bars represent the standard deviation of quadruplicate samples.

While the application has been particularly shown and described as referenced to the embodiments thereof, those skilled in the art will understand that the foregoing and other changes in form and detail may be made therein without departing from the spirit and scope. All references cited or referred to in this application are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

SI-11 ANTI-PD-1 ANTIBODY SEQUENCES

SEQ ID NO:1

AB1 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAAGTGCTGACCCAGACTGCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGTC
AGAGTGTTTATGATAACAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCATGCTCCTGATCTATAC
AGTATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC
AGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCACTTATTATAGTAGTGGTTGGAACTTTGCTT
TCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATG
AGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG
GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCT
ACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC
ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:2

AB1 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

CAAGTGCTGACCCAGACTGCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGTC
AGAGTGTTTATGATAACAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCATGCTCCTGATCTATAC
AGTATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC
AGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAGGCACTTATTATAGTAGTGGTTGGAACTTTGCTT
TCGGCGGAGGGACCGAGGTGGTGGTCAAA

SEQ ID NO:3

AB1 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

QVLTQTASSVSAAVGGTVTISCQSSQSVYDNNWLAWYQQKPGQPPMLLIYTVSTLASGVSSRFKGSGSGTQFTLTISGV
QCDDAATYYCQGTYYSSGWNFAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:4

AB1 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QVLTQTASSVSAAVGGTVTISCQSSQSVYDNNWLAWYQQKPGQPPMLLIYTVSTLASGVSSRFKGSGSGTQFTLTISGV
QCDDAATYYCQGTYYSSGWNFAFGGGTEVVVK

SEQ ID NO:5

AB1 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCAAAGCCTCTGG
ATTCGACTTCAGTAGCGGCTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTTGATCGCATG
CATTTATGCTGGTACTAGTGGTAGTACTTCCTACGCGAGCTGGGCGAGAGGCCGATTCACCATCTCCGAAACCTCG
TCGACCACGGTGACTCTGCAAATGACCAGTCTGACAGCCGCGGACTCGGCCACCTATTTCTGTGCGAGAAATCTTT
ACACTTACAATAGCTTGTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCT
TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC
CGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTC
CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC
GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGC
CCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA
TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACT
GGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCG
TGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA
AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:6

AB1 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCAAAGCCTCTGG
ATTCGACTTCAGTAGCGGCTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTTGATCGCATG
CATTTATGCTGGTACTAGTGGTAGTACTTCCTACGCGAGCTGGGCGAGAGGCCGATTCACCATCTCCGAAACCTCG
TCGACCACGGTGACTCTGCAAATGACCAGTCTGACAGCCGCGGACTCGGCCACCTATTTCTGTGCGAGAAATCTTT
ACACTTACAATAGCTTGTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO:7

AB1 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSLEESGGDLVKPEGSLTLTCKASGFDFSSGYWICWVRQAPGKGLELIACIYAGTSGSTSYASWARGRFTISETSSTTVTL
QMTSLTAADSATYFCARNLYTYNSLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:8

AB1 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSLEESGGDLVKPEGSLTLTCKASGFDFSSGYWICWVRQAPGKGLELIACIYAGTSGSTSYASWARGRFTISETSSTTVTL
QMTSLTAADSATYFCARNLYTYNSLWGQGTLVTVSS

SEQ ID NO:9

AB1HU HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTTATGATAACAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA
TACAGTATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACC
ATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCACTTATTATAGTAGTGGTTGGAACTTTGC
TTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT
GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACC
TACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACC
CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:10

AB1HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTTATGATAACAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA
TACAGTATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACC
ATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCACTTATTATAGTAGTGGTTGGAACTTTGC
TTTCGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:11

AB1HU HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQSSQSVYDNNWLAWYQQKPGKAPKLLIYTVSTLASGVPSRFSGSGSGTEFTLTISSL
QPDDFATYYCQGTYYSSGWNFAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA
LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:12

AB1HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQSSQSVYDNNWLAWYQQKPGKAPKLLIYTVSTLASGVPSRFSGSGSGTEFTLTISSL
QPDDFATYYCQGTYYSSGWNFAFGGGTKVEIK

SEQ ID NO:13

AB1HU HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCGACTTCAGTAGCGGCTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTTGATCGC
ATGCATTTATGCTGGTACTAGTGGTAGTACTTCCTACGCGAGCTGGGCGAGAGGCAGATTCACCATCTCCGAAACC
TCCAAGAACACGGTGACTCTTCAAATGAACAGCCTGAGAGCCGAGGACTCGGCTGTGTATTACTGTGCGAGAAAT
CTTTACACTTACAATAGCTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCG
GTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT
TCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACAC
ATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACC
CTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC
AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGT
ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCA
ACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACA
CCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAG
CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT
GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:14

AB1HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCGACTTCAGTAGCGGCTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTTGATCGC
ATGCATTTATGCTGGTACTAGTGGTAGTACTTCCTACGCGAGCTGGGCGAGAGGCAGATTCACCATCTCCGAAACC
TCCAAGAACACGGTGACTCTTCAAATGAACAGCCTGAGAGCCGAGGACTCGGCTGTGTATTACTGTGCGAGAAAT
CTTTACACTTACAATAGCTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:15

AB1HU HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCAASGFDFSSGYWICWVRQAPGKGLELIACIYAGTSGSTSYASWARGRFTISETSKNTV
TLQMNSLRAEDSAVYYCARNLYTYNSLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:16

AB1HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCAASGFDFSSGYWICWVRQAPGKGLELIACIYAGTSGSTSYASWARGRFTISETSKNTV
TLQMNSLRAEDSAVYYCARNLYTYNSLWGQGTLVTVSS

SEQ ID NO:17

AB2 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGTCTGCAGTTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTTACAGCTACTTAAACTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTG
CATCCAATCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGTAGTTGGTTGAGTGGTGCTGTTGGTAATGCTTTC
GGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGA
AGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTAC
AGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT
CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:18

AB2 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGTCTGCAGTTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTTACAGCTACTTAAACTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTG
CATCCAATCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGTAGTTGGTTGAGTGGTGCTGTTGGTAATGCTTTC
GGCGGAGGGACCGAGGTGGTGGTCAAA

SEQ ID NO:19

AB2 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DVVMTQTPASVSAVVGGTVTIKCQASQSIYSYLNWYQQKPGQPPKLLIYGASNLASGVSSRFKGSGSGTEFTLTISDLEC
ADAATYYCQCSWLSGAVGNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:20

AB2 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DVVMTQTPASVSAVVGGTVTIKCQASQSIYSYLNWYQQKPGQPPKLLIYGASNLASGVSSRFKGSGSGTEFTLTISDLEC
ADAATYYCQCSWLSGAVGNAFGGGTEVVVK

SEQ ID NO:21

AB2 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAACTGGTGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCTTCT
GGATTCTCCTTCAGTAGCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATG
CATTACGACTGGTAGTGGTAGCACTTACTACGCGAGCTGGGCGAAGCGCCGATTCACCATCTCCAAAACCTCGTCG
ACCACGGTGACTCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTACGAGAGCATTTGACT
TGTGGGGCCCGGGGACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG
TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTC
CCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
AGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCA
CCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC
TGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCG
TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTC
ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAG
GAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTC
TATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:22

AB2 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAACTGGTGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCTTCT
GGATTCTCCTTCAGTAGCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATG
CATTACGACTGGTAGTGGTAGCACTTACTACGCGAGCTGGGCGAAGCGCCGATTCACCATCTCCAAAACCTCGTCG
ACCACGGTGACTCTGCAAATGACCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTACGAGAGCATTTGACT
TGTGGGGCCCGGGGACCCTGGTCACCGTCTCGAGC

SEQ ID NO:23

AB2 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QEQLVESGGGLVQPEGSLTLTCTASGFSFSSYWMCWVRQAPGKGLEWIGCITTGSGSTYYASWAKRRFTISKTSSTTVT
LQMTSLTAADTATYFCTRAFDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC

KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:24

AB2 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQLVESGGGLVQPEGSLTLTCTASGFSFSSYWMCWVRQAPGKGLEWIGCITTGSGSTYYASWAKRRFTISKTSSTTVT
LQMTSLTAADTATYFCTRAFDLWGPGTLVTVSS

SEQ ID NO:25

AB2HU HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTTACAGCTACTTAAACTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGC
ATCCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAAAGCAGTTGGTTGAGTGGTGCTGTTGGTAATGCTTTCG
GCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC
AGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAA
GGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:26

AB2HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTTACAGCTACTTAAACTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGC
ATCCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAAAGCAGTTGGTTGAGTGGTGCTGTTGGTAATGCTTTCG
GCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:27

AB2HU HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQASQSIYSYLNWYQQKPGKAPKLLIYGASNLASGVPSRFSGSGSGTDFTLTISSLQPE
DFATYYCQSSWLSGAVGNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:28

AB2HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQASQSIYSYLNWYQQKPGKAPKLLIYGASNLASGVPSRFSGSGSGTDFTLTISSLQPE
DFATYYCQSSWLSGAVGNAFGGGTKVEIK

SEQ ID NO:29

AB2HU HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCT
GGATTCTCCTTTAGCAGCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATG
CATTACGACTGGTAGTGGTAGCACTTACTACGCGAGCTGGGCGAAGCGCCGGTTCACCATCTCCAAAGACAATTCC
AAGAACACGGTGACTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTACGAGAGCATTT
GACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCA
CCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAA
GCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCC
AGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC
GTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCA
GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC
CGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:30

AB2HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCT
GGATTCTCCTTTAGCAGCTACTGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATG
CATTACGACTGGTAGTGGTAGCACTTACTACGCGAGCTGGGCGAAGCGCCGGTTCACCATCTCCAAAGACAATTCC
AAGAACACGGTGACTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTACGAGAGCATTT
GACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:31

AB2HU HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA1 CONSTANT DOMAIN IS UNDERLINED

QEQLLESGGGLVQPGGSLRLSCTASGFSFSSYWMCWVRQAPGKGLEWIGCITTGSGSTYYASWAKRRFTISKDNSKNT
VTLQMNSLRAEDTAVYYCTRAFDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:32

AB2HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQLLESGGGLVQPGGSLRLSCTASGFSFSSYWMCWVRQAPGKGLEWIGCITTGSGSTYYASWAKRRFTISKDNSKNT
VTLQMNSLRAEDTAVYYCTRAFDLWGQGTLVTVSS

SEQ ID NO:33

AB3 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAAGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTC
CGAGTGTTTATAGTAACTACTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATTATGCA
TCCACTCTGGCATCTGGGGTCCCTTCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCG
ACGTGCAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTTATAGTAGTAGTACTCGTGCTTTCGGCGGAG
GGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA
ATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT
AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:34

AB3 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

CAAGTGCTGACCCAGACTCCATCTCCCGTGTCTGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTC
CGAGTGTTTATAGTAACTACTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATTATGCA
TCCACTCTGGCATCTGGGGTCCCTTCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCG
ACGTGCAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTTATAGTAGTAGTACTCGTGCTTTCGGCGGAG
GGACCGAGGTGGTGGTCAAA

SEQ ID NO:35

AB3 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

QVLTQTPSPVSAAVGGTVSISCQSSPSVYSNYLSWFQQKPGQPPKLLIYYASTLASGVPSRFKGSGSGTQFTLTISDVQCD
DAATYYCAGGYSSSTRAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:36

AB3 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QVLTQTPSPVSAAVGGTVSISCQSSPSVYSNYLSWFQQKPGQPPKLLIYYASTLASGVPSRFKGSGSGTQFTLTISDVQCD
DAATYYCAGGYSSSTRAFGGGTEVVVK

SEQ ID NO:37

AB3 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAGGTGAAGGAGACCGGGGGAGGCCTGGTCCAGCCTGGGGGATCCCTGACACTCTCCTGCAAAGCCTC
TGGATTTACCATCAGTAGCTATGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCAT
TGATTTTTCCTGGTATTGGTTTCAAAGACTACGCGAGCTGGGTGAATGGCCGATTCACCCTCTCCAGCGACAACGC
CCAGAACACTGTGGAACTTCAGATGAACAGTCTGACAGCGGCGGACACGGCCGCCTATTTCTGTGCGAGAGATTT
GGACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGC
ACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT
GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC
GTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC
CGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:38

AB3 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAGGTGAAGGAGACCGGGGGAGGCCTGGTCCAGCCTGGGGGATCCCTGACACTCTCCTGCAAAGCCTC
TGGATTTACCATCAGTAGCTATGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCAT
TGATTTTTCCTGGTATTGGTTTCAAAGACTACGCGAGCTGGGTGAATGGCCGATTCACCCTCTCCAGCGACAACGC

CCAGAACACTGTGGAACTTCAGATGAACAGTCTGACAGCGGCGGACACGGCCGCCTATTTCTGTGCGAGAGATTT
GGACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC

SEQ ID NO:39

AB3 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QEQVKETGGGLVQPGGSLTLSCKASGFTISSYGVSWVRQAPGKGLEWIALIFPGIGFKDYASWVNGRFTLSSDNAQNT
VELQMNSLTAADTAAYFCARDLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:40

AB3 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQVKETGGGLVQPGGSLTLSCKASGFTISSYGVSWVRQAPGKGLEWIALIFPGIGFKDYASWVNGRFTLSSDNAQNT
VELQMNSLTAADTAAYFCARDLDLWGQGTLVTVSS

SEQ ID NO:41

AB3HU HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCCGAGTGTTTATAGTAACTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATTAT
GCATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATAGTAGTAGTACTCGTGCTTTCGGCGG
AGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTG
GATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:42

AB3HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCCGAGTGTTTATAGTAACTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATTAT
GCATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATAGTAGTAGTACTCGTGCTTTCGGCGG
AGGGACCAAGGTGGAGATCAAA

SEQ ID NO:43

AB3HU HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSPSVYSNYLSWYQQKPGKVPKLLIYYASTLASGVPSRFSGSGSGTDFTLTISSLQPE
DVATYYCAGGYSSSTRAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:44

AB3HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSPSVYSNYLSWYQQKPGKVPKLLIYYASTLASGVPSRFSGSGSGTDFTLTISSLQPE
DVATYYCAGGYSSSTRAFGGGTKVEIK

SEQ ID NO:45

AB3HU HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAGGTGAAGGAGACCGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCATCAGCAGCTATGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCAT
TGATTTTTCCCGGGATTGGTTTCAAAGACTACGCGAGCTGGGTGAATGGCCGGTTCACCCTCTCCAGCGACAACGC
CCAGAACACTGTGGAACTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAGATTT
GGACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGC
ACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT
GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC
GTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC
CGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:46

AB3HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAGGTGAAGGAGACCGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCATCAGCAGCTATGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCAT
TGATTTTTCCCGGGATTGGTTTCAAAGACTACGCGAGCTGGGTGAATGGCCGGTTCACCCTCTCCAGCGACAACGC
CCAGAACACTGTGGAACTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAGATTT
GGACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:47

AB3HU HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA1 CONSTANT DOMAIN IS UNDERLINED

QEQVKETGGGLVQPGGSLRLSCAASGFTISSYGVSWVRQAPGKGLEWVALIFPGIGFKDYASWVNGRFTLSSDNAQN
TVELQMNSLRAEDTAVYYCARDLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:48

AB3HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQVKETGGGLVQPGGSLRLSCAASGFTISSYGVSWVRQAPGKGLEWVALIFPGIGFKDYASWVNGRFTLSSDNAQN
TVELQMNSLRAEDTAVYYCARDLDLWGQGTLVTVSS

SEQ ID NO:49

AB4 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCCTTGTGATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCA
GTCAGAACATTTACAGCAATTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAGCCTCCTGATCTACCAGGC
ATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAGCGGCAGTGGATATGGGACAGAGTTCACTCTCACCATCAGC
GACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAAGGCGGTTATTATAGTGCTGCCCTTAATACTTTCGGCG
GAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT
GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGT
GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:50

AB4 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCCTTGTGATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCA
GTCAGAACATTTACAGCAATTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAGCCTCCTGATCTACCAGGC

ATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAGCGGCAGTGGATATGGGACAGAGTTCACTCTCACCATCAGC
GACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAAGGCGGTTATTATAGTGCTGCCCTTAATACTTTCGGCG
GAGGGACCGAGGTGGTGGTCAAA

SEQ ID NO:51

AB4 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

ALVMTQTPSSVSAAVGGTVTINCQASQNIYSNLAWYQQKPGQPPSLLIYQASTLASGVSSRFSGSGYGTEFTLTISDLEC
ADAATYYCQGGYYSAALNTFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:52

AB4 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

ALVMTQTPSSVSAAVGGTVTINCQASQNIYSNLAWYQQKPGQPPSLLIYQASTLASGVSSRFSGSGYGTEFTLTISDLEC
ADAATYYCQGGYYSAALNTFGGGTEVVVK

SEQ ID NO:53

AB4 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGATACATT
GGTGATACTACTGGCATAGCCTACGCGAGCTGGGCGAATGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAGATCACCAGTCCGACAACCGGGGACACGGCCACCTATTTCTGTGCCAGAGGCTGGTCCTACTTAGAC
ATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG
TGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTC
CCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
AGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCA
CCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC
TGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCG
TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTC
ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAG
GAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTC
TATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:54

AB4 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGATACATT
GGTGATACTACTGGCATAGCCTACGCGAGCTGGGCGAATGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAGATCACCAGTCCGACAACCGGGGACACGGCCACCTATTTCTGTGCCAGAGGCTGGTCCTACTTAGAC
ATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGC

SEQ ID NO:55

AB4 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSLEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGKGLEYIGYIGDTTGIAYASWANGRFTISKTSTTVDLKITS
PTTGDTATYFCARGWSYLDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:56

AB4 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSLEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGKGLEYIGYIGDTTGIAYASWANGRFTISKTSTTVDLKITS
PTTGDTATYFCARGWSYLDIWGQGTLVTVSS

SEQ ID NO:57

AB4HU HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCCTTGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAACATTTACAGCAATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATCAGGC
CTCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAGGCGGTTATTATAGTGCTGCCCTTAATACTTTCGGCG
GAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT
GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGT
GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:58

AB4HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCCTTGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAACATTTACAGCAATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATCAGGC
CTCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATATGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAGGCGGTTATTATAGTGCTGCCCTTAATACTTTCGGCG
GAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:59

AB4HU HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

ALVMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPGKVPKLLIYQASTLASGVPSRFSGSGYGTDFTLTISSLQPE
DVATYYCQGGYYSAALNTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:60

AB4HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

ALVMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPGKVPKLLIYQASTLASGVPSRFSGSGYGTDFTLTISSLQPE
DVATYYCQGGYYSAALNTFGGGTKVEIK

SEQ ID NO:61

AB4HU HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGCTA
CATTGGTGATACTACTGGCATAGCCTACGCGAGCTGGGCGAATGGCAGATTCACCATCTCCAAAGACAATACCAA
GAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGCTGGT
CCTACTTAGACATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCC
CCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA
ACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCA
CCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:62

AB4HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGCTA
CATTGGTGATACTACTGGCATAGCCTACGCGAGCTGGGCGAATGGCAGATTCACCATCTCCAAAGACAATACCAA
GAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGCTGGT
CCTACTTAGACATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGC

SEQ ID NO:63

AB4HU HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSSYAMSWVRQAPGKGLEYIGYIGDTTGIAYASWANGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARGWSYLDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:64

AB4HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSSYAMSWVRQAPGKGLEYIGYIGDTTGIAYASWANGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARGWSYLDIWGQGTLVTVSS

SEQ ID NO:65

AB5 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGACTCCATCCTCCGTGTCTGCCGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCA
GTCAGAGCATTAACAACCAACTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGC
ATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCACCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGC
GGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCATGTTCATTATTGCAGTGGTGGTAGTTGTTTTTGGGCTTT
CGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGG
AAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA
CAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:66

AB5 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGACTCCATCCTCCGTGTCTGCCGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCA
GTCAGAGCATTAACAACCAACTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATGGTGC
ATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCACCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGC
GGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCATGTTCATTATTGCAGTGGTGGTAGTTGTTTTTGGGCTTT
CGGCGGAGGGACCGAGGTGGTGGTCAAA

SEQ ID NO:67

AB5 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AYDMTQTPSSVSAAVGGTVTINCQASQSINNQLSWYQQKPGQPPKLLIYGASTLASGVPSRFTGSGSGTEFTLTISGVQ
CDDAATYYCHVHYCSGGSCFWAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:68

AB5 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

AYDMTQTPSSVSAAVGGTVTINCQASQSINNQLSWYQQKPGQPPKLLIYGASTLASGVPSRFTGSGSGTEFTLTISGVQ
CDDAATYYCHVHYCSGGSCFWAFGGGTEVVVK

SEQ ID NO:69

AB5 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTC
TGGATTCTCCTTCAGTAGCAGCCACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGC
ATGCATTTATACTGGTAGTATTGATGTCTTTTACTGTGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAACCCT
CGTCGACCACGGTGACTCTGCAAGTGCCCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGCCG
CTAATACTGATACTACCTACTTTAACTTGTGGGGCCCAGGGACCCTCGTCACCGTCTCGAGCGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCT
ACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAA
CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGG
TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGG
TGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG

CTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO:70

AB5 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTC
TGGATTCTCCTTCAGTAGCAGCCACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGC
ATGCATTTATACTGGTAGTATTGATGTCTTTTACTGTGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAACCCT
CGTCGACCACGGTGACTCTGCAAGTGCCCAGTCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGCCG
CTAATACTGATACTACCTACTTTAACTTGTGGGGCCCAGGGACCCTCGTCACCGTCTCGAGC

SEQ ID NO:71

AB5 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QEQLEESGGDLVKPEGSLTLTCTASGFSFSSSHWICWVRQAPGKGLEWIACIYTGSIDVFYCASWAKGRFTISKPSSTTVT
LQVPSLTAADTATYFCARAANTDTTYFNLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:72

AB5 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQLEESGGDLVKPEGSLTLTCTASGFSFSSSHWICWVRQAPGKGLEWIACIYTGSIDVFYCASWAKGRFTISKPSSTTVT
LQVPSLTAADTATYFCARAANTDTTYFNLWGPGTLVTVSS

SEQ ID NO:73

AB5HU HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCA
GTCAGAGCATTAACAACCAACTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATGGTGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCACCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCATGTTCATTATTGCAGTGGTGGTAGTTGTTTTTGGGCTTT
CGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGG
AAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA
CAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:74

AB5HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCA
GTCAGAGCATTAACAACCAACTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATGGTGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCACCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCATGTTCATTATTGCAGTGGTGGTAGTTGTTTTTGGGCTTT
CGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:75

AB5HU HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AYDMTQSPSSLSASVGDRVTINCQASQSINNQLSWYQQKPGKVPKLLIYGASTLASGVPSRFTGSGSGTDFTLTISSLQP
EDVATYYCHVHYCSGGSCFWAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:76

AB5HU HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

AYDMTQSPSSLSASVGDRVTINCQASQSINNQLSWYQQKPGKVPKLLIYGASTLASGVPSRFTGSGSGTDFTLTISSLQP
EDVATYYCHVHYCSGGSCFWAFGGGTKVEIK

SEQ ID NO:77

AB5HU HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCTTTAGCAGCAGCCACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGC
ATGCATTTATACTGGTAGTATTGATGTCTTTTACTACGCGAGCTGGGCGAAAGGCCGGTTCACCATCTCCAGAGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGA
GCCGCTAATACTGATACTACCTACTTTAACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCA
AGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCC
CGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCA
GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCT
GAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGT
ACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGT
GCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC

CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GT

SEQ ID NO:78

AB5HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCTTTAGCAGCAGCCACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGC
ATGCATTTATACTGGTAGTATTGATGTCTTTTACTACGCGAGCTGGGCGAAAGGCCGGTTCACCATCTCCAGAGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGA
GCCGCTAATACTGATACTACCTACTTTAACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:79

AB5HU HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA1 CONSTANT DOMAIN IS UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSHWICWVRQAPGKGLEWIACIYTGSIDVFYYASWAKGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARAANTDTTYFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE
AAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:80

AB5HU HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLEMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSHWICWVRQAPGKGLEWIACIYTGSIDVFYYASWAKGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARAANTDTTYFNLWGQGTLVTVSS

CLAIMS

What is claimed is:

1. An isolated mAb or antigen-binding fragment thereof having a binding specificity to human PD-1, comprising an amino acid sequence having a percentage homology with SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, or SEQ ID NO:80, wherein the percentage homology is not less than 90%

2. The isolated mAb or antigen-binding fragment according to Claim 1, wherein the percentage homology is not less than 98%.

3. The isolated mAb or antigen-binding fragment according to Claim 1, having a binding affinity to human PD-1 with a Kd not greater than 70nM.

4. The isolated mAb or antigen-binding fragment according to Claim 1, exhibiting one or more functional properties selected from high affinity binding to human PD-1, inhibiting binding of human PD-L1 to PD-1, enhancing T cell activation, stimulating antibody response, reversing the suppressive function of an immunosuppressive cell, or a combination thereof.

6. The isolated mAb or antigen-binding fragment according to Claim 4, wherein the enhancing T-cell activation comprises T-cell proliferation, IFN-γ and/or IL-2 secretion, or a combination thereof.

8. The isolated mAb or antigen-binding fragment thereof according to claim 1, wherein the isolated mAb is a humanized antibody, a chimeric antibody, or a recombinant antibody.

9. The isolated mAb or antigen-binding fragment thereof according to claim 1, wherein the isolated mAb comprises an IgG.

10. The isolated mAb or antigen-binding fragment thereof according to claim 1, wherein the antigen-binding fragment comprises a Fv, a Fab, a F(ab')2, a scFV or a scFV2 fragment.

11. The isolated mAb or antigen-binding fragment thereof according to claim 1, wherein the isolated mAb comprises a bispecific antibody, tri-specific antibody, or multi-specific antibody.

12. An IgG1 heavy chain for the isolated mAb or antigen-binding fragment having a binding specificity to PD1, comprising an amino acid sequence having a percentage homology with SEQ ID NO:7, SEQ ID NO:15, SEQ ID NO:23, SEQ ID NO:31, SEQ ID NO:39, SEQ ID NO:47, SEQ ID NO:55, SEQ ID NO:63, SEQ ID NO:71, or SEQ ID NO:79, wherein the percentage homology is not less than 98%.

13. A kappa light chain for the isolated mAb or antigen-binding fragment having a binding specificity to PD1, comprising an amino acid sequence having a percentage homology with SEQ ID NO:3, SEQ ID NO:11, SEQ ID NO:19, SEQ ID NO:27, SEQ ID NO:35, SEQ ID NO:43, SEQ ID NO:51, SEQ ID NO:59, SEQ ID NO:67, or SEQ ID NO:75, wherein the percentage homology is not less than 98%.

14. A variable light chain for the isolated mAb or antigen-binding fragment having a binding specificity to PD1, comprising an amino acid sequence having a percentage homology with SEQ ID NO:4, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:36, SEQ ID NO:44, SEQ ID NO:52, SEQ ID NO:60, SEQ ID NO: 68, or SEQ ID NO:76, wherein the percentage homology is not less than 98%.

15. A variable heavy chain for the isolated mAb or antigen-binding fragment having a binding specificity to PD1, comprising an amino acid sequence having a percentage homology with SEQ ID NO:8, SEQ ID NO:16, SEQ ID NO:24, SEQ ID NO:32, SEQ ID NO:40, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:64, SEQ ID NO:72, or SEQ ID NO:80, wherein the percentage homology is not less than 98%.

16. An isolated nucleic acid encoding the isolated mAb or antigen-binding fragment according to Claim 1, the IgG1 heavy Chain of Claim 12, the kappa light chain of Claim 13, the variable light chain of Claim 14, or the variable heavy chain of Claim 15.

17. An expression vector comprising the isolated nucleic acid of Claim 16.

18. A host cell comprising the nucleic acid of Claim 14, wherein the host cell is a prokaryotic cell or a eukaryotic cell.

19. A method of producing an antibody comprising culturing the host cell of Claim 18, so that the antibody is produced.

20. An immuno-conjugate, comprising the isolated mAb or an antigen-binding fragment thereof according to Claim 1 and a drug unit, wherein a covalent bond selected from an ester bond, an ether bond, an amine bond, an amide bond, a disulphide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, a hydrazone bond or a combination thereof.

21. The immuno-conjugate according to claim 20, wherein the drug unit is selected from a cytotoxic agent, an immune regulatory reagent, a combination thereof.

22. The immuno-conjugate according to claim 21, wherein the cytotoxic agent is selected from a growth inhibitory agent or a chemotherapeutic agent from a class of tubulin binders, DNA intercalators, DNA alkylators, enzyme inhibitors, immune modulators, antimetabolite agents, radioactive isotopes, or a combination thereof.

23. The immuno-conjugate according to claim 21, wherein the cytotoxic agent is selected from a calicheamicin, ozogamicin, monomethyl auristatin E, emtansine, a derivative or a combination thereof.

24. The immuno-conjugate according to claim 21, wherein the immune regulatory reagents activate or suppress immune cells, T cell, NK cell, B cell, macrophage, or dendritic cell.

25. A pharmaceutical composition, comprising the isolated mAb or antigen-binding fragment thereof according to Claim 1 or the immuno-conjugate of Claim 20 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of Claim 25, further comprising a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a radioactive isotope, a toxin, a therapeutic agent, or a combination thereof.

27. A method of treating a subject with a cancer, comprising administering to the subject an effective amount of the isolated mAb or antigen-binding fragment thereof according to Claim 1, wherein the cancer comprises cells expressing PD-1.

28. The method of Claim 27, wherein the cancer comprises breast cancer, colorectal cancer, pancreatic cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, non-small lung cell cancer, glioma, esophageal cancer, nasopharyngeal cancer, anal cancer, rectal cancer, gastric cancer, bladder cancer, cervical cancer, or brain cancer.

29. The method of Claim 27, further comprising co-administering an effective amount of a therapeutic agent, wherein the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof.

30. The method of Claim 29, wherein the therapeutic agent comprises capecitabine, cisplatin, Cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, Mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, Epirubicin, pemetrexed, folinic acid, gemicitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, , fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lafatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, Everolimus, temsirolimus, Dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, Bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

31. The method of Claim 27, wherein the subject is a human.

32. A solution comprising an effective concentration of the isolated mAb or an antigen-binding fragment thereof according to Claim 1, wherein the solution is blood plasma in a subject.

FIGURE 1 shows rabbit IgG antibodies in B cell culture supernatant binding to recombinant PD-1.

plate 5. 0.75 PD-1+IgG+ cells/well

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.241	0.33	0.224	0.216	0.125	0.13	0.146	0.124	0.135	0.101	0.13	0.127
B	0.145	0.225	0.172	0.178	0.2	0.171	0.198	0.386	0.139	0.086	0.148	0.173
C	0.18	0.161	0.165	0.168	0.173	0.168	0.134	0.181	0.112	0.107	0.15	0.134
D	0.125	0.185	0.132	2.139	0.126	0.143	0.121	0.204	0.142	0.134	0.14	0.126
E	0.121	0.194	0.178	0.209	0.186	0.25	0.181	0.163	0.202	0.131	0.147	0.157
F	0.154	0.145	0.119	0.142	0.136	0.19	0.188	0.145	0.137	2.722	0.158	0.129
G	0.157	0.144	0.087	0.148	0.151	0.137	0.253	0.152	0.143	0.164	0.138	0.146
H	0.144	0.171	0.123	0.164	0.137	0.097	0.146	0.143	0.129	0.132	0.157	0.201

FIGURE 2 FACS analysis of recombinant humanized PD-1 specific antibodies binding to PD-1 expressed on Jurkat cells .

Mean Fluorescence Intensity (MFI)

10^4
10^3
10^2
10^1
10^0

10^{-2} 10^{-1} 10^0 10^1 10^2 10^3 10^4 10^5

Antibody [pM]

Negative control
Postive control
AB1HU
AB2HU
AB3HU
AB4HU
AB5HU

FIGURE 3 FACS analysis of recombinant humanized PD-1 specific antibodies inhibiting binding of recombinant human PD-L1 binding to PD-1 expressed on Jurkat cells.

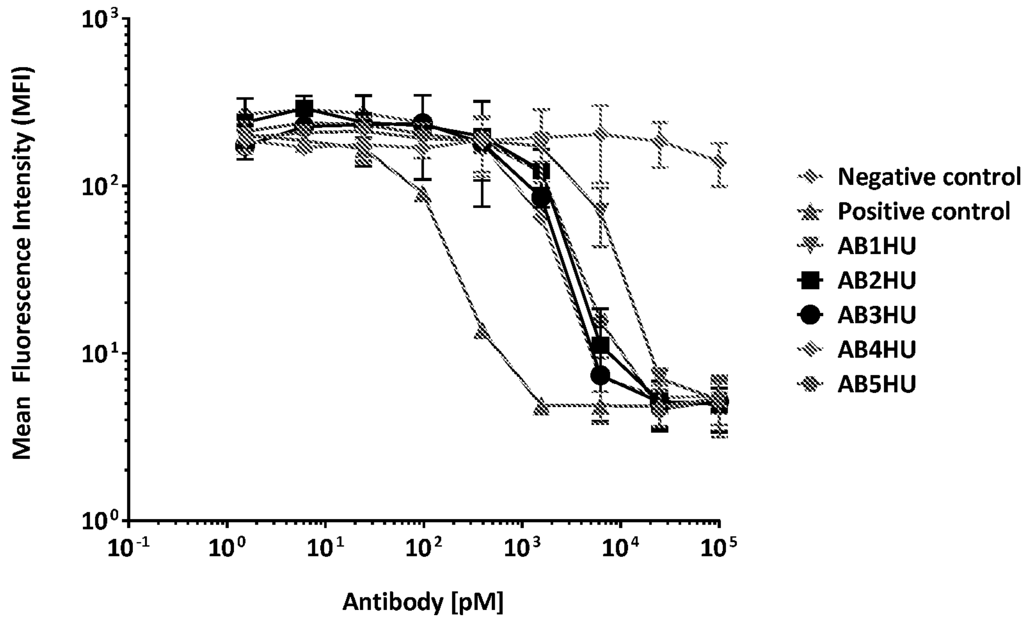


FIGURE 4 FACS analysis of recombinant humanized PD-1 specific antibodies inhibiting binding of recombinant human PD-L2 binding to PD-1 expressed on Jurkat cells.

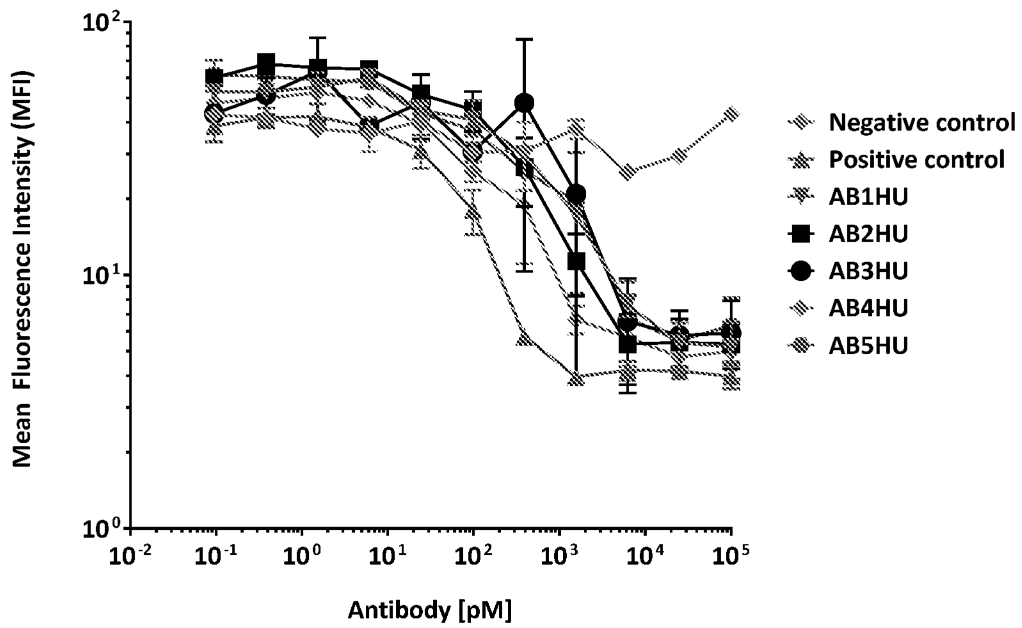
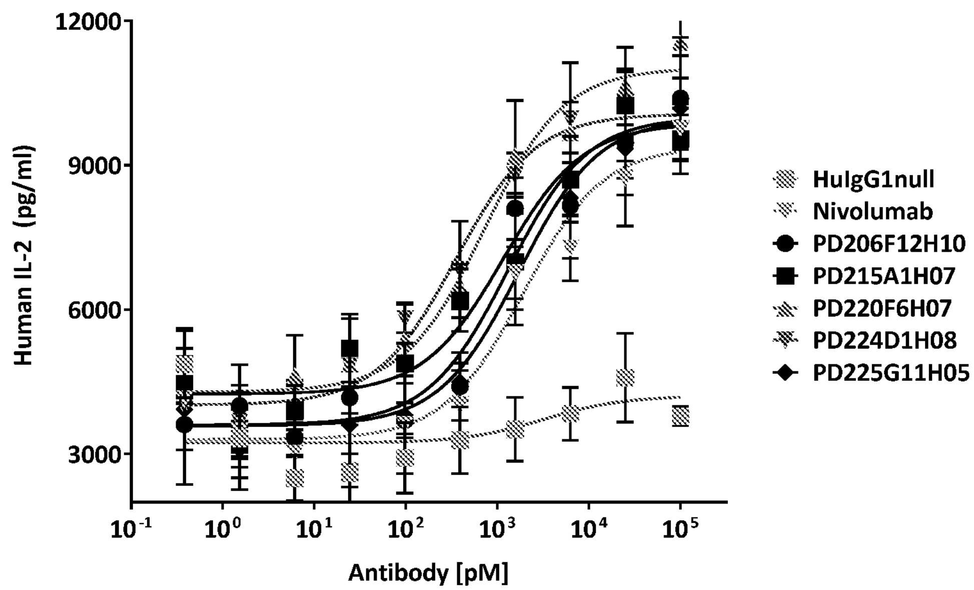


FIGURE 5 show that PD-1 specific chimeric antibodies enhance non-antigen specific SEB induced T cell responses.



PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT
(PCT Article 17(2)(a), Rules 13*ter*.1(c) and (d) and 39)

Applicant's or agent's file reference SIBA011PCT	IMPORTANT DECLARATION	Date of mailing *(day/month/year)* 07 SEP 2018
International application No. PCT/US18/39147	International filing date *(day/month/year)* 22 June 2018	(Earliest) Priority Date *(day/month/year)* 25 June 2017
International Patent Classification (IPC) or both national classification and IPC IPC: C12Q 1/68; CPC: C12Q 2600/158		
Applicant SYSTIMMUNE, INC.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☐ The subject matter of the international application relates to:
   - a. ☐ scientific theories
   - b. ☐ mathematical theories
   - c. ☐ plant varieties
   - d. ☐ animal varieties
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
   - f. ☐ schemes, rules or methods of doing business
   - g. ☐ schemes, rules or methods of performing purely mental acts
   - h. ☐ schemes, rules or methods of playing games
   - i. ☐ methods for treatment of the human body by surgery or therapy
   - j. ☐ methods for treatment of the animal body by surgery or therapy
   - k. ☐ diagnostic methods practised on the human or animal body
   - l. ☐ mere presentations of information
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☐ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

   ☐ the description ☐ the claims ☐ the drawings
3. ☒ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:

   ☒ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in a form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

   ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

   ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).
4. Further comments:

   Applicant failed to submit a valid electronic seq. listing in respone to the ISA/225.

Name and mailing address of the ISA/	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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