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(54) Title: ANTI-ROR1 ANTIBODIES AND METHODS OF MAKING AND USING THEREOF

(57) Abstract:

ANTI-ROR1 ANTIBODIES AND METHODS OF MAKING AND USING THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of filing dates of U.S. Provisional Patent Application No. 62551035, filed August 28, 2017, U.S. Provisional Patent Application No. 62551032 filed August 28, 2017, U.S. Provisional Patent Application No. 62524554 filed June 25, 2017, U.S. Provisional Patent Application No. 62524557 filed June 25, 2017, U.S. Provisional Patent Application No. 62524558 filed June 25, 2017, U.S. Provisional Patent Application No. 62545603 filed August 15, 2017, U.S. Provisional Patent Application No. 62551032 filed August 28, 2017, and U.S. Provisional Patent Application No. 62551065 filed August 28, 2017, the entire disclosures of which are expressly incorporated by reference herein.

TECHNICAL FIELD

The present disclosure generally relates to the technical field of antibodies, and more particularly relates to making and using anti-ROR1 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.

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 (see, Lafferty et al., Ausl. J. Exp. Biol. Med. Sci. 53: 27-42, 1975). Negative secondary signals can result in T-cell suppression and tolerance.

Tyrosine-protein kinase transmembrane receptor ROR1, also known as neurotrophic tyrosine kinase, receptor-related 1 (NTRKR1), is an enzyme that in humans is encoded by the ROR1 gene. (see, Masiakowski P and Carroll RD, J. Bio. Chem. 267 (36): 26181–90. 1992; Reddy UR, et al, Oncogene. 13 (7): 1555–9, 1996). ROR1 is a member of the receptor tyrosine kinase-like orphan receptor (ROR) family. ROR1 has recently been shown to be expressed on ovarian cancer stem cell, on which it seems to play a functional role in promoting migration/invasion or spheroid formation in vitro and tumour engraftment in immune-deficient mice. Treatment with a humanized mAb specific for ROR1 (UC-961) could inhibit the capacity of ovarian cancer cells to migrate, form spheroids, or engraft immune-deficient mice. Moreover, such treatment inhibited the growth of tumour xenografts, which in turn had a reduced capacity to engraft immune-deficient mice and were relatively depleted of cells with features of CSC, suggesting that treatment with UC-961 could impair CSC renewal. Collectively, these studies indicate that ovarian CSCs express ROR1, which may be targeted for anti-CSC therapy. (see, Zhang S, et al, PNAS. 111 (48): 17266–71, 2014).

ROR1 is expressed in a number of malignancies with low levels of expression in normal adult tissue. Much like the physiological functions of ROR1, ROR1 in cancer can have kinase activity-dependent or -independent function, which could be a result of tissue specific expression of co-receptor or effector proteins. The induction of apoptosis with ROR1 knockdown, EGFR signalling potentiation and ROR1-mediated upregulation of EMT genes support the notion that ROR1 plays an important role in cancer progression. Further research is required to elucidate the tumour-specific mechanisms of ROR1 overexpression and the contribution of ROR1 to initiation and progression of cancer.

SUMMARY

In one aspect, the present disclosure provides, among others, anti-ROR1 monoclonal antibodies, antigen binding portions thereof, therapeutic compositions thereof and/or nucleic acid encoding the same.

In one embodiment, the disclosure provides one or more isolated monoclonal antibodies (mAb) or antigen-binding fragment thereof that binds specifically to human ROR1. In one embodiment, the isolated one or more mAb or antigen-binding fragment includes an antigenic peptide sequence having a sequence as disclosed herein. In one embodiment, the isolated mAb or antigen-binding fragment is selected from the sequences as disclosed herein.

In one embodiment, an isolated monoclonal antibody (mAb) or antigen-binding fragment have 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, SEQ ID NO:76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:116, SEQ ID NO:120, SEQ ID NO:124, SEQ ID NO:128, or SEQ ID NO:132. In one embodiment, the percentage homology is not less than 70%, 80%, 90%, 95%, 98%, or 99%

In one embodiment, the isolated one or more mAb or antigen-binding fragment has a binding affinity to ROR1 with a Kd not greater than 30nM, 40nM, 50nM, 60nM, 70nM, 80nM, 90nM or 100nM. In one embodiment, the ROR1 is a human ROR1.

In one embodiment, the isolated mAb or antigen-binding fragment exhibits one or more functional properties. Example functional properties include without limitation high affinity binding to ROR1, enhancing T cell activation, 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 enhancing T-cell activation comprises T-cell proliferation, IFN-γ and/or IL-2 secretion, or a combination thereof. In one embodiment, the immunosuppressive cell comprises a regulatory cell.

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 having a binding specificity to ROR1 and an IgG1 heavy chain. The IgG heavy chain comprises 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, SEQ ID NO:79, SEQ ID NO:87, SEQ ID NO:91, SEQ ID NO:99, SEQ ID NO:107, SEQ ID NO:115, SEQ ID NO:123, or SEQ ID NO:131. 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 having a binding specificity to ROR1 and a kappa light chain. The kappa light chain comprises 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, SEQ ID NO:75, SEQ ID NO:83, SEQ ID NO:95, SEQ ID NO:103, SEQ ID NO:111, SEQ ID NO:119, or SEQ ID NO:127. 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 having a binding specificity to ROR1 and a variable light chain. The variable chain comprises 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, SEQ ID NO:76, SEQ ID NO:84, SEQ ID NO:96, SEQ ID NO:104, SEQ ID NO:112, SEQ ID NO:120, or SEQ ID NO:128. 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 having a binding specificity to ROR1 and a variable heavy chain. The variable heavy chain comprises an amino acid sequence having at least 90% identity 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, SEQ ID NO:80, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:100, SEQ ID NO:108, SEQ ID NO:116, SEQ ID NO:124, or SEQ ID NO:132. The percentage homology is not less than 70%, 80%, 90%, 95%, 98%, or 99%.

The application further provides isolated nucleic acids encode at least a portion of the isolated mAb or antigen-binding fragment disclosed herein. In one embodiment, the isolated mAb or antigen-binding fragment has a percentage homology with the IgG1 heavy chain 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, SEQ ID NO:79, SEQ ID NO:87, SEQ ID NO:91, SEQ ID NO:99, SEQ ID NO:107, SEQ ID NO:115, SEQ ID NO:123, or SEQ ID NO:131. In one embodiment, the isolated mAb or antigen-binding fragment has a percentage homology with the kappa light: 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, SEQ ID NO:75, SEQ ID NO:83, SEQ ID NO:95, SEQ ID NO:103, SEQ ID NO:111, SEQ ID NO:119, or SEQ ID NO:127. In one embodiment, the isolated mAb or antigen-binding fragment has a percentage homology with the the variable light chain: 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, SEQ ID NO:76, SEQ ID NO:84, SEQ ID NO:96, SEQ ID NO:104, SEQ ID NO:112, SEQ ID NO:120, or SEQ ID NO:128. In one embodiment, the isolated mAb or antigen-binding fragment has a percentage homology with the variable heavy: 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, SEQ ID NO:80, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:100, SEQ ID NO:108, SEQ ID NO:116, SEQ ID NO:124, or SEQ ID NO:132. The percentage homology is not less than 70%, 80%, 90%, 95%, 98%, or 99%.

The application further provides expression vectors containing the isolated nucleic acid encoding an amino acid sequence having a percentage homology with the amino acid sequences disclosed herein. The percentage homology is not less than 70%, 80%, 90%, 95%, 98%, or 99%. In one embodiment, the expression vector is expressible in a cell.

The application further provides host cells comprising nucleic acids that encode an amino acid sequence having a percentage homology with the amino acid sequences disclosed herein. The percentage homology is not less than 70%, 80%, 90%, 95%, 98%, or 99%. 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 or its antigen-binding fragment thereof having a binding specificity to human ROR1. In one embodiment, 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 with at least 70%, 80%, 90%, 95%, 98%, or 99% identity, to produce an antibody by the expression of the nucleic acids.

The application further provides immuno-conjugates. In one embodiment, the immuno-conjugates include a drug unit or an imaging agent linked to an isolated mAb or antigen-binding fragment disclosed herein through a linker.

The linker may be cleavable or non-cleavable. In one embodiment, the linker is a chemical linker. In one embodiment, the linker comprises a covalent bond such as 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 linker comprises a peptide bond.

In one embodiment, the drug unit in the immuno-conjugate comprises a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, or a combination thereof. In one embodiment, the drug unit comprises a calicheamicin, ozogamicin, monomethyl auristatin E, emtansine, a derivative or a combination thereof. In one embodiment, the drug unit comprises a calicheamicin, 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 a pharmaceutical composition. In one embodiment, the pharmaceutical composition comprises the isolated mAb or antigen-binding fragment disclosed herein and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition comprises an immuno-conjugate disclosed herein and pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition further a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, a toxin, a therapeutic agent, or a combination thereof.

In a further aspect, the application provides a method of treating a subject with a cancer using the isolated mAb or antigen-binding fragment thereof as disclosed herein. In one embodiment, the method comprises the step of administering to the subject an effective amount of the isolated mAb or antigen-binding fragment as 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.

Varieties of cancer may be treated using the disclosed mAB, antigen-binding fragment thereof, or compositions. In one embodiment, the cancer has cells that express ROR-1. Example cancers include without limitation 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 further includes co-administering an effective amount of a therapeutic agent. Example therapeutic a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, an antibody, an enzyme, or a combination thereof. In one embodiment, the therapeutic agent can be 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, letrozole, 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, or a derivative or a combination thereof.

The subject receiving treatment may be a human. In one embodiment, the application provides a solution comprising 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

The foregoing and other features of this disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only several embodiments arranged in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings, in which:

FIGURE 1 provides immunization strategy of NZW rabbits with human or mouse ROR1;

FIGURE 2 provides immunization timeline;

FIGURE 3 shows the harvest of spleen and lymph tissue from ROR1-immunized rabbits;

FIGURE 4 shows the summary of B cell culture screening for ROR1-specific IgG and screening of chimeric rabbit/human IgG;

FIGURE 5 shows the binding and off-rate analysis of different ROR1-specific humanized rabbit antibodies; and

FIGURE 6 is a graph showing analytic results of rabbit serum for human and mouse ROR1-specific IgG before and after immunization, according to one embodiment.

DETAILED DESCRIPTION

In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and

illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

The disclosure provides, among others, isolated antibodies having specificity against ROR1, antigen binding fragment thereof, methods of making such antibodies, bispecific or multi-specific molecules, antibody-drug conjugates and/or immuno-conjugates composed from such antibodies or antigen binding fragment, pharmaceutical compositions containing the antibodies or antigen binding fragment, bispecific or multi-specific molecules, antibody-drug conjugates and/or immuno-conjugates, and methods for using the disclosed antibodies, antigen binding fragments and compositions for treating cancer.

In one aspect, the application provides monoclonal antibodies that bind specifically to human or mouse ROR1. In one embodiment, antibodies exhibit one or more desirable functional properties, such as high affinity binding to ROR1. In one embodiment, the antibodies are derived from specific heavy and light chain amino acid sequences and/or structural features such as rabbit/human chimeric antibodies composed of specific amino acid sequences.

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 one embodiment, antibodies were created by the immunization of rabbits with either human or mouse ROR1 extracellular domain (ECD) or HEK 293 cells transiently transfected with mouse or human ROR1. 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-ROR1 antibodies. The antibody variable genes were isolated using recombinant DNA techniques and the resulting antibodies were expressed recombinantly. This general method of antibody discovery is similar to that described in Seeber et al. PLOS One. 9:e86184 (2014).

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, simianized, 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 an 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 that immunospecifically bind 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 disclosure 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).

The monoclonal antibodies 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 disclosure antibodies were created by the immunization of rabbits with both human PD-L1 protein and cells transiently expressing human PD-L1 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-L1 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-L1 to PD-1, the ability to bind to non-human primate PD-L1 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 (ROR1 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 subfragments 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 disclosure 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 may contain 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 VH-VL 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)).

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.

"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} M, 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. Typically, 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.

"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 disclosure may be caused for instance by addition, deletion, substitution, insertion or recombination.

The application further provides immuno-conjugates including a drug unit linked to the antibodies and antigen-binding fragments disclosed herein through a linker. The linker may be cleavable or noncleavable. In one embodiment, the linker is a chemical linker. In one embodiment, the linker comprises a covalent bond such as an ester bond, an ether bond, an amid bond, a disulphide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, or a combination thereof. In one embodiment, the linker comprises a hydrophobic poly(ethylene glycol) linker. In one embodiment, the linker comprises a peptide bond.

In one embodiment, the drug unit may be a chemotherapeutic agent, a growth inhibitory agent, a drug unit from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, a toxin, 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 another aspect, the application provides pharmaceutical compositions. In one embodiment, the pharmaceutical composition includes the antibodies or antigen-binding fragments thereof and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition includes the immuno-conjugate disclosed herein and a pharmaceutically acceptable carrier.

The antibodies and antigen-binding fragments or immuno-conjugates 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 disclosed herein may include any functionally equivalent antibody or functional parts thereof, in particular, the monoclonal antibody including any functionally equivalent antibody or functional parts thereof is combined with a pharmaceutically acceptable carrier, diluent and/or excipient to form a therapeutic composition. 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.

The pharmaceutical composition may further comprise proteinaceous carriers such as, for example, serum albumin or immunoglobulin, particularly of human origin. In one embodiment, the 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 disclosure, 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 disclosure. 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 disclosure.

"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 disclosure can be accomplished according to standard methodology know to those of ordinary skill in the art.

Further biologically active agents may be present in the pharmaceutical composition of the disclosure dependent on the intended use. In one embodiment, the composition disclosed herein may be administered in combination with other compositions comprising a biologically active/therapeutical substance or compound, particularly at least one compound selected from the group consisting of the therapeutic agent comprises capecitabine, cisplatin, trastuzumab, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, letrozole, erlotinib, lafatinib, dasatinib, gefitinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, calicheamicin, antimitotic agent, monomethyl auristatin E, emtansine, ozogamicin, a derivative or a combination thereof.

In another aspect, the application provides methods for treating a subject using anti-ROR1 antibodies or other molecules containing the antigen-binding portion of an anti-ROR1 antibody. In one embodiment, the method inhibits growth of tumour cells. In some embodiments, the method uses the disclosed antibodies or compositions to stimulate a protective autoimmune response, to modify an immune response or to stimulate antigen-specific immune responses.

In one embodiment, the method include the step of administering to a subject in need of such treatment an effective amount of the anti-ROR1 antibodies or other molecules 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 tumour 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 addition, 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 tumour. 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.

In one embodiment, 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.

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.

Varieties of cancer may be treated using the disclosed mAb, antigen-binding fragments, or compositions. Cancers, including 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, may express ROR1 genes. In one embodiment, administering a therapeutically effective amount of composition comprising anti-ROR1 monoclonal antibodies or antigen-binding fragment or its immuno-conjugates thereof is used to cure, prevent, ameliorate, and delay the development or metastasis of cancers.

The present disclosure may be understood more readily by reference to the following detailed description of specific embodiments included herein. Although the present disclosure 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 disclosure.

EXAMPLES

Example 1: Generation of Anti-ROR1 Antibodies

Monoclonal antibodies against human ROR1 were developed by immunizing New Zealand white rabbits. As shown in FIGURE 1, animals were immunized with recombinant human or mouse ROR1 extracellular domain (ECD) or HEK 293 cells transiently transfected with mouse or human ROR1 mixed 1:1 v/v with Complete or incomplete Freund's adjuvant (Cohort 1) or Titermax Gold (Cohort 2) alternating with Alhydrogel 2% (Alum) plus CpG 2007 and were performed by subcutaneous injection. Subsequent boosts were performed at days 7, 14, 21, 28 and 37 as shown in FIGURE 2.

On week 5 the serum from the animals was tested for ROR1 titer by ELISA. Serum from each rabbit is obtained before immunization as a negative control. After immunization serum is again collected from each animal and compared to the pre-immunization serum from the same animal for the presence of ROR1-specific IgG antibodies. As shown in FIGURE 6 all animals immunized with human and mouse ROR1 developed detectable titres of human or mouse ROR1-specific IgG antibodies.

As shown in FIGURE 3, spleen and lymph nodes were harvest from 2 animals each on days 4, 13, and 21 following a final immunization. ROR1-specific IgG+ B cells were sorted at 1 per well into multiple 96 well tissue culture plates and cultured for 9 days to allow their differentiation into plasma cells and for secretion of antibodies. The supernatants from these plasma cell cultures were screened by ELISA and flow cytometry for the presence of ROR1-specific antibodies in a series of binding assays as listed below:

Human ROR1 directly coated on the plate – detection of ROR1-specific IgG ELISA

Mouse ROR1 directly coated on the plate – detection of ROR1-specific IgG ELISA

Human ROR2 directly coated on the plate – detection of ROR1-specific IgG ELISA

Biotinylated human ROR1 added to an avidin coated plate - detection of ROR1-specific IgG ELISA

Biotinylated human ROR1 "Kringle domain" added to an avidin coated plate - detection of ROR1-Kringle-specific IgG ELISA

Biotinylated human ROR1 "Frizzled-Kringle domain" added to an avidin coated plate - detection of ROR1-Frizzled-Kringle-specific IgG ELISA

Biotinylated human ROR1 "Ig-Frizzled domain" added to an avidin coated plate - detection of ROR1-Ig-Frizzled-specific IgG ELISA

Human ROR1 “Frizzled-Kringle domain” directly coated on the plate - detection of ROR1-Frizzled-Kringle-specific IgG ELISA

Human ROR1 “Ig-Frizzled domain” directly coated on the plate - detection of ROR1-Ig-Frizzled-specific IgG ELISA

Human ROR1-CHO cells – detection of ROR1-specific IgG by FACS

On day 9 of B cell culture the supernatants were separated from the B cells and stored in a separate plate for later analysis. RNAlater tissue storage reagent was added to each well in the B cell culture plate to preserve the RNA in the B cells for RT-PCR amplification of antibody variable regions.

B cell culture wells identified through ELISA and FACS screening as having the desired antibodies we advanced to molecular “rescue” of the antibody variable regions. 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 to produce rabbit/human chimeric antibodies. Recombinant antibody supernatants were confirmed to contain anti-ROR1 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 ROR1 was observed by real-time interferometry by placing the biosensors in wells containing recombinant human ROR1 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.

A summary of the primary BCC screening data and the corresponding screening data for 27 recombinant chimeric rabbit/human IgG antibodies is shown in Tables 4a and 4b.

The heavy and light chain variable regions for 8 of 27 chimeric rabbit/human IgG antibodies listed in FIGURE 4 were humanized. Humanized variants for 8 of 27 antibodies showed similar binding kinetics to human ROR1 by octet analysis which is summarized in FIGURE 5.

While the disclosure 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 disclosure are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

ANTI-ROR1 ANTIBODY SEQUENCES

SEQ ID NO:1

226E12 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCA
GTCAGAGAATTTACAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGG
CATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTGCTAGTATGGTTGATGTTGAGAATATGTTC
GGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGA
AGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTAC
AGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT
CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:2

226E12 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCTATGATATGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCA
GTCAGAGAATTTACAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGG
CATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTGCTAGTATGGTTGATGTTGAGAATATGTTC
GGCGGAGGGACCGAGGTGGTGGTCAAA

SEQ ID NO:3

226E12 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AYDMTQTPSSVSAAVGGTVTIKCQASQRIYSYLAWYQQKPGQPPKLLIYRASTLASGVPSRFKGSGSGTEYTLTISDLECA
DAATYYCQQGASMVDVENMFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:4

226E12 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

AYDMTQTPSSVSAAVGGTVTIKCQASQRIYSYLAWYQQKPGQPPKLLIYRASTLASGVPSRFKGSGSGTEYTLTISDLECA
DAATYYCQQGASMVDVENMFGGGTEVVVK

SEQ ID NO:5

226E12 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGAA
TTCTCCCTCAGTAACTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAGTGGATCGGAGCCATT
AATGCTGACAGTGATAATACATGGTACCCGAGCTGGGTGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCA
CGGTGGATCTGAAGATCACCAGTCCGACAATTGAGGACACGGCCACCTATTTCTGTGCCAGAAGTGTGAGTAATA
ATTTCGCCGAATATAACATCTGGGGCCCGGGCACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGG
TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT
CCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACA
GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGC
AACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACA
TGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC
TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCA
ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTA
CCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAA
CAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC
CCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:6

226E12 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGAA
TTCTCCCTCAGTAACTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAGTGGATCGGAGCCATT
AATGCTGACAGTGATAATACATGGTACCCGAGCTGGGTGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCA
CGGTGGATCTGAAGATCACCAGTCCGACAATTGAGGACACGGCCACCTATTTCTGTGCCAGAAGTGTGAGTAATA
ATTTCGCCGAATATAACATCTGGGGCCCGGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO:7

226E12 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSLEESGGRLVTPGTPLTLTCTASEFSLSNYYMSWVRQAPGEGLEWIGAINADSDNTWYPSWVKGRFTISKTSSTTVDL
KITSPTIEDTATYFCARSVSNNFAEYNIWGPGTLVTVSS<u>ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG</u>

SEQ ID NO:8

226E12 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSLEESGGRLVTPGTPLTLTCTASEFSLSNYYMSWVRQAPGEGLEWIGAINADSDNTWYPSWVKGRFTISKTSSTTVDL
KITSPTIEDTATYFCARSVSNNFAEYNIWGPGTLVTVSS

SEQ ID NO:9

323H7 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAAGCCGTGGTGACCCAGACTCCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCC
AGTCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCT
ACTATGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCGC
CATCAGCGACCTGGAGTGTGACGATTCTGCCACTTACTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACG
TTTGCTTTCGGCGGAGGCACCGAGGTGGAGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCAT
CTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA
GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAG
TCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:10

323H7 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

CAAGCCGTGGTGACCCAGACTCCATCGTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCC
AGTCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCT
ACTATGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCGC
CATCAGCGACCTGGAGTGTGACGATTCTGCCACTTACTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACG
TTTGCTTTCGGCGGAGGCACCGAGGTGGAGGTCAAA

SEQ ID NO:11

323H7 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

QAVVTQTPSSVSAAVGGTVTISCQSSQSVYNNNDLAWYQQKPGQPPKLLIYYASTLASGVSSRFKGSGSGTQFTLAISD
LECDDSATYYCAGGYDTDGLDTFAFGGGTEVEVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:12

323H7 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QAVVTQTPSSVSAAVGGTVTISCQSSQSVYNNNDLAWYQQKPGQPPKLLIYYASTLASGVSSRFKGSGSGTQFTLAISD
LECDDSATYYCAGGYDTDGLDTFAFGGGTEVEVK

SEQ ID NO:13

323H7 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGGAGCAGCTGAAGGAGTCCGGAGGAGGCCTGGTAACGCCTGGAGGAACCCTGACACTCACCTGCACAGCCTC
TGGATTCACCATCAGTCGCTACCACATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGTCA
TATTTATGTTAATAATGATGACACAGACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGACC
ACGGTGGATCTGAAGATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATTGGATGTTGGT
GGTGGTGGTGCTTATATTGGGGACATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAG
GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCT
ACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAA
CTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGG
TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGG
TGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTA
TCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCT
TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:14

323H7 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGGAGCAGCTGAAGGAGTCCGGAGGAGGCCTGGTAACGCCTGGAGGAACCCTGACACTCACCTGCACAGCCTC
TGGATTCACCATCAGTCGCTACCACATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGTCA
TATTTATGTTAATAATGATGACACAGACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGACC
ACGGTGGATCTGAAGATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATTGGATGTTGGT
GGTGGTGGTGCTTATATTGGGGACATCTGGGGCCAAGGGACCCTGGTCACCGTCTCGAGC

SEQ ID NO:15

323H7 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QEQLKESGGGLVTPGGTLTLTCTASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASWAKGRFTISKTSTTVD
LKITSPTTEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA
GAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW

LNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:16

323H7 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QEQLKESGGGLVTPGGTLTLTCTASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASWAKGRFTISKTSTTVD
LKITSPTTEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSS

SEQ ID NO:17

324C7 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATTGTGATGACCCAGACTCCAGCCTCTGTGGAGGTCGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAACATTGGTAGTGATTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATACTA
CATCCAATCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGGTTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCAGTTACTGCTGTCAAGGCGGTTATTTTAGTGGTCGTAATATTTATGGGAAT
GCTTTCGGCGGAGGCACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTG
ATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCA
CCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCA
CCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:18

324C7 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATTGTGATGACCCAGACTCCAGCCTCTGTGGAGGTCGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAACATTGGTAGTGATTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTATACTA
CATCCAATCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGGTTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCAGTTACTGCTGTCAAGGCGGTTATTTTAGTGGTCGTAATATTTATGGGAAT
GCTTTCGGCGGAGGCACCGAGGTGGTGGTCAAA

SEQ ID NO:19

324C7 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIVMTQTPASVEVAVGGTVTIKCQASQNIGSDLAWYQQKPGQPPKLLIYTTSNLASGVPSRFKGSGSGTGFTLTISDLEC
ADAASYCCQGGYFSGRNIYGNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA
LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:20

324C7 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIVMTQTPASVEVAVGGTVTIKCQASQNIGSDLAWYQQKPGQPPKLLIYTTSNLASGVPSRFKGSGSGTGFTLTISDLEC
ADAASYCCQGGYFSGRNIYGNAFGGGTEVVVK

SEQ ID NO:21

324C7 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATACAT
TGATAGTGGTGCTACCACATACTACGCGAGCTGGGCAAAAGGCCGATTCACCATCTCCAAAGCCTCGACCACGGT
GGATCTGAAAATCGCCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGATACTACGGCATGGA
CCCCTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCC
TCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACT
CCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCC
CAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGC
ACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCC
TCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCC
CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGG
ATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
TCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG
CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:22

324C7 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATACAT
TGATAGTGGTGCTACCACATACTACGCGAGCTGGGCAAAAGGCCGATTCACCATCTCCAAAGCCTCGACCACGGT
GGATCTGAAAATCGCCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGATACTACGGCATGGA
CCCCTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO:23

324C7 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSGAGVSWVRQAPGKGLEWIGYIDSGATTYYASWAKGRFTISKASTTVDLKIA
SPTTEDTATYFCARGYYGMDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCA
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:24

324C7 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSGAGVSWVRQAPGKGLEWIGYIDSGATTYYASWAKGRFTISKASTTVDLKIA
SPTTEDTATYFCARGYYGMDPWGQGTLVTVSS

SEQ ID NO:25

323D10 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCATCGATTTGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAATCACCATCAATTGCCAAGCC
AGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGCAGCGTCCCAAGCTCCTGATCTACGAA
ACATCCAAACTGGCATCTGGGGTCCCACCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCA
GCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAAGTTATTATCGTATTAATAATATTGGTTACGATAAT
GCTTTCGGCGGAGGCACCGAGGTGGAGTTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTG
ATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCA
CCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCA
CCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:26

323D10 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCATCGATTTGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAATCACCATCAATTGCCAAGCC
AGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGCAGCGTCCCAAGCTCCTGATCTACGAA
ACATCCAAACTGGCATCTGGGGTCCCACCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCA
GCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCAAAGTTATTATCGTATTAATAATATTGGTTACGATAAT
GCTTTCGGCGGAGGCACCGAGGTGGAGTTCAAA

SEQ ID NO:27

323D10 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AIDLTQTPASVEAAVGGTITINCQASESISSWLAWYQQKPGQRPKLLIYETSKLASGVPPRFSGSGSGTQFTLTISGVQCD
DAATYYCQSYYRINNIGYDNAFGGGTEVEFKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:28

323D10 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

AIDLTQTPASVEAAVGGTITINCQASESISSWLAWYQQKPGQRPKLLIYETSKLASGVPPRFSGSGSGTQFTLTISGVQCD
DAATYYCQSYYRINNIGYDNAFGGGTEVEFK

SEQ ID NO:29

323D10 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAGGAATGCAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGATACATT
AGCACTAGTGGTACCACATTCTACGCGAACTGGGTGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGACTATAACTACGCCATGG
ACATCTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC
CTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC
GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAG
CACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGAC
CCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTC
CTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCC
CCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG
GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAG
TGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC
CTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAG
GCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:30

323D10 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAGGAATGCAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGATACATT
AGCACTAGTGGTACCACATTCTACGCGAACTGGGTGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGACTATAACTACGCCATGG
ACATCTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO:31

323D10 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSRNAMNWVRQAPGKGLEYIGYISTSGTTFYANWVKGRFTISKTSTTVDLKM
TSLTTEDTATYFCARDYNYAMDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:32

323D10 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSRNAMNWVRQAPGKGLEYIGYISTSGTTFYANWVKGRFTISKTSTTVDLKM
TSLTTEDTATYFCARDYNYAMDIWGQGTLVTVSS

SEQ ID NO:33

324E2 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCTCAAGTGCTGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCA
GTCAGAGTGTTAATAACAACGACTTAGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTACTG
GGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCATTCTCACCATC
AGCGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTTATAGTGGTAATATTTATGGTTTCGGCG
GAGGCACCGAGGTGGAGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT
GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGT
GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:34

324E2 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCTCAAGTGCTGACCCAGACTCCATCCTCCGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCA
GTCAGAGTGTTAATAACAACGACTTAGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTACTG
GGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCATTCTCACCATC
AGCGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTGCAGGCGGTTATAGTGGTAATATTTATGGTTTCGGCG
GAGGCACCGAGGTGGAGGTCAAA

SEQ ID NO:35

324E2 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AQVLTQTPSSVSAAVGGTVTINCQSSQSVNNNDLAWFQQKPGQPPKRLIYWASKLASGVPSRFKGSGSGTQFILTISDL
ECDDAATYYCAGGYSGNIYGFGGGTEVEVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:36

324E2 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

AQVLTQTPSSVSAAVGGTVTINCQSSQSVNNNDLAWFQQKPGQPPKRLIYWASKLASGVPSRFKGSGSGTQFILTISDL
ECDDAATYYCAGGYSGNIYGFGGGTEVEVK

SEQ ID NO:37

324E2 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAACAATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGAATCATT
AGTAGTAGTGGTACCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACG
GTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCGGAGCATTTAGCGTCTGG
GGCCCGGGCACCCTCGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA
AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAA
CACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGA
AGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAG
GTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGC
TGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAG
CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA
CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:38

324E2 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAACAATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGAATCATT
AGTAGTAGTGGTACCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACG
GTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCGGAGCATTTAGCGTCTGG
GGCCCGGGCACCCTCGTCACCGTCTCGAGC

SEQ ID NO:39

324E2 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSNNAITWVRQAPGKGLEYIGIISSSGTTYYASWAKGRFTISKTSSTTVDLKMTS
LTTEDTATYFCAGAFSVWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:40

324E2 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSNNAITWVRQAPGKGLEYIGIISSSGTTYYASWAKGRFTISKTSSTTVDLKMTS
LTTEDTATYFCAGAFSVWGPGTLVTVSS

SEQ ID NO:41

324C6 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTGATAGTTGGTTATCCTGGTATCAACAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACCAGG
CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGCGCTTATGGTGTTAGTGGTACTAGTAGTTATTTAT
ATACTTTCGGCGGAGGCACCGAGGTGGAGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATC
TGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAG
CACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGT
CACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:42

324C6 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTGATAGTTGGTTATCCTGGTATCAACAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACCAGG

CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGCGCTTATGGTGTTAGTGGTACTAGTAGTTATTTAT
ATACTTTCGGCGGAGGCACCGAGGTGGAGGTCAAA

SEQ ID NO:43

324C6 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DVVMTQTPASVEAAVGGTVTIKCQASQSIDSWLSWYQQKPGQPPKLLIYQASTLASGVSSRFKGSGSGTEFTLTISDLEC
ADAATYYCQCAYGVSGTSSYLYTFGGGTEVEVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA
LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:44

324C6 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DVVMTQTPASVEAAVGGTVTIKCQASQSIDSWLSWYQQKPGQPPKLLIYQASTLASGVSSRFKGSGSGTEFTLTISDLEC
ADAATYYCQCAYGVSGTSSYLYTFGGGTEVEVK

SEQ ID NO:45

324C6 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGA
TTCTCCCTCAGTAGGTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTGGAACCATT
TATACTAGTGGTAGTACATGGTACGCGAGCTGGACAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATCACTAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATCCTATTATGGCGGTGATA
AGACTGGTTTAGGCATCTGGGGCCCAGGCACCCTCGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCT
TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC
CGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTC
CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC
GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGC
CCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA
TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACT
GGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCG
TGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAA
AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:46

324C6 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGCCTCTGGA
TTCTCCCTCAGTAGGTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTGGAACCATT
TATACTAGTGGTAGTACATGGTACGCGAGCTGGACAAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATCACTAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATCCTATTATGGCGGTGATA
AGACTGGTTTAGGCATCTGGGGCCCAGGCACCCTCGTCACCGTCTCGAGC

SEQ ID NO:47

324C6 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSLEESGGRLVTPGTPLTLTCTASGFSLSRYYMTWVRQAPGKGLEWIGTIYTSGSTWYASWTKGRFTISKTSTTVDLKITS
PTTEDTATYFCARSYYGGDKTGLGIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:48

324C6 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSLEESGGRLVTPGTPLTLTCTASGFSLSRYYMTWVRQAPGKGLEWIGTIYTSGSTWYASWTKGRFTISKTSTTVDLKITS
PTTEDTATYFCARSYYGGDKTGLGIWGPGTLVTVSS

SEQ ID NO:49

338H4 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATTGTGATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCC
AGTCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATCTGG
CATCTACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAAGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAG
CGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTCAAAGCAATTATAACGGTAATTATGGTTTCGGCGGAGG
GACCGAGGTGGAGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
TCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATA
ACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCA
GCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA
GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:50

338H4 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATTGTGATGACCCAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCC
AGTCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATCTGG
CATCTACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAAGCAGTGGATCTGGGACAGAGTACACTCTCACCATCAG
CGACCTGGAGTGTGACGATGCTGCCACTTACTACTGTCAAAGCAATTATAACGGTAATTATGGTTTCGGCGGAGG
GACCGAGGTGGAGGTCAAA

SEQ ID NO:51

338H4 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIVMTQTPASVSAAVGGTVTINCQASQNIYSYLSWYQQKPGQPPKRLIYLASTLASGVPSRFKSSGSGTEYTLTISDLECD
DAATYYCQSNYNGNYGFGGGTEVEVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:52

338H4 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIVMTQTPASVSAAVGGTVTINCQASQNIYSYLSWYQQKPGQPPKRLIYLASTLASGVPSRFKSSGSGTEYTLTISDLECD
DAATYYCQSNYNGNYGFGGGTEVEVK

SEQ ID NO:53

338H4 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAATGGATCGGAATCATT
TATGCTAGTGGTAGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAATTTATGACGGCATGGACC
TCTGGGGCCCAGGGACCCTCGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTC
CTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT
GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCC
CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
AGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCA
CCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGC
GTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT
CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCCC
CATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA

TGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT
CTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGC
TCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:54

338H4 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACCGTCTCTGGA
TTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAATGGATCGGAATCATT
TATGCTAGTGGTAGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAAAATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAATTTATGACGGCATGGACC
TCTGGGGCCCAGGGACCCTCGTCACCGTCTCGAGC

SEQ ID NO:55

338H4 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGRGLEWIGIIYASGSTYYASWAKGRFTISKTSTTVDLKITS
PTTEDTATYFCARIYDGMDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:56

338H4 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGRGLEWIGIIYASGSTYYASWAKGRFTISKTSTTVDLKITS
PTTEDTATYFCARIYDGMDLWGPGTLVTVSS

SEQ ID NO:57

330F11 CHIMERIC LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTAATAACTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGG
CATCCACTCTGGAATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAAAGCTATAATGGTGTTGGTAGGACTGCTTTCGGCGGA
GGGACCGAGGTGGAGTTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGA
AATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCA

GCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:58

330F11 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GATGTTGTGATGACCCAGACTCCAGCCTCCGTGGAGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCC
AGTCAGAGCATTAATAACTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTGATCTACAGGG
CATCCACTCTGGAATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAG
CGACCTGGAGTGTGCCGATGCTGCCACTTACTATTGTCAAAGCTATAATGGTGTTGGTAGGACTGCTTTCGGCGGA
GGGACCGAGGTGGAGTTCAAA

SEQ ID NO:59

330F11 CHIMERIC LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DVVMTQTPASVEAAVGGTVTIKCQASQSINNYLAWYQQKPGQPPKLLIYRASTLESGVPSRFKGSGSGTQFTLTISDLEC
ADAATYYCQSYNGVGRTAFGGGTEVEFKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:60

330F11 CHIMERIC LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DVVMTQTPASVEAAVGGTVTIKCQASQSINNYLAWYQQKPGQPPKLLIYRASTLESGVPSRFKGSGSGTQFTLTISDLEC
ADAATYYCQSYNGVGRTAFGGGTEVEFK

SEQ ID NO:61

330F11 CHIMERIC HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAATAACTACTGGATGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCGGAACCATT
AGTAGTGGTGCGTATACATGGTTCGCCACCTGGGCGACAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAGCATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATATTCTTCTACTACTGATTG
GACCTACTTTAACATCTGGGGCCCGGGCACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTC
CCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCT
CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGG
TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT

GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:62

330F11 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGA
TTCTCCCTCAATAACTACTGGATGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCGGAACCATT
AGTAGTGGTGCGTATACATGGTTCGCCACCTGGGCGACAGGCCGATTCACCATCTCCAAAACCTCGACCACGGTG
GATCTGAGCATCACCAGTCCGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGATATTCTTCTACTACTGATTG
GACCTACTTTAACATCTGGGGCCCGGGCACCCTGGTCACCGTCTCGAGC

SEQ ID NO:63

330F11 CHIMERIC HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLNNYWMSWVRQAPGEGLEWIGTISSGAYTWFATWATGRFTISKTSTTVDLSI
TSPTTEDTATYFCARYSSTTDWTYFNIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:64

330F11 CHIMERIC HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGRLVTPGTPLTLTCTVSGFSLNNYWMSWVRQAPGEGLEWIGTISSGAYTWFATWATGRFTISKTSTTVDLSI
TSPTTEDTATYFCARYSSTTDWTYFNIWGPGTLVTVSS

SEQ ID NO:65

226E12 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGAATTTACAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATAGGGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAACAGGGTGCTAGTATGGTTGATGTTGAGAATATGTTCG
GCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC

AGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAA
GGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:66

226E12 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGAATTTACAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATAGGGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAACAGGGTGCTAGTATGGTTGATGTTGAGAATATGTTCG
GCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:67

226E12 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQASQRIYSYLAWYQQKPGKVPKLLIYRASTLASGVPSRFSGSGSGTDFTLTISSLQPE
DVATYYCQQGASMVDVENMFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:68

226E12 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQASQRIYSYLAWYQQKPGKVPKLLIYRASTLASGVPSRFSGSGSGTDFTLTISSLQPE
DVATYYCQQGASMVDVENMFGGGTKVEIK

SEQ ID NO:69

226E12 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCTCCCTCAGTAACTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGC
CATTAATGCTGACAGTGATAATACATGGTACCCGAGCTGGGTGAAAGGCCGGTTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAAGTGTG
AGTAATAATTTCGCCGAATATAACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG
ACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTG
TCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAAC
TCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAG

GACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTC
AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGG
TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGG
TGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTA
TCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCT
TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:70

226E12 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCTCCCTCAGTAACTACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGC
CATTAATGCTGACAGTGATAATACATGGTACCCGAGCTGGGTGAAAGGCCGGTTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAAGTGTG
AGTAATAATTTCGCCGAATATAACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:71

226E12 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFSLSNYYMSWVRQAPGKGLEWIGAINADSDNTWYPSWVKGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARSVSNNFAEYNIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA
AGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:72

226E12 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFSLSNYYMSWVRQAPGKGLEWIGAINADSDNTWYPSWVKGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARSVSNNFAEYNIWGQGTLVTVSS

SEQ ID NO:73

323H7 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTA
TTATGCATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA

TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACGTT
TGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT
GATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTC
ACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:74

323H7 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTA
TTATGCATCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACGTT
TGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:75

323H7 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAWYQQKPGKVPKLLIYYASTLASGVPSRFSGSGSGTDFTLTISSL
QPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:76

323H7 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAWYQQKPGKVPKLLIYYASTLASGVPSRFSGSGSGTDFTLTISSL
QPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIK

SEQ ID NO:77

323H7 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCATCAGTCGCTACCACATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGACAT
ATTTATGTTAATAATGATGACACAGACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCCA
AGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCACCTATTTCTGTGCGAGATTGGATG
TTGGTGGTGGTGGTGCTTATATTGGGGACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCA
AGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCC
CGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCA

GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCT
GAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGT
ACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGT
GCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GT

SEQ ID NO:78

323H7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCATCAGTCGCTACCACATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGACAT
ATTTATGTTAATAATGATGACACAGACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCCA
AGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCACCTATTTCTGTGCGAGATTGGATG
TTGGTGGTGGTGGTGCTTATATTGGGGACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:79

323H7 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASSAKGRFTISRDNSKNT
LYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP
EAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:80

323H7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLLESGGGLVQPGGSLRLSCAASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASSAKGRFTISRDNSKNT
LYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSS

SEQ ID NO:81

324C7 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCAGGCCA
GTCAGAACATTGGTAGTGATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATACTAC
ATCCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAAGGCGGTTATTTTAGTGGTCGTAATATTTATGGGAATGC
TTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT
GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACC
TACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACC
CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:82

<u>324C7 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE</u>

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCAGGCCA
GTCAGAACATTGGTAGTGATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATACTAC
ATCCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAAGGCGGTTATTTTAGTGGTCGTAATATTTATGGGAATGC
TTTCGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:83

<u>324C7 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED</u>

DIQMTQSPSSVSASVGDRVTITCQASQNIGSDLAWYQQKPGKAPKLLIYTTSNLASGVPSRFSGSGSGTDFTLTISSLQPE
DFATYYCQGGYFSGRNIYGNAFGGGTKVEIK<u>RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u>

SEQ ID NO:84

<u>324C7 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED</u>

DIQMTQSPSSVSASVGDRVTITC<u>QASQNIGSDLA</u>WYQQKPGKAPKLLIY<u>TTSNLAS</u>GVPSRFSGSGSGTDFTLTISSLQPE
DFATYYC<u>QGGYFSGRNIYGNA</u>FGGGTKVEIK

SEQ ID NO:85

<u>324C7 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE – VARIANT 1</u>

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGGT
ACATTGATAGTGGTGCTACCACATACTACGCGAGCAGTGCAAAAGGCAGATTCACCATCTCCAGAGACAATTCCAA
GAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGATACTA
CGGCATGGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCC

CCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA
ACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCA
CCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:86

<u>324C7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE – VARIANT 1</u>

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGGT
ACATTGATAGTGGTGCTACCACATACTACGCGAGCAGTGCAAAAGGCAGATTCACCATCTCCAGAGACAATTCCAA
GAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGATACTA
CGGCATGGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:87

<u>324C7 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE – VARIANT 1. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED</u>

EVQLVESGGGLVQPGGSLRLSCAASGFSLSGAGVSWVRQAPGKGLEWIGYIDSGATTYYASSAKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCARGYYGMDPWGQGTLVTVSS<u>ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG</u>

SEQ ID NO:88

<u>324C7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE – VARIANT 1. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED</u>

EVQLVESGGGLVQPGGSLRLSCAASGFSLS<u>GAGVS</u>WVRQAPGKGLEWIG<u>YIDSGATTYYASSAKG</u>RFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAR<u>GYYGMDP</u>WGQGTLVTVSS

SEQ ID NO:89

324C7 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE – VARIANT 2

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGGT
ACATTGATAGTGGTGCTACCACATACTACGCGAGCAGTGCAAAAGGCAGATTCACCATCTCCAAAGACAATGCCA
AGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGATAC
TACGGCATGGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTC
CCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCT
CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGG
TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:90

324C7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE – VARIANT 2

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTGGCGCTGGAGTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGGT
ACATTGATAGTGGTGCTACCACATACTACGCGAGCAGTGCAAAAGGCAGATTCACCATCTCCAAAGACAATGCCA
AGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGATAC
TACGGCATGGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:91

324C7 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE – VARIANT 2. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSGAGVSWVRQAPGKGLEWIGYIDSGATTYYASSAKGRFTISKDNAKNTVD
LQMNSLRAEDTAVYYCARGYYGMDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:92

324C7 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE – VARIANT 2. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSGAGVSWVRQAPGKGLEWIGYIDSGATTYYASSAKGRFTISKDNAKNTVD
LQMNSLRAEDTAVYYCARGYYGMDPWGQGTLVTVSS

SEQ ID NO:93

323D10 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GCCATCGATTTGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGGCACAATCACCATCAATTGCCAAGCCAG
TGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGAAAC
ATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAAGTTATTATCGTATTAATAATATTGGTTACGATAATG
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGA
TGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAG
TGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCAC
CTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAC
CCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:94

323D10 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GCCATCGATTTGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGGCACAATCACCATCAATTGCCAAGCCAG
TGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGAAAC
ATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAG
CAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAAGTTATTATCGTATTAATAATATTGGTTACGATAATG
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:95

323D10 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

AIDLTQSPSTLSASVGGTITINCQASESISSWLAWYQQKPGKAPKLLIYETSKLASGVPSRFSGSGSGTEFTLTISSLQPDDF
ATYYCQSYYRINNIGYDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:96

323D10 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

AIDLTQSPSTLSASVGGTITINCQASESISSWLAWYQQKPGKAPKLLIYETSKLASGVPSRFSGSGSGTEFTLTISSLQPDDF
ATYYCQSYYRINNIGYDNAFGGGTKVEIK

SEQ ID NO:97

323D10 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACCGCCTCT
GGATTCTCCCTCAGTAGGAATGCAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGATA
CATTAGCACTAGTGGTACCACATTCTACGCGAACAGCGTGAAAGGCAGATTCACCATCTCCAAAGACAATACCAAG
AACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACTATAAC
TACGCCATGGACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTC
CCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCT
CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGG
TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:98

323D10 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACCGCCTCT
GGATTCTCCCTCAGTAGGAATGCAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGATA
CATTAGCACTAGTGGTACCACATTCTACGCGAACAGCGTGAAAGGCAGATTCACCATCTCCAAAGACAATACCAAG
AACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACTATAAC
TACGCCATGGACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:99

323D10 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSRNAMNWVRQAPGKGLEYIGYISTSGTTFYANSVKGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARDYNYAMDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG

KEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:100

323D10 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSRNAMNWVRQAPGKGLEYIGYISTSGTTFYANSVKGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARDYNYAMDIWGQGTLVTVSS

SEQ ID NO:101

324E2 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATT
GGGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAA
TCAGCAACCTGCAGCCTGAAGATTTTGCAACTTATTACTGTGCAGGCGGTTATAGTGGTAATATTTATGGTTTCGGC
GGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG
TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGG
TGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGC
CTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG
GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:102

324E2 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCA
GTCAGAGTGTTAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATT
GGGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAA
TCAGCAACCTGCAGCCTGAAGATTTTGCAACTTATTACTGTGCAGGCGGTTATAGTGGTAATATTTATGGTTTCGGC
GGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:103

324E2 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSQSVNNNDLAWYQQKPGKAPKRLIYWASKLASGVPSRFSGSGSGTEFTLTISNL
QPEDFATYYCAGGYSGNIYGFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:104

324E2 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTITCQSSQSVNNNDLAWYQQKPGKAPKRLIYWASKLASGVPSRFSGSGSGTEFTLTISNL QPEDFATYYCAGGYSGNIYGFGGGTKVEIK

SEQ ID NO:105

324E2 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACCGCCTCTGG
ATTCTCCCTCAGTAACAATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGAATCAT
TAGTAGTAGTGGTACCACATACTACGCGAGCTCCGCGAAAGGCAGATTCACCATCTCCAAAGACACCTCCAAGAAC
ACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGGGAGCATTTAGCGTC
TGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCT
CCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGT
CGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCT
CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAG
CAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACC
TGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT
GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT
GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCA
TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATG
AGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTA
TAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:106

324E2 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACCGCCTCTGG
ATTCTCCCTCAGTAACAATGCAATAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACATCGGAATCAT
TAGTAGTAGTGGTACCACATACTACGCGAGCTCCGCGAAAGGCAGATTCACCATCTCCAAAGACACCTCCAAGAAC
ACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGGGAGCATTTAGCGTC
TGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:107

324E2 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSVEESGGGLVQPGGSLRLSCTASGFSLSNNAITWVRQAPGKGLEYIGIISSSGTTYYASSAKGRFTISKDTSKNTVDLQM
NSLRAEDTAVYYCAGAFSVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:108

324E2 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSVEESGGGLVQPGGSLRLSCTASGFSLSNNAITWVRQAPGKGLEYIGIISSSGTTYYASSAKGRFTISKDTSKNTVDLQM
NSLRAEDTAVYYCAGAFSVWGQGTLVTVSS

SEQ ID NO:109

324C6 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTGATAGTTGGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATCAGGC
ATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAATCTGCTTATGGTGTTAGTGGTACTAGTAGTTATTTATA
TACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT
GATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTC
ACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:110

324C6 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTGATAGTTGGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATCAGGC
ATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAATCTGCTTATGGTGTTAGTGGTACTAGTAGTTATTTATA
TACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

SEQ ID NO:111

324C6 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQASQSIDSWLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTEFTLTISSLQPD
DFATYYCQSAYGVSGTSSYLYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:112

324C6 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQASQSIDSWLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTEFTLTISSLQPD
DFATYYCQSAYGVSGTSSYLYTFGGGTKVEIK

SEQ ID NO:113

324C6 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

CAGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGA
TTCTCCCTCAGTAGGTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAACCATT
TATACTAGTGGTAGTACATGGTACGCGAGCTGGACAAAAGGCAGATTCACCATCTCCAAAGACAATACCAAGAAC
ACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGATCCTATTATGGC
GGTGATAAGACTGGTTTAGGCATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCC
ATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA
CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC
CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACA
TCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTC
ACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA
CACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCT
CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC
CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:114

324C6 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

CAGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGA
TTCTCCCTCAGTAGGTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAACCATT
TATACTAGTGGTAGTACATGGTACGCGAGCTGGACAAAAGGCAGATTCACCATCTCCAAAGACAATACCAAGAAC
ACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGATCCTATTATGGC
GGTGATAAGACTGGTTTAGGCATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:115

324C6 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

QSLVESGGGLVQPGGSLRLSCTASGFSLSRYYMTWVRQAPGKGLEWIGTIYTSGSTWYASWTKGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARSYYGGDKTGLGIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAA
GAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:116

324C6 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

QSLVESGGGLVQPGGSLRLSCTASGFSLSRYYMTWVRQAPGKGLEWIGTIYTSGSTWYASWTKGRFTISKDNTKNTVD
LQMNSLRAEDTAVYYCARSYYGGDKTGLGIWGQGTLVTVSS

SEQ ID NO:117

338H4 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCA
GTCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCGCCTGATCTATCTGGC
ATCTACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTACACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAAGCAATTATAACGGTAATTATGGTTTCGGCGGAGGGA
CCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAA
CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCA
GCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGA
GCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:118

338H4 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCA
GTCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCGCCTGATCTATCTGGC
ATCTACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTACACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAAGCAATTATAACGGTAATTATGGTTTCGGCGGAGGGA
CCAAGGTGGAGATCAAA

SEQ ID NO:119

338H4 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSSLSASVGDRVTINCQASQNIYSYLSWYQQKPGKVPKRLIYLASTLASGVPSRFSGSGSGTDYTLTISSLQPE
DVATYYCQSNYNGNYGFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:120

338H4 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSSLSASVGDRVTINCQASQNIYSYLSWYQQKPGKVPKRLIYLASTLASGVPSRFSGSGSGTDYTLTISSLQPE
DVATYYCQSNYNGNYGFGGGTKVEIK

SEQ ID NO:121

338H4 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGATCGGAA
TCATTTATGCTAGTGGTAGCACATACTACGCGAGCTCGGCGAAAGGCAGATTCACCATCTCCAAAGACAATACCAA
GAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAATTTATGA
CGGCATGGACCTCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGCCCATCGGTCTTCCC
CCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA
ACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCA
CCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC
GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:122

338H4 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTC
TGGATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGATCGGAA
TCATTTATGCTAGTGGTAGCACATACTACGCGAGCTCGGCGAAAGGCAGATTCACCATCTCCAAAGACAATACCAA
GAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAATTTATGA
CGGCATGGACCTCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:123

338H4 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSSYAMSWVRQAPGRGLEWIGIIYASGSTYYASSAKGRFTISKDNTKNTVDL
QMNSLRAEDTAVYYCARIYDGMDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGAPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:124

338H4 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCTASGFSLSSYAMSWVRQAPGRGLEWIGIIYASGSTYYASSAKGRFTISKDNTKNTVDL
QMNSLRAEDTAVYYCARIYDGMDLWGQGTLVTVSS

SEQ ID NO:125

330F11 HUMANIZED LIGHT CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTAATAACTACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAGGGC
ATCCACTCTGGAATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAAGCTATAATGGTGTTGGTAGGACTGCTTTCGGCGGAG
GGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA
ATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT
AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG
AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO:126

330F11 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN NUCLEOTIDE SEQUENCE

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCA
GTCAGAGCATTAATAACTACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAGGGC

ATCCACTCTGGAATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAAGCTATAATGGTGTTGGTAGGACTGCTTTCGGCGGAG
GGACCAAGGTGGAGATCAAA

SEQ ID NO:127

330F11 HUMANIZED LIGHT CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN KAPPA CONSTANT DOMAIN IS UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQASQSINNYLAWYQQKPGKAPKLLIYRASTLESGVPSRFSGSGSGTEFTLTISSLQPD
DFATYYCQSYNGVGRTAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:128

330F11 HUMANIZED LIGHT CHAIN VARIABLE LIGHT CHAIN AMINO ACID SEQUENCE. COMPIMENTARITY DETERMINING REGIONS ARE UNDERLINED

DIQMTQSPSTLSASVGDRVTITCQASQSINNYLAWYQQKPGKAPKLLIYRASTLESGVPSRFSGSGSGTEFTLTISSLQPD
DFATYYCQSYNGVGRTAFGGGTKVEIK

SEQ ID NO:129

330F11 HUMANIZED HEAVY CHAIN FULL-LENGTH NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCTCCCTCAATAACTACTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAA
CCATTAGTAGTGGTGCGTATACATGGTTCGCCACCTGGGCGACAGGCAGATTCACCATCTCCAGAGACAATTCCAA
GAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGATATTCTTCT
ACTACTGATTGGACCTACTTTAACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG
ACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTG
TCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAAC
TCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAG
GACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTC
AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACA
GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGG
TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGG
TGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTA
TCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCT
TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO:130

330F11 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN NUCLEOTIDE SEQUENCE

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCTCCCTCAATAACTACTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAA
CCATTAGTAGTGGTGCGTATACATGGTTCGCCACCTGGGCGACAGGCAGATTCACCATCTCCAGAGACAATTCCAA
GAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGATATTCTTCT
ACTACTGATTGGACCTACTTTAACATCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

SEQ ID NO:131

330F11 HUMANIZED HEAVY CHAIN FULL-LENGTH AMINO ACID SEQUENCE. HUMAN GAMMA-1 CONSTANT DOMAIN IS UNDERLINED

EVQLVESGGGLVQPGGSLRLSCAASGFSLNNYWMSWVRQAPGKGLEWIGTISSGAYTWFATWATGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARYSSTTDWTYFNIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE
AAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:132

330F11 HUMANIZED HEAVY CHAIN VARIABLE HEAVY CHAIN AMINO ACID SEQUENCE. COMPLIMENTARITY DETERMINING REGIONS ARE UNDERLINED

EVQLVESGGGLVQPGGSLRLSCAASGFSLNNYWMSWVRQAPGKGLEWIGTISSGAYTWFATWATGRFTISRDNSKN
TLYLQMNSLRAEDTAVYYCARYSSTTDWTYFNIWGQGTLVTVSS

CLAIMS

What is claimed is:

1. An isolated mA) or antigen-binding fragment thereof having a binding specificity to human ROR1, 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, SEQ ID NO:76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:116, SEQ ID NO:120, SEQ ID NO:124, SEQ ID NO:128, or SEQ ID NO:132, 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 ROR1 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 ROR1, inhibiting human ROR1 activity, induction of apoptosis, regulation of EGFR signalling pathway, upregulation of EMT genes, enhancing T cell activation, stimulating antibody response, reversing the suppressive function of an immunosuppressive cell, or a combination thereof.

5. 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.

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

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

8. 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.

9. 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.

10. An IgG1 heavy chain for an isolated mAb or antigen-binding fragment thereof having a binding specificity to human ROR1, 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, SEQ ID NO:79, SEQ ID NO:87, SEQ ID NO:91, SEQ ID NO:99, SEQ ID NO:107, SEQ ID NO:115, SEQ ID NO:123, or SEQ ID NO:131, wherein the percentage homology is not less than 90%.

11. A kappa light chain for an isolated mAb or antigen-binding fragment thereof having a binding specificity to human ROR1, 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, SEQ ID NO:75, SEQ ID NO:83, SEQ ID NO:95, SEQ ID NO:103, SEQ ID NO:111, SEQ ID NO:119, or SEQ ID NO:127, wherein the percentage homology is not less than 90%.

12. A variable light chain for an isolated mAb or antigen-binding fragment thereof having a binding specificity to human ROR1, 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, SEQ ID NO:76, SEQ ID NO:84, SEQ ID NO:96, SEQ ID NO:104, SEQ ID NO:112, SEQ ID NO:120, or SEQ ID NO:128, wherein the percentage homology is not less than 90%.

13. A variable heavy chain an isolated mAb or antigen-binding fragment thereof having a binding specificity to human ROR1, 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, SEQ ID NO:80, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:100, SEQ ID NO:108, SEQ ID NO:116, SEQ ID NO:124, or SEQ ID NO:132, wherein the percentage homology is not less than 90%.

14. An isolated nucleic acid encoding the isolated mAb or antigen-binding fragment according to Claim 1, the IgG1 heavy Chain of Claim 10, the kappa light chain of Claim 11, the variable light chain of Claim 12, or the variable heavy chain of Claim 13.

15. An expression vector comprising the isolated nucleic acid of Claim 14, , wherein the vector is expressible in a cell.

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

17. A method of producing an antibody comprising culturing the host cell of one of Claim 16, so that the antibody is produced.

18. An immuno-conjugate, comprising the isolated mAb or antigen-binding fragment thereof according to Claim 1 and a drug unit, wherein the drug unit is linked to the isolated mAb or an antigen-binding fragment through a linker, and wherein the linker comprises 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.

19. The immuno-conjugate according to claim18, wherein the drug unit is selected from a cytotoxic agent, an immune regulatory reagent, a combination thereof.

20. The immuno-conjugate according to claim 18, 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.

21. The immuno-conjugate according to claim 20, wherein the cytotoxic agent is selected from a calicheamicin, ozogamicin, monomethyl auristatin E, emtansine, a derivative or a combination thereof.

22. The immuno-conjugate according to claim 20, wherein the immune regulatory reagents activate or suppress immune cells, T cell, NK cell, B cell, macrophage, or dendritic cell.

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

24. The pharmaceutical composition of Claim 23, further comprising 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, 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.

25. A pharmaceutical composition, comprising the immuno-conjugate of Claim 21 and a pharmaceutically acceptable carrier.

26. 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 ROR1.

27. The method of Claim 26, 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.

28. The method of Claim 26, further comprising co-administering an effective amount of of a therapeutic agent, wherein the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, or a combination thereof.

29. The method of Claim 28, 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, letrozole, 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, or a derivative or a combination thereof.

30. The method of Claim 26, wherein the subject is a human.

31. 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 the Immunization strategy

			Adjuvant		
Immunization No.	Day	Antigen	Cohort 1	Cohort 2	Dose per rabbit
1	0	Human ROR1 ECD	Complete Freunds	Titermax	30 ug
2	7	Human ROR1 cells	Alum/CpG 2007	Alum/CpG 2007	10 x 10e6
3	14	Mouse ROR1 ECD	Incomplete Freunds	Titermax	10 ug
4	21	Mouse ROR1 cells	Alum/CpG 2007	Alum/CpG 2007	10 x 10e6
5	28	Human ROR1 ECD	Incomplete Freunds	Titermax	10 ug
6	37	Human ROR1 cells	No adjuvant - IP only	No adjuvant - IP only	10 x 10e6

FIGURE 2 shows the Immunization Schedule

	Sept				Oct				Nov
Immunogen	9	16	23	30	7	16	20	30	6
Human ROR1-HIS	0								
Human ROR1-Cells		7							
Mouse ROR1-HIS			14						
Mouse ROR1-Cells				21					
Human ROR1-HIS					28				
Serology days 29-35									
Human ROR1-Cells						37			
Harvest day 4 post-immunization							41		
Harvest day 14 post-immunization								51	
Harvest day 21 post-immunization									58

FIGURE 3 shows day of tissue harvest post-final immunization

	Freunds/(Alum/CpG)			Titermax/(Alum/CpG)		
Cohort	1			2		
Rabbit ID#	6378R	6392R	R6234	6606R	6068R	R6513
Days post	4	13	21	4	13	21

FIGURE 4 Summary of native rabbit IgG antibody in B cell culture supernatant or chimeric recombinant rabbit/human IgG antibody binding activity.

		BCC well ID	Human ROR1 directly coated on the plate – detection of ROR1-specific IgG ELISA (OD_{450})	Biotinylated human ROR1 added to an avidin coated plate - detection of ROR1-specific IgG ELISA (OD_{450})	Biotinylated human ROR1 "Kringle domain" added to an avidin coated plate - detection of ROR1-Kringle-specific IgG ELISA (OD_{450})	Human ROR2 directly coated on the plate – detection of ROR1-specific IgG ELISA (OD_{450})	Mouse ROR1 directly coated on the plate – detection of ROR1-specific IgG ELISA (OD_{450})	Human ROR1 "Frizzled-Kringle domain" directly coated on the plate - detection of ROR1-Frizzled-Kringle-specific IgG ELISA (OD_{450})	Biotinylated human ROR1 "Frizzled-Kringle domain" added to an avidin coated plate - detection of ROR1-Frizzled-Kringle-specific IgG ELISA (OD_{450})	Human ROR1 "Ig-Frizzled domain" directly coated on the plate - detection of ROR1-Ig-Frizzled-specific IgG ELISA (OD_{450})	Biotinylated human ROR1 "Ig-Frizzled domain" added to an avidin coated plate - detection of ROR1-Ig-Frizzled-specific IgG ELISA (OD_{450})	Human ROR1-CHO cells – detection of ROR1-specific IgG by FACS (MFI)
Kringle-specific (mouse cross-reactive)	1	226E12	nd	nd	0.41	0.09	0.25	nd	nd	nd	nd	13
	2	340F4	1.80	0.46	4.00	0.15	2.27	1.03	0.45	0.19	0.16	7
	3	339G5	1.15	0.23	4.00	0.12	2.38	0.87	0.34	0.15	0.27	7
	4	340D5	0.59	0.13	0.89	0.11	1.17	0.36	0.21	0.10	0.13	7
	5	341F4	0.41	0.12	2.33	0.19	1.09	0.27	0.21	0.15	0.13	7
	6	329E12	0.55	nd	nd	0.24	4.00	1.86	2.50	0.25	0.18	9
	7	330F11	0.98	nd	nd	0.25	4.00	1.98	1.71	0.28	0.15	5
Ig domain-specific (mouse cross-reactive)	8	327C2	2.70	nd	nd	0.21	4.00	0.20	0.13	2.15	1.19	198
	9	322C10	1.83	nd	nd	0.20	4.00	0.18	0.16	2.04	2.30	196
	10	330F2	1.13	nd	nd	0.17	0.65	0.16	0.17	2.11	0.40	106
	11	324E2	0.48	nd	nd	0.21	2.17	0.18	0.10	1.29	0.62	25
	12	324G10	1.47	nd	nd	0.17	4.00	0.17	0.17	2.28	1.05	22
	13	323D10	2.32	nd	nd	0.23	4.00	0.32	0.17	1.94	2.23	20
	14	331E1	0.77	nd	nd	0.25	4.00	0.12	0.11	2.66	1.25	10
Ig domain-specific (NOT mouse cross-reactive)	15	323A3	1.97	nd	nd	0.18	0.29	0.18	0.17	2.46	2.34	340
	16	327F11	2.91	nd	nd	0.21	0.20	0.17	0.21	2.36	2.56	330
	17	324H4	2.61	nd	nd	0.21	0.23	0.17	0.15	1.99	1.03	296
	18	330F7	1.23	nd	nd	0.20	0.17	0.16	0.16	2.27	1.43	264
	19	326C11	2.80	nd	nd	0.16	0.18	0.22	0.11	2.27	1.14	234
	20	324G3	2.36	nd	nd	0.17	0.18	0.15	0.13	1.83	1.93	222
	21	326E12	0.46	nd	nd	0.20	0.19	0.15	0.13	2.49	1.21	216
	22	324C7	2.74	nd	nd	0.18	0.21	0.13	0.13	2.46	2.67	190
	23	332A7	1.32	nd	nd	0.26	0.19	0.16	0.14	1.94	0.98	104
	24	323H7	1.82	nd	nd	0.18	0.20	0.16	0.16	1.67	1.78	90
Frizzled domain-specific (mouse cross-reactive)	25	324C6	1.05	nd	nd	0.17	4.00	2.04	2.71	2.66	1.12	49
	26	338H4	4.00	nd	nd	0.17	4.00	3.01	1.80	2.27	0.22	277
	27	339B7	4.00	nd	nd	0.21	3.38	2.95	3.21	3.16	2.96	61

FIGURE 4a Rabbit IgG in B cell culture supernatant analyzed for binding to various full length forms of recombinant human or mouse ROR1, human ROR2, or truncated recombinant fragments of human ROR1.

		BCC well ID	Mono-valent binding to human ROR1 kdis(1/s)	Bi-valent binding to human ROR1 kdis(1/s)	Mouse ROR1 kdis(1/s)	Human ROR2 kdis(1/s)	Human ROR1 "Frizzled-Kringle domain kdis(1/s)	Human ROR1 "Ig-Frizzled domain" kdis(1/s)	Human ROR1-CHO FACS	Mouse ROR1-CHO FACS
Kringle-specific (mouse cross-reactive)	1	226E12	nd	3.40E-03	nd	nd	nd	nd	YES	nd
	2	340F4	WEAK	2.28E-10	YES	NEG	YES	NEG	NEG	nd
	3	339G5	WEAK	3.59E-10	YES	NEG	YES	NEG	YES	nd
	4	340D5	NEG	6.72E-10	NEG	NEG	NEG	NEG	NEG	nd
	5	341F4	WEAK	2.78E-10	YES	NEG	YES	NEG	NEG	nd
	6	329E12	WEAK	1.79E-10	YES	NEG	YES	NEG	YES	nd
	7	330F11	1.26E-08	6.87E-10	YES	NEG	YES	NEG	YES	nd
Ig domain-specific (mouse cross-reactive)	8	327C2	1.64E-08	1.85E-08	NEG	NEG	NEG	YES	YES	YES
	9	322C10	3.42E-10	5.44E-03	YES	NEG	NEG	YES	YES	YES
	10	330F2	NEG	9.33E-03	NEG	NEG	NEG	NEG	YES	YES
	11	324E2	1.60E-10	5.72E-03	YES	NEG	NEG	YES	YES	YES
	12	324G10	3.16E-06	4.37E-06	YES	NEG	NEG	YES	YES	YES
	13	323D10	5.31E-10	9.61E-03	YES	NEG	NEG	YES	YES	YES
	14	331E1	1.83E-09	1.24E-02	YES	NEG	NEG	YES	YES	YES
Ig domain-specific (NOT mouse cross-reactive)	15	323A3	NEG	9.89E-03	NEG	NEG	NEG	NEG	YES	NEG
	16	327F11	NEG	3.22E-08	NEG	NEG	NEG	YES	YES	WEAK
	17	324H4	1.31E-08	9.74E-09	NEG	NEG	NEG	YES	YES	WEAK
	18	330F7	6.88E-10	9.19E-03	NEG	NEG	NEG	YES	YES	WEAK
	19	326C11	5.76E-09	1.58E-08	NEG	NEG	NEG	YES	YES	NEG
	20	324G3	4.93E-09	9.72E-09	NEG	NEG	NEG	YES	YES	NEG
	21	326E12	2.87E-10	1.30E-02	NEG	NEG	NEG	YES	YES	WEAK
	22	324C7	1.35E-08	3.55E-08	NEG	NEG	NEG	YES	YES	NEG
	23	332A7	1.23E-08	5.25E-03	NEG	NEG	NEG	YES	YES	WEAK
	24	323H7	2.08E-08	6.20E-03	NEG	NEG	NEG	YES	YES	NEG
Frizzled domain-specific (mouse cross-reactive)	25	324C6	1.69E-05	2.35E-07	NEG	NEG	YES	YES	YES	YES
	26	338H4	1.17E-08	1.01E-10	YES	NEG	YES	YES	YES	YES
	27	339B7	4.00E-08	8.50E-05	YES	NEG	YES	YES	YES	YES

FIGURE 4b Chimeric rabbit/human IgG analyzed for binding to various full length forms of recombinant human or mouse ROR1, ROR2, or truncated recombinant fragments of human ROR1

FIGURE 5 Full length human IgG1 antibodies with humanized ROR1-specific variable region binding domains analyzed for the rate of antibody dissociation from monovalent binding to recombinant full length human ROR1 by Octet.

	Humanized ROR1-specific antibody	Monovalent binding to human ROR1 kdis(1/s)
1	226E12-L1H1	4.15E-02
2	323H7-L1H4	7.00E-04
3	324C7-L1H1	1.87E-03
4	323D10-L3H2	4.24E-03
5	324E2-L6H3	6.10E-03
6	324C6-L1H2	4.03E-02
7	338H4-L4H3	2.38E-03
8	330F11-L1H1	2.97E-02

FIGURE 6 ELISA analysis of rabbit serum IgG binding to human and mouse ROR1

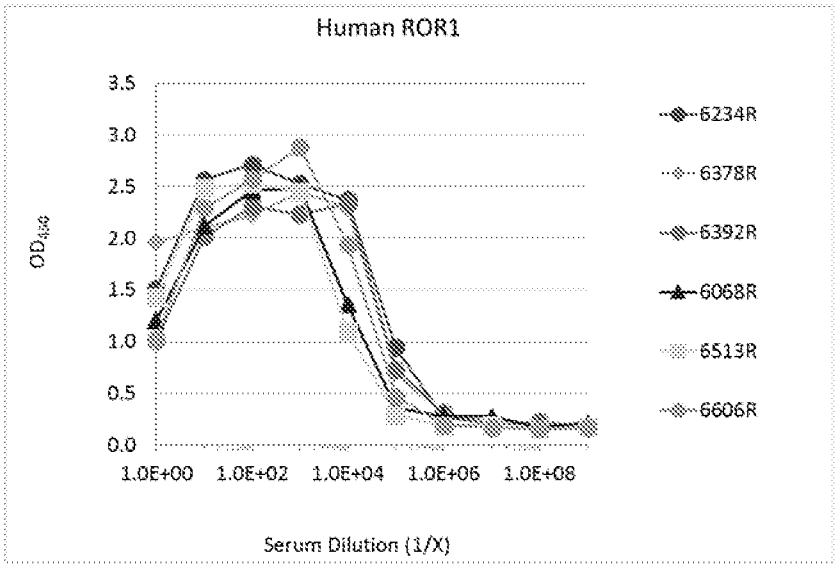

FIGURE 6A Serum from rabbits immunized with human and mouse cell expressed ROR1 analyzed for IgG binding of recombinant human ROR1 by ELISA.

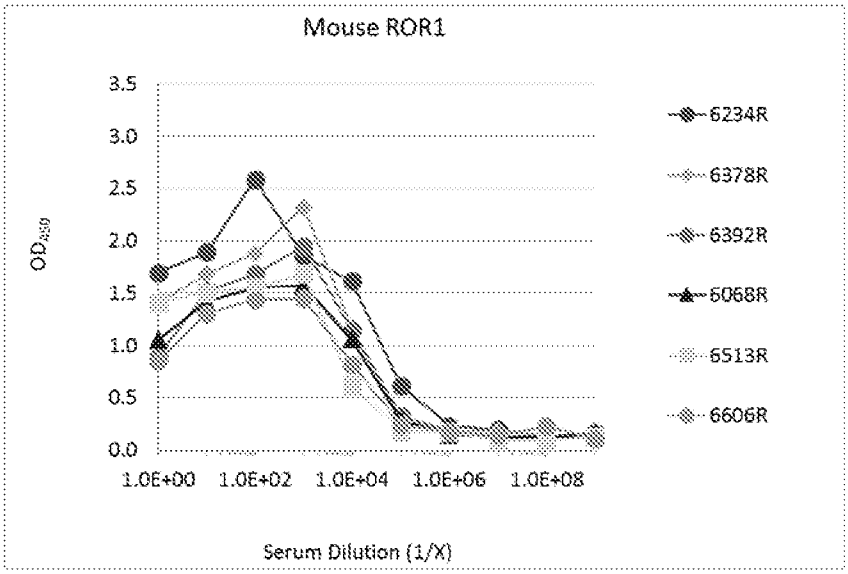

FIGURE 6B Serum from rabbits immunized with human and mouse cell expressed ROR1 analyzed for IgG binding of recombinant mouse ROR1 by ELISA.

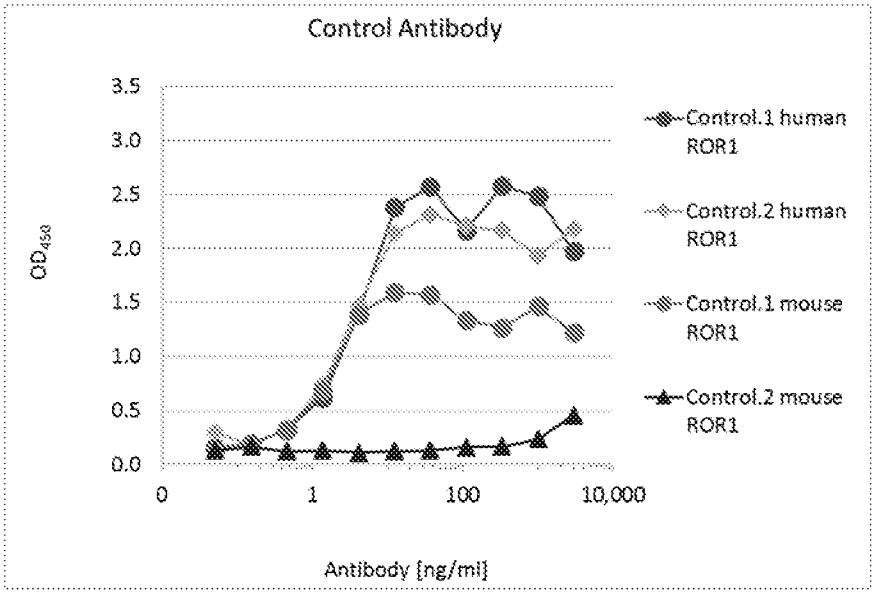

FIGURE 6C Control human IgG1 antibodies analyzed for binding to recombinant human or mouse ROR1 by ELISA.

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 SIBA013PCT	**IMPORTANT DECLARATION**	Date of mailing *(day/month/year)* 07 SEP 2018
International application No. PCT/US18/39152	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/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774