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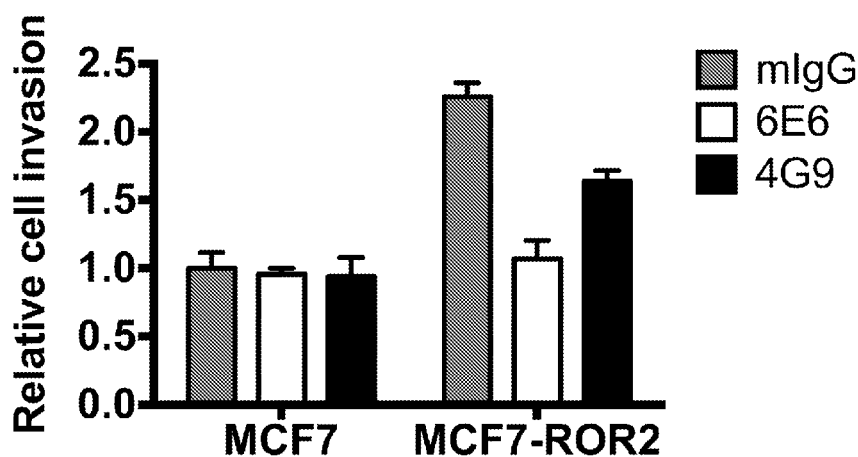
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(54) Title: ANTI-ROR-2 ANTIBODIES AND METHODS OF USE

FIG. 11A



(57) Abstract: Provided herein are, *inter alia*, antibodies (e.g., humanized antibodies, monoclonal antibodies), antibody fragments (e.g., scFvs) and antibody compositions (e.g., chimeric antigen receptors, bispecific antibodies), which bind human tyrosine kinase-like orphan receptor 2 (ROR2) with high efficiency and specificity. The antibodies and antibody compositions provided herein include novel light and heavy chain domain CDRs and framework regions and are, *inter alia*, useful for diagnosing and treating cancer and other ROR2-related diseases.

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Anti-ROR-2 Antibodies and Methods of Use

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/936,900, filed November 18, 2019, which is hereby incorporated by reference in its entirety and for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with government support under CA236361 and CA81534 awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO A SEQUENCE LISTING, A TABLE OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII TEXT FILE

[0003] The Sequence Listing written in file 48537-632001WO_ST25.TXT, created on November, 18, 2020, 122,880 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

BACKGROUND

[0004] Receptor tyrosine kinase-like orphan receptor 2 (ROR2) is a developmentally restricted receptor for Wnt5a. Human ROR2 is a 943 amino acid single-pass type I membrane protein with a calculated molecular weight of 104.8 kDa. It is highly conserved across several species with a 92% amino acid identity between the mouse and human proteins. ROR2 can repress transcription of Wnt target genes and modulate Wnt signaling by sequestering canonical Wnt ligands, thereby serving as a tumor suppressor in different cell contexts. Recently, ROR2 has been implicated in progression of numerous cancers including breast, ovarian, pancreatic, cervical, gastric, renal, head and neck, bone, skin and prostate. Therefore, there is a need for antibodies, antibody fragments, bispecific antibodies and chimeric antigen receptors that specifically target human ROR2, inhibit its function and thereby serve as effective therapeutics and diagnostics. The compositions and methods provided herein address these and other needs in the art.

BRIEF SUMMARY OF THE INVENTION

[0005] In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy

chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

- 5 **[0006]** In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in
10 SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

- [0007]** In another aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and wherein the light
15 chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

- [0008]** In another aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as
20 set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

- [0009]** In an aspect is provided a method of treating cancer in a subject in need thereof, the method including administering to a subject a therapeutically effective amount of an antibody
25 provided herein including embodiments thereof.

[0010] In an aspect is provided a method of inhibiting metastasis of a ROR2 expressing cancer in a subject in need thereof, the method including administering to a subject a therapeutically effective amount of an antibody provided herein, including embodiments thereof.

- [0011]** In another aspect is provided a method of detecting a ROR2 expressing cell, the method
30 including (i) contacting a ROR2-expressing cell with an antibody provided herein including

embodiments thereof; and (ii) detecting binding of the antibody to a ROR2 protein expressed by the cell.

[0012] In another aspect is provided a method of delivering a therapeutic agent to a ROR2 expressing cell, the method including contacting a ROR2 expressing cell with an antibody provided herein including embodiments thereof, wherein the antibody is attached to a therapeutic agent.

[0013] In another aspect is provided a method of inhibiting migration of a ROR2-expressing cell, the method including contacting a ROR2 expressing cell with an antibody provided herein including embodiments thereof.

[0014] In an aspect is provided a anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0015] In an aspect is provided a anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:2; and a light chain variable domain of SEQ ID NO:4.

[0016] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:1; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:3.

[0017] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0018] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:6; and a light chain variable domain of SEQ ID NO:8.

[0019] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:5; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:7.

5 [0020] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in
10 SEQ ID NO:42.

[0021] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:10; and a light chain variable domain of SEQ ID NO:12.

[0022] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds
15 the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:9; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:11.

[0023] In an aspect is provided an anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain
20 including: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0024] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds
25 the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:14; and a light chain variable domain of SEQ ID NO:16.

[0025] In an aspect is provided an anti-ROR2 antibody, wherein the anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:13; and a light chain variable domain encoded by the
30 nucleic acid sequence of SEQ ID:15.

[0026] In another aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO: 28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID NO:27; and (ii) a transmembrane domain.

[0027] In an aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID NO:33; and (ii) a transmembrane domain.

[0028] In an aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38, and a CDR H3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain.

[0029] In an aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44, and a CDR H3 as set forth in SEQ ID NO:45; and (ii) a transmembrane domain.

[0030] In another aspect is provided a method of treating cancer in a subject in need thereof the method including, administering a therapeutically effective amount of a chimeric antigen receptor provided herein including embodiments thereof to a subject.

[0031] In another aspect is provided an anti-receptor tyrosine kinase-like orphan receptor 2 (ROR2) antibody, capable of binding an extracellular domain of ROR2 including an amino acid sequence of SEQ ID NO:22.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **FIG. 1.** Comparison of the extracellular regions of human and mouse ROR2.

Alignment of the amino acid sequences of the extracellular region of human (upper sequence) and mouse (lower sequence) ROR2 are shown. Dots indicate homology at that position, whereas differences are designated by the single letter amino acid codons. The Ig-like, CRD and kringle domains are labeled and indicated by lines above the sequence.

[0033] **FIG.s 2A-2D.** Amino acid sequence and alignment to the closest mouse IGHV (upper sequence) or IGKV (lower sequence) germline gene depicted for each of the four mouse anti-human ROR2 hybridomas, designated (**FIG. 2A**) 6E6, (**FIG. 2B**) 4G9, (**FIG. 2C**) 5C11 and (**FIG. 2D**) 5G3. For each alignment the upper sequence depicts the amino acid sequence of the heavy or light chain variable region beginning at the first codon of the first framework region and ending with the last codon of the fourth framework region. The lower sequence depicts the amino acid sequence of the heavy or light chain variable region of the most homologous mouse IGHV or IGKV germline gene. The framework (FR) and complementarity determining (CDR) regions are marked above the sequences, and the differences between the two sequences are noted below the aligned sequences, and are designated as single letter amino acid codons in bold font.

[0034] **FIG. 3.** Assessment of binding of anti-ROR2 mAb to recombinant human ROR2 at varying amounts of immobilized protein and concentrations of soluble mAb. Wells were coated overnight with recombinant human ROR2-extracellular domain (ROR2-ECD), at 27, 9, 3 and 1 nM, washed and blocked with sample buffer (1X BBS+1% BSA) at 37° C for 90 minutes. Serial dilutions ranging from 500-31 ng/ml of 6E6, 4G9, 5C11 or 5G3 mAb were added to wells, incubated at ambient temperature for 60 minutes, washed and detected with HRP-conjugated goat anti-mouse IgG and developed with TMB microwell peroxidase substrate. Development was terminated by addition of 1M O-phosphoric acid and absorbance read at 450 nM on a SpectraMax340 Microplate Reader. Absorbance values are plotted on the ordinate relative to mAb concentration (ng/ml) on the abscissa. Higher absorbance values at lower plate coat concentration and lower amounts of soluble mAb indicate a relative higher binding affinity for 6E6 and 4G9 compared to 5C11 and 5G3

[0035] **FIG.s 4A and 4B.** Affinity measurement of binding of the 6E6 and 4G9 mAb to recombinant ROR2 protein. (**FIG. 4A**) Analysis was performed using a KinExA 3200 instrument. The proportion of anti-human ROR2 mAb bound to particles coated with ROR2 protein (y-axis) in the presence of increasing molar (M) concentration of soluble ROR2

competitor (x-axis) is shown for 6E6 (upper panel) and 4G9 (lower panel). **(FIG. 4B)** Illustration of the 95% confidence interval for the measured K_d of 6E6 (upper panel) and 4G9 (lower panel) for binding to human ROR2.

[0036] FIG. 5. Identification of the binding regions of anti-human ROR2 mAb by assessment

of binding to chimeric human/mouse recombinant ROR2 protein. The left panel shows schematics of the chimeric constructs of the extracellular portion of ROR2 used to map the binding region of each of the four ROR2 mAb. The dark regions of each construct indicate human ROR2 and the hatched portions regions of mouse ROR2. h1-111 and h1-160 refer to the first 111 and 160 amino acids of human ROR2, respectively. hCRD and hKringles contain the cysteine rich domain and the Kringles domain of human ROR2. Each recombinant protein was transferred onto nylon membrane, probed with the 6E6, 4G9, 5C11, 5G3 or anti-his tag mAb, and detected with an anti-mouse IgG antibody conjugated with horse radish peroxidase, as shown in the right panel. The 6E5 and 5C11 mAbs bind to ROR2 recombinant proteins that contain the human kringles domain. The 4G9 and 5G3 mAbs bind to ROR2 recombinant proteins within the first 111 aa of human ROR2, which includes the Ig-like domain.

[0037] FIG. 6. Identification of amino acids required for binding of anti-human ROR2 mAb to the Kringles domain of human ROR2. Binding of 6E6, 4G9 and 5C11 mAb was assessed using recombinant human ROR2 proteins in which one amino acid that differs between human and mouse ROR2 within the kringles domain was replaced with the corresponding amino acid of mouse ROR2. Each recombinant protein was transferred onto nylon membrane, probed with the 6E6, 4G9, or 5C11 mAb, and detected with an anti-mouse IgG antibody conjugated with horse radish peroxidase, as shown in the top panel. Alignment of the protein sequences of the kringles domain of human and mouse ROR2 are shown in the lower panel, and the boxed amino acids indicate the amino acids changes made for each recombinant protein.

[0038] FIG.s 7A and 7B. 6E6 and 4G9 anti-human ROR2 mAb specifically bind human ROR2. **(FIG. 7A)** Binding of the 6E6 and 4G9 mAb to human ROR was assessed by flow cytometric staining and analysis of several cell lines known to express ROR2. Cells were stained on ice for 20 minutes with 10 ug/ml of 6E6 or 4G9 anti-human ROR2-Alexa647 conjugated mAb (shaded histograms) or equal amounts of isotype matched control mAb (open histograms), washed and analyzed. Histograms depict the relative fluorescence intensity (x axis) of viable cells as determined by light scatter characteristics. **(FIG. 7B)** Specificity was validated by the

absence of binding to HCT116 colorectal cancer cells and HEK293 cells in which ROR2 expression was eliminated using CRISPR-cas9, compared to parental cell lines.

[0039] FIG. 8. 6E6 and 4G9 anti-human ROR2 mAb bind to ROR2 expressed by BR1936 breast cancer PDX cells. BR1936 and BR1367 (ROR2 negative) breast cancer PDX cells were stained with 10 ug/ml of 6E6 or 4G9 anti-human ROR2-Alexa647 conjugated mAb (shaded histograms) or equal amounts of isotype matched control mAb (open histograms). Cells were stained on ice for 20 minutes, washed and analyzed by flow cytometry. Histograms depict the relative fluorescence intensity (x axis) of viable cells as determined by light scatter characteristics. Both 6E6 and 4G9 bind to BR1936 cells, but not BR1367 cells that do not express human ROR2.

[0040] FIG. 9. 6E6 and 4G9 anti-human ROR2 mAb do not bind to peripheral blood mononuclear cells (PBMC) or lymphocytes isolated from healthy donors. PBMC were isolated by ficoll density centrifugation from whole blood obtained with consent from healthy donors. Cells were stained with 5 ug/ml of 6E6 or 4G9 anti-human ROR2-Alexa647 conjugated mAb (shaded histograms) or equal amounts of isotype matched control mAb (open histograms) on ice for 20 minutes, washed and analyzed by flow cytometry. Histograms depict staining of live viable mononuclear cells or lymphocytes as determined by light scatter characteristics. Staining of K562 cells was performed as a positive control.

[0041] FIG.s 10A and 10B. 6E6 and 4G9 anti-human ROR2 mAb are internalized by K562 but not JEKO cells. K562 and JEKO (ROR2 negative) cells were stained with 10 ug/ml of 6E6 or 4G9 anti-human ROR2-pHrodo conjugated mAb on ice for 30 minutes, washed and aliquoted into four fractions. One plate was kept on ice, and the other three transferred to 37°C for 30, 60 or 120 minutes. Following incubation, cells were washed and analyzed by flow cytometry. **(FIG. 10A)** Histograms depict the relative fluorescence intensity (x axis) of viable cells as determined by light scatter characteristics. Shaded histograms depict stained cells incubated at 37°C for 120 min, dashed histograms depict stained cells incubated at 4°C for 120 min, and open histograms depict unstained cells incubated at 37°C for 120 min. Increased relative fluorescence is noted for both 6E6 (upper panel) and 4G9 (lower panel) pHrodo-conjugated mAb for K562 cells that express ROR2, but not ROR2 negative JEKO cells, as compared to stained cells incubated at 4°C for 120 min or unstained cells incubated at 37°C for 120 min. **(FIG. 10B)** Graphic representation of the increase of the mean fluorescence (y-axis) of 6E6 or 4G9 pHrodo conjugated mAb on K562 cells over time (x-axis). Δ MFI is the mean fluorescence intensity of

K562 cells stained with either pHrodo conjugated mAb incubated at 37°C minus the mean fluorescence intensity of an aliquot of the same stained cells incubated at 4°C for the equivalent amount of time.

[0042] FIG.s 11A and 11B. 6E6 and 4G9 anti-human ROR2 mAb inhibit Wnt5a induced invasion of MCF7-ROR breast cancer cells. MCF7 breast cancer cells transfected with either control vector or ROR2-expression vector were cultured overnight in Dulbecco's modified Eagle's medium (DMEM) supplemented with 0.5% fetal bovine serum (FBS) without growth factors. The following day, cells were removed and 10^5 cells suspended in 0.5% FBS DMEM media with 100 ng/ml recombinant Wnt5a and 25 ug/ml of mouse IgG, 6E6, or 4G9 anti-human ROR2 mAb in Matrigel-coated, growth-factor-reduced, 8 uM pore size invasion chambers. Following incubation at 37°C for 24 hours, wells were washed with phosphate buffered saline (PBS) and fixed with 4% paraformaldehyde. Cells on the apical side of each insert were removed by scraping, while cells that migrated to the basal side of the membrane were stained by Diff-Quick staining reagents and visualized with a Nikon inverted microscope. **(FIG. 11A)** Histograms display the average number of invading cells in each of three chambers of MCF7 cells or MCF7-ROR2 cells treated with mouse IgG (gray bars), 6E6 mAb (white bars) or 4G9 (black bars), normalized to MCF7 treated with control mIgG. Data are shown as mean $\pm$ SD (n=3). **(FIG. 11B)** Representative photomicrographs of invasive cells from MCF7 cells (upper panels) or MCF7-ROR2 cells (lower panels) treated with either 25 ug/ml of control antibody (left panels) 6E6 anti-ROR2 mAb (center panels) or 4G9 anti-human ROR2 mAb.

[0043] FIG.s 12A and 12B. Affinity measurement and binding specificity of the 6E6 single chain variable fragment (scFv) for human ROR2. Analysis was performed using a KinExA 3200 instrument. **(FIG. 12A)** The proportion of the 6E6 anti-human ROR2 scFv bound to particles coated with recombinant ROR2 protein (y-axis) in the presence of increasing molar (M) concentration of soluble ROR2 competitor (x-axis) is shown. **(FIG. 12B)** Illustration of the 95% confidence interval for the measured Kd of 6E6 scFv for binding to recombinant human ROR2. **(FIG. 12C)** Binding of the 6E6 scFv to ROR2 was assessed by flow cytometric staining and analysis of K562 (ROR2 positive) and JEKO (ROR2 negative) cells. Cells were stained on ice for 20 minutes with ~ 1 ug/ml of 6E6 anti-human ROR2 scfv, washed, stained for an additional 20 minutes on ice with phycoerythrin (PE)-conjugated anti-human IgG1 antibody, washed and analyzed by flow cytometry. Shaded histograms depict the relative fluorescence intensity (x axis) of viable cells, as determined by light scatter characteristics, stained with 6E6 scfv compared to

viable cells stained with the anti-human IgG1-PE antibody only (open histograms). The 6E6 scFv binds to K562 cells, but not JEKO cells that do not express human ROR2.

[0044] FIG. 13. 6E6 and 4G9 anti-human ROR2 chimeric antigen receptors (CAR) bind specifically to recombinant human ROR2 protein. HEK293 cells were transfected with either a 6E6 or 4G9 anti-human ROR2 chimeric antigen receptor construct or an anti-human ROR1 CAR construct. All cells were assessed after 48 hours by flow cytometry for binding of recombinant human ROR2-Ig protein comprised of the ROR2 extracellular domain and the CH2-CH3 constant region domains of human IgG1. Cells were stained on ice for 20 minutes with 1 ug/ml of recombinant ROR2-Ig (upper panel) or 1 ug/ml of control ROR1-Ig (lower panel), washed, stained for an additional 20 minutes on ice with phycoerythrin (PE)-conjugated anti-human IgG1 antibody, washed and analyzed by flow cytometry. Shaded histograms depict the relative fluorescence intensity (x axis) of viable cells, as determined by light scatter characteristics, stained with either ROR2-Ig or ROR1-Ig compared to cells stained with the anti-human IgG1-PE antibody only (open histograms). HEK293 cells transfected with either 6E6 or 4G9 CAR constructs bind ROR2-Ig (upper panels), but not ROR1-Ig, which is comprised of the same human IgG domains fused to the extracellular region of human ROR1. Conversely, ROR1 CAR transfected cells bind only to ROR1-Ig.

DETAILED DESCRIPTION

[0045] While various embodiments and aspects of the present invention are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0046] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0047] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0048] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, e.g., Singleton et al., *DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY* 2nd ed., J. Wiley & Sons (New York, NY 1994); Sambrook et al., *MOLECULAR CLONING, A LABORATORY*
5 *MANUAL*, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989). Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0049] "Nucleic acid" refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides) and
10 polymers thereof in either single-, double- or multiple-stranded form, or complements thereof; or nucleosides (e.g., deoxyribonucleosides or ribonucleosides). In embodiments, "nucleic acid" does not include nucleosides. The terms "polynucleotide," "oligonucleotide," "oligo" or the like refer, in the usual and customary sense, to a linear sequence of nucleotides. The term "nucleoside" refers, in the usual and customary sense, to a glycosylamine including a nucleobase
15 and a five-carbon sugar (ribose or deoxyribose). Non limiting examples, of nucleosides include, cytidine, uridine, adenosine, guanosine, thymidine and inosine. The term "nucleotide" refers, in the usual and customary sense, to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double
20 stranded RNA, and hybrid molecules having mixtures of single and double stranded DNA and RNA. Examples of nucleic acid, e.g. polynucleotides contemplated herein include any types of RNA, e.g. mRNA, siRNA, miRNA, and guide RNA and any types of DNA, genomic DNA, plasmid DNA, and minicircle DNA, and any fragments thereof. The term "duplex" in the context of polynucleotides refers, in the usual and customary sense, to double strandedness.
25 Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, e.g., such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0050] Nucleic acids, including e.g., nucleic acids with a phosphothioate backbone, can
30 include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, e.g., a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an

amino acid reactive moiety that reacts with an amino acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

[0051] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphodiester derivatives including, e.g., phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate having double bonded sulfur replacing oxygen in the phosphate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see Eckstein, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, Oxford University Press) as well as modifications to the nucleotide bases such as in 5-methyl cytidine or pseudouridine.; and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (e.g. phosphorodiamidate morpholino oligos or locked nucleic acids (LNA) as known in the art), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, CARBOHYDRATE MODIFICATIONS IN ANTISENSE RESEARCH, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0052] Nucleic acids can include nonspecific sequences. As used herein, the term "nonspecific sequence" refers to a nucleic acid sequence that contains a series of residues that are not designed to be complementary to or are only partially complementary to any other nucleic acid sequence. By way of example, a nonspecific nucleic acid sequence is a sequence of nucleic acid residues that does not function as an inhibitory nucleic acid when contacted with a cell or organism.

[0053] A polynucleotide is typically composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); and thymine (T) (uracil (U) for thymine (T) when the polynucleotide is RNA). Thus, the term “polynucleotide sequence” is the alphabetical representation of a polynucleotide molecule; alternatively, the term may be applied to the polynucleotide molecule itself. This alphabetical representation can be input into databases in a computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. Polynucleotides may optionally include one or more non-standard nucleotide(s), nucleotide analog(s) and/or modified nucleotides.

[0054] The term “complement,” as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanosine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0055] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other, may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[0056] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. The terms "non-naturally occurring amino acid" and "unnatural amino acid" refer to amino acid analogs, synthetic amino acids, and amino acid mimetics which are not found in nature.

[0057] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0058] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may In embodiments be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. A "fusion protein" refers to a chimeric protein encoding two or more separate protein sequences that are recombinantly expressed as a single moiety.

[0059] An amino acid or nucleotide base "position" is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that must be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the

reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0060] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence. An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. One skilled in the art will immediately recognize the identity and location of residues corresponding to a specific position in a protein (*e.g.*, ROR-1) in other proteins with different numbering systems. For example, by performing a simple sequence alignment with a protein (*e.g.*, ROR-1) the identity and location of residues corresponding to specific positions of the protein are identified in other protein sequences aligning to the protein. For example, a selected residue in a selected protein corresponds to glutamic acid at position 138 when the selected residue occupies the same essential spatial or other structural relationship as a glutamic acid at position 138. In some embodiments, where a selected protein is aligned for maximum homology with a protein, the position in the aligned selected protein aligning with glutamic acid 138 is the to correspond to glutamic acid 138. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, *e.g.*, where the structure of the selected protein is aligned for maximum correspondence with the glutamic acid at position 138, and the overall structures compared. In this case, an amino acid that occupies the same essential position as glutamic acid 138 in the structural model is the to correspond to the glutamic acid 138 residue.

[0061] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, "conservatively modified variants" refers to those nucleic acids that encode identical or essentially identical amino acid sequences. Because of the degeneracy of the genetic code, a number of nucleic acid sequences will encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be

altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each
5 codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0062] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters,
10 adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified
15 variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the disclosure.

[0063] The following eight groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Glycine (G);
- 20 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);
- 25 7) Serine (S), Threonine (T); and
- 8) Cysteine (C), Methionine (M)

(see, e.g., Creighton, *Proteins* (1984)).

[0064] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or

have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0065] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0066] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of, e.g., a full length sequence or from 20 to 600, about 50 to about 200, or about 100 to about 150 amino acids or nucleotides in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat'l. Acad. Sci. USA* 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software

Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g., Ausubel et al., Current Protocols in Molecular Biology* (1995 supplement)).

[0067] An example of an algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al., supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0068] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g., Karlin and Altschul* (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered

similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0069] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0070] Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. A natural antibody molecule contains two identical pairs of polypeptide chains, each pair having one light chain and one heavy chain. Each light chain and heavy chain in turn consists of two regions: a variable ("V") region, involved in binding the target antigen, and a constant ("C") region that interacts with other components of the immune system. The light and heavy chain variable regions (also referred to herein as light chain variable (VL) domain and heavy chain variable (VH) domain, respectively) come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). Within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called the complementarity determining regions ("CDRs"). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The position and length of the CDRs have been precisely defined by Kabat, E. et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1983, 1987. The part of a variable region not contained in the CDRs is called the framework ("FR"), which forms the environment for the CDRs.

[0071] An "antibody variant" as provided herein refers to a polypeptide capable of binding to an antigen and including one or more structural domains (e.g., light chain variable domain, heavy chain variable domain) of an antibody or fragment thereof. Non-limiting examples of antibody

variants include single-domain antibodies or nanobodies, monospecific Fab₂, bispecific Fab₂, trispecific Fab₃, monovalent IgGs, scFv, bispecific antibodies, bispecific diabodies, trispecific triabodies, scFv-Fc, minibodies, IgNAR, V-NAR, hIgG, VhH, or peptibodies. A “peptibody” as provided herein refers to a peptide moiety attached (through a covalent or non-covalent linker) to the Fc domain of an antibody. Further non-limiting examples of antibody variants known in the art include antibodies produced by cartilaginous fish or camelids. A general description of antibodies from camelids and the variable regions thereof and methods for their production, isolation, and use may be found in references WO97/49805 and WO 97/49805 which are incorporated by reference herein in their entirety and for all purposes. Likewise, antibodies from cartilaginous fish and the variable regions thereof and methods for their production, isolation, and use may be found in WO2005/118629, which is incorporated by reference herein in its entirety and for all purposes.

[0072] The terms “CDR L1”, “CDR L2” and “CDR L3” as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a CDR L1, a CDR L2 and a CDR L3. Likewise, the terms “CDR H1”, “CDR H2” and “CDR H3” as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a CDR H1, a CDR H2 and a CDR H3.

[0073] The terms “FR L1”, “FR L2”, “FR L3” and “FR L4” as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a FR L1, a FR L2, a FR L3 and a FR L4. Likewise, the terms “FR H1”, “FR H2”, “FR H3” and “FR H4” as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a FR H1, a FR H2, a FR H3 and a FR H4.

[0074] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one “light” (about 25 kD) and one “heavy” chain (about 50-70 kD). The N-terminus of each chain defines a

variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL), variable light chain (VL) domain or light chain variable region and variable heavy chain (VH), variable heavy chain (VH) domain or heavy chain variable region refer to these light and heavy chain regions, respectively. The terms
5 variable light chain (VL), variable light chain (VL) domain and light chain variable region as referred to herein may be used interchangeably. The terms variable heavy chain (VH), variable heavy chain (VH) domain and heavy chain variable region as referred to herein may be used interchangeably. The Fc (i.e. fragment crystallizable region) is the "base" or "tail" of an immunoglobulin and is typically composed of two heavy chains that contribute two or three
10 constant domains depending on the class of the antibody. By binding to specific proteins, the Fc region ensures that each antibody generates an appropriate immune response for a given antigen. The Fc region also binds to various cell receptors, such as Fc receptors, and other immune molecules, such as complement proteins.

[0075] The term "antibody" is used according to its commonly known meaning in the art.

15 Antibodies exist, e.g., as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)₂, a dimer of Fab which itself is a light chain joined to V_H-C_{H1} by a disulfide bond. The F(ab)₂ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)₂ dimer
20 into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either
25 produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty *et al.*, *Nature* 348:552-554 (1990)). The term "antibody" as referred to herein further includes antibody variants such as single domain antibodies. Thus, in embodiments an antibody includes a single monomeric variable antibody domain. Thus, in
30 embodiments, the antibody, includes a variable light chain (VL) domain or a variable heavy chain (VH) domain. In embodiments, the antibody is a variable light chain (VL) domain or a variable heavy chain (VH) domain.

[0076] For preparation of monoclonal or polyclonal antibodies, any technique known in the art can be used (*see, e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4:72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy* (1985)). "Monoclonal" antibodies (mAb) refer to antibodies derived from a single
5 clone. Techniques for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies. Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990);
10 Marks *et al.*, *Biotechnology* 10:779-783 (1992)).

[0077] A single-chain variable fragment (scFv) is typically a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of 10 to about 25 amino acids. The linker may usually be rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can either connect the N-
15 terminus of the VH with the C-terminus of the VL, or vice versa.

[0078] The epitope of a mAb is the region of its antigen to which the mAb binds. Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1x, 5x, 10x, 20x or 100x excess of one antibody inhibits binding of the other by at least 30% but preferably 50%, 75%, 90% or even 99% as
20 measured in a competitive binding assay (*see, e.g.*, Junghans *et al.*, *Cancer Res.* 50:1495, 1990). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0079] For preparation of suitable antibodies of the invention and for use according to the invention, *e.g.*, recombinant, monoclonal, or polyclonal antibodies, many techniques known in the art can be used (*see, e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4: 72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. (1985); Coligan, *Current Protocols in Immunology* (1991); Harlow
25 & Lane, *Antibodies, A Laboratory Manual* (1988); and Goding, *Monoclonal Antibodies: Principles and Practice* (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, *e.g.*, the genes encoding a monoclonal antibody
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can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (see, e.g., Kuby, Immunology (3rd ed. 1997)). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Patent 4,946,778, U.S. Patent No. 4,816,567) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (see, e.g., U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks et al., Bio/Technology 10:779-783 (1992); Lonberg et al., Nature 368:856-859 (1994); Morrison, Nature 368:812-13 (1994); Fishwild et al., Nature Biotechnology 14:845-51 (1996); Neuberger, Nature Biotechnology 14:826 (1996); and Lonberg & Huszar, Intern. Rev. Immunol. 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, e.g., McCafferty et al., Nature 348:552-554 (1990); Marks et al., Biotechnology 10:779-783 (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (see, e.g., WO 93/08829, Traunecker et al., EMBO J. 10:3655-3659 (1991); and Suresh et al., Methods in Enzymology 121:210 (1986)). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (see, e.g., U.S. Patent No. 4,676,980, WO 91/00360; WO 92/200373; and EP 03089).

[0080] Methods for humanizing or primatizing non-human antibodies are well known in the art (e.g., U.S. Patent Nos. 4,816,567; 5,530,101; 5,859,205; 5,585,089; 5,693,761; 5,693,762; 5,777,085; 6,180,370; 6,210,671; and 6,329,511; WO 87/02671; EP Patent Application 0173494; Jones et al. (1986) Nature 321:522; and Verhoyen et al. (1988) Science 239:1534). Humanized antibodies are further described in, e.g., Winter and Milstein (1991) Nature 349:293. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (see, e.g., Morrison et al., PNAS USA, 81:6851-6855 (1984), Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Morrison and Oi, Adv. Immunol., 44:65-92 (1988), Verhoeyen et al., Science 239:1534-1536 (1988) and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992), Padlan, Molec. Immun., 28:489-498 (1991); Padlan, Molec. Immun., 31(3):169-217 (1994)), by

substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies. For example, polynucleotides comprising a first sequence coding for humanized immunoglobulin framework regions and a second sequence set coding for the desired immunoglobulin complementarity determining regions can be produced synthetically or by combining appropriate cDNA and genomic DNA segments. Human constant region DNA sequences can be isolated in accordance with well known procedures from a variety of human cells.

[0081] A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. The preferred antibodies of, and for use according to the invention include humanized and/or chimeric monoclonal antibodies.

[0082] The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies can be selected to obtain only a subset of antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, Using

Antibodies, A Laboratory Manual (1998) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0083] A "ligand" refers to an agent, e.g., a polypeptide or other molecule, capable of binding to a receptor or antibody, antibody variant, antibody region or fragment thereof.

- 5 **[0084]** Techniques for conjugating therapeutic agents to antibodies are well known (see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery" in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers
- 10 Of Cytotoxic Agents In Cancer Therapy: A Review" in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982)). As used herein, the term "antibody-drug conjugate" or "ADC" refers to a therapeutic agent conjugated or otherwise covalently bound to to an antibody.
- 15 **[0085]** The term "ROR2 protein" or "ROR2" as used herein includes any of the recombinant or naturally-occurring forms of Receptor tyrosine kinase-like orphan receptor 2, also known as Tyrosine-protein kinase transmembrane receptor ROR2, Neurotrophic tyrosine kinase receptor-related 2, or variants or homologs thereof that maintain ROR2 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to ROR2). In some aspects,
- 20 the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring ROR2 protein. In embodiments, the ROR2 protein is substantially identical to the protein identified by SEQ ID NO:18. In embodiments, the ROR2 protein is substantially identical to the protein identified by
- 25 the UniProt reference number Q01974 or a variant or homolog having substantial identity thereto. In embodiments, the ROR2 protein is substantially identical to the protein identified by the UniProt reference number A1L4F5 or a variant or homolog having substantial identity thereto. In embodiments, the ROR2 protein is substantially identical to the protein identified by the UniProt reference number Q8C3W2 or a variant or homolog having substantial identity
- 30 thereto.

[0086] For specific proteins described herein, the named protein includes any of the protein's naturally occurring forms, variants or homologs that maintain the protein transcription factor

activity (e.g., within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the native protein). In some embodiments, variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring form. In other embodiments, the protein is the protein as identified by its NCBI sequence reference. In other embodiments, the protein is the protein as identified by its NCBI sequence reference, homolog or functional fragment thereof.

[0087] The term "gene" means the segment of DNA involved in producing a protein; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). The leader, the trailer as well as the introns include regulatory elements that are necessary during the transcription and the translation of a gene. Further, a "protein gene product" is a protein expressed from a particular gene.

[0088] The terms "plasmid", "vector" or "expression vector" refer to a nucleic acid molecule that encodes for genes and/or regulatory elements necessary for the expression of genes. Expression of a gene from a plasmid can occur in cis or in trans. If a gene is expressed in cis, the gene and the regulatory elements are encoded by the same plasmid. Expression in trans refers to the instance where the gene and the regulatory elements are encoded by separate plasmids.

[0089] The terms "transfection", "transduction", "transfecting" or "transducing" can be used interchangeably and are defined as a process of introducing a nucleic acid molecule or a protein to a cell. Nucleic acids are introduced to a cell using non-viral or viral-based methods. The nucleic acid molecules may be gene sequences encoding complete proteins or functional portions thereof. Non-viral methods of transfection include any appropriate transfection method that does not use viral DNA or viral particles as a delivery system to introduce the nucleic acid molecule into the cell. Exemplary non-viral transfection methods include calcium phosphate transfection, liposomal transfection, nucleofection, sonoporation, transfection through heat shock, magnetofection and electroporation. In some embodiments, the nucleic acid molecules are introduced into a cell using electroporation following standard procedures well known in the art. For viral-based methods of transfection any useful viral vector may be used in the methods described herein. Examples for viral vectors include, but are not limited to retroviral, adenoviral, lentiviral and adeno-associated viral vectors. In some embodiments, the nucleic acid molecules are introduced into a cell using a retroviral vector following standard procedures well known in

the art. The terms "transfection" or "transduction" also refer to introducing proteins into a cell from the external environment. Typically, transduction or transfection of a protein relies on attachment of a peptide or protein capable of crossing the cell membrane to the protein of interest. See, e.g., Ford *et al.* (2001) *Gene Therapy* 8:1-4 and Prochiantz (2007) *Nat. Methods* 4:119-20.

[0090] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ³²P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any appropriate method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, *Bioconjugate Techniques* 1996, Academic Press, Inc., San Diego.

[0091] When the label or detectable moiety is a radioactive metal or paramagnetic ion, the agent may be reacted with another long-tailed reagent having a long tail with one or more chelating groups attached to the long tail for binding to these ions. The long tail may be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which the metals or ions may be added for binding. Examples of chelating groups that may be used according to the disclosure include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), DOTA, NOTA, NETA, TETA, porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups. The chelate is normally linked to the PSMA antibody or functional antibody fragment by a group, which enables the formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MRI, when used along with the antibodies and carriers described herein. Macrocyclic chelates such as NOTA, DOTA, and TETA are of use with a variety of metals and radiometals including, but not limited to, radionuclides of gallium, yttrium and copper, respectively. Other ring-type chelates such as macrocyclic polyethers, which are of interest for stably binding nuclides, such as ²²³Ra for RAIT may be used. In certain embodiments, chelating moieties may be used to attach a PET imaging agent, such as an Al-¹⁸F complex, to a targeting molecule for use in PET analysis.

[0092] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. antibodies and antigens) to become sufficiently proximal to react, interact, or physically touch. It should be appreciated; however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0093] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be, for example, a pharmaceutical composition as provided herein and a cell. In embodiments contacting includes, for example, allowing a pharmaceutical composition as described herein to interact with a cell.

[0094] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include, but are not limited to, yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells.

[0095] The term "recombinant" when used with reference, e.g., to a cell, nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. Transgenic cells and plants are those that express a heterologous gene or coding sequence, typically as a result of recombinant methods.

[0096] The term "isolated", when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid

chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0097] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[0098] The term "exogenous" refers to a molecule or substance (*e.g.*, a compound, nucleic acid or protein) that originates from outside a given cell or organism. For example, an "exogenous promoter" as referred to herein is a promoter that does not originate from the cell or organism it is expressed by. Conversely, the term "endogenous" or "endogenous promoter" refers to a molecule or substance that is native to, or originates within, a given cell or organism.

[0099] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to cell proliferation (e.g., cancer cell proliferation) means negatively affecting (e.g., decreasing proliferation) or killing the cell. In some embodiments, inhibition refers to reduction of a disease or symptoms of disease (e.g., cancer, cancer cell proliferation). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. ROR2 protein). Similarly an "inhibitor" is a compound or protein that inhibits a receptor or another protein, *e.g.*, by binding, partially or totally blocking, decreasing, preventing, delaying, inactivating, desensitizing, or down-regulating activity (e.g., a receptor activity or a protein activity).

[0100] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein (e.g. ROR2 protein) relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of ROR2 relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of ROR2.

Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of ROR2. In embodiments, inhibition refers to a reduction of activity of ROR2 resulting from a direct interaction (e.g. an inhibitor binds to ROR2). In embodiments, inhibition refers to a reduction of activity of ROR2 from an indirect interaction (e.g. an inhibitor binds to a protein that activates ROR2, thereby preventing target protein activation).

[0101] Thus, the terms “inhibitor,” “repressor” or “antagonist” or “downregulator” interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein (e.g. ROR2 protein). The antagonist can decrease ROR2 expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, ROR2 expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist.

[0102] The term “expression” includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0103] “Biological sample” or “sample” refer to materials obtained from or derived from a subject or patient. A biological sample includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histological purposes. Such samples include bodily fluids such as blood and blood fractions or products (e.g., serum, plasma, platelets, red blood cells, and the like), sputum, tissue, cultured cells (e.g., primary cultures, explants, and transformed cells) stool, urine, synovial fluid, joint tissue, synovial tissue, synoviocytes, fibroblast-like synoviocytes, macrophage-like synoviocytes, immune cells, hematopoietic cells, fibroblasts, macrophages, T cells, etc. A biological sample is typically obtained from a eukaryotic organism, such as a mammal such as a primate e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish.

[0104] A “control” or “standard control” refers to a sample, measurement, or value that serves as a reference, usually a known reference, for comparison to a test sample, measurement, or value. For example, a test sample can be taken from a patient suspected of having a given

disease (e.g. cancer) and compared to a known normal (non-diseased) individual (e.g. a standard control subject). A standard control can also represent an average measurement or value gathered from a population of similar individuals (e.g. standard control subjects) that do not have a given disease (i.e. standard control population), e.g., healthy individuals with a similar medical background, same age, weight, etc. A standard control value can also be obtained from the same individual, e.g. from an earlier-obtained sample from the patient prior to disease onset. For example, a control can be devised to compare therapeutic benefit based on pharmacological data (e.g., half-life) or therapeutic measures (e.g., comparison of side effects). Controls are also valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant. One of skill will recognize that standard controls can be designed for assessment of any number of parameters (e.g. RNA levels, protein levels, specific cell types, specific bodily fluids, specific tissues, etc).

[0105] One of skill in the art will understand which standard controls are most appropriate in a given situation and be able to analyze data based on comparisons to standard control values. Standard controls are also valuable for determining the significance (e.g. statistical significance) of data. For example, if values for a given parameter are widely variant in standard controls, variation in test samples will not be considered as significant.

[0106] “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a composition or pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0107] The terms “disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. The cancer may refer to a solid tumor malignancy. Solid tumor malignancies include malignant tumors that may be devoid of fluids or cysts. For example, the solid tumor malignancy may include breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer. In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular,

glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including acute myeloid leukemia (AML), ALL, and CML), or multiple myeloma.

- 5 **[0108]** As used herein, the term “cancer” refers to all types of cancer, neoplasm or malignant tumors found in mammals (*e.g.*, humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include breast cancer, colon cancer, kidney cancer, leukemia, lung cancer, melanoma, ovarian cancer, prostate cancer, pancreatic cancer, brain cancer, liver cancer, gastric cancer or a sarcoma.
- 10 **[0109]** The term “leukemia” refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3)
- 15 the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute myeloid leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia,
- 20 basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma
- 25 cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.
- 30 **[0110]** The term “sarcoma” generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method

provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectatic sarcoma.

[0111] The term “melanoma” is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, or superficial spreading melanoma.

[0112] The term “carcinoma” refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma,

Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0113] As used herein, the terms "metastasis," "metastatic," and "metastatic cancer" can be used interchangeably and refer to the spread of a proliferative disease or disorder, e.g., cancer, from one organ or another non-adjacent organ or body part. Cancer occurs at an originating site, e.g., breast, which site is referred to as a primary tumor, e.g., primary breast cancer. Some cancer cells in the primary tumor or originating site acquire the ability to penetrate and infiltrate surrounding normal tissue in the local area and/or the ability to penetrate the walls of the lymphatic system or vascular system circulating through the system to other sites and tissues in the body. A second clinically detectable tumor formed from cancer cells of a primary tumor is referred to as a metastatic or secondary tumor. When cancer cells metastasize, the metastatic tumor and its cells are presumed to be similar to those of the original tumor. Thus, if lung cancer metastasizes to the breast, the secondary tumor at the site of the breast consists of abnormal lung cells and not abnormal breast cells. The secondary tumor in the breast is referred to a metastatic lung cancer. Thus, the phrase metastatic cancer refers to a disease in which a subject has or had a primary tumor and has one or more secondary tumors. The phrases non-metastatic cancer or subjects with cancer that is not metastatic refers to diseases in which subjects have a primary tumor but not one or more secondary tumors. For example, metastatic lung cancer refers to a disease in a subject with or with a history of a primary lung tumor and with one or more secondary tumors at a second location or multiple locations, e.g., in the breast.

[0114] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, a cancer

associated with ROR2 activity, ROR2 associated cancer, ROR2 associated disease (e.g., cancer, inflammatory disease, autoimmune disease, or infectious disease)) means that the disease (e.g. cancer, inflammatory disease, autoimmune disease, or infectious disease) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a cancer associated with ROR2 activity or function or a ROR2 associated disease (e.g., cancer, inflammatory disease, autoimmune disease, or infectious disease), may be treated with a ROR2 modulator or ROR2 inhibitor, in the instance where increased ROR2 activity or function (e.g. signaling pathway activity) causes the disease (e.g., cancer, inflammatory disease, autoimmune disease, or infectious disease). For example, an inflammatory disease associated with ROR2 activity or function or an ROR2 associated inflammatory disease, may be treated with an ROR2 modulator or ROR2 inhibitor, in the instance where increased ROR2 activity or function (e.g. signaling pathway activity) causes the disease.

[0115] The term “signaling pathway” as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

[0116] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0117] A "therapeutic agent" as referred to herein, is a composition useful in treating or preventing a disease such as cancer (e.g., leukemia). In embodiments, the therapeutic agent is an anti-cancer agent. “Anti-cancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In embodiments, an anti-cancer agent is a chemotherapeutic. In embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In embodiments, an

anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer.

[0118] An “anticancer agent” as used herein refers to a molecule (e.g. compound, peptide, protein, nucleic acid, 0103) used to treat cancer through destruction or inhibition of cancer cells or tissues. Anticancer agents may be selective for certain cancers or certain tissues. In embodiments, anticancer agents herein may include epigenetic inhibitors and multi-kinase inhibitors. “Anti-cancer agent” and “anticancer agent” are used in accordance with their plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin), triazenes (decabazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-

activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide,

5 gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine;

10 ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine;

15 atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-aethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C;

20 camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin;

25 crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron;

30 doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitofur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;

- fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat;
- 5 imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
- 10 leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone;
- 15 meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-
- 20 based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone;
- 25 ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A;
- 30 placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine

nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide;

5 roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin;

10 spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine;

15 thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth

20 inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate;

25 aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate;

30 cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epiropidine;

epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride;

5 hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine

10 hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman;

15 piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone

20 hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate;

25 vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296),

30 ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone

C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663),

5 Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko),

10 AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State

15 University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of

20 Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaeyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-

25 68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate

30 sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone

acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbix™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0119] As used herein, “treating” or “treatment of” a condition, disease or disorder or symptoms associated with a condition, disease or disorder refers to an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of condition, disorder or disease, stabilization of the state of condition, disorder or disease, prevention of development of condition, disorder or disease, prevention of spread of condition, disorder or disease, delay or slowing of condition, disorder or disease progression, delay or slowing of condition, disorder or disease onset, amelioration or palliation of the condition, disorder or disease state, and remission, whether partial or total. “Treating” can also mean prolonging survival of a subject beyond that expected in the absence of treatment. “Treating” can also mean inhibiting the progression of the condition, disorder or disease, slowing the progression of the condition, disorder or disease temporarily, although in some instances, it involves halting the progression of the condition, disorder or disease permanently. As used herein the terms treatment, treat, or treating refers to a method of reducing the effects of one or more symptoms of a disease or condition characterized by expression of the protease or symptom of the disease or condition characterized by expression of the protease.

Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease, condition, or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition. Further, as used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level and such terms can include but do not necessarily include complete elimination.

[0120] The terms “dose” and “dosage” are used interchangeably herein. A dose refers to the amount of active ingredient given to an individual at each administration. The dose will vary depending on a number of factors, including the range of normal doses for a given therapy, frequency of administration; size and tolerance of the individual; severity of the condition; risk of side effects; and the route of administration. One of skill will recognize that the dose can be modified depending on the above factors or based on therapeutic progress. The term “dosage form” refers to the particular format of the pharmaceutical or pharmaceutical composition, and depends on the route of administration. For example, a dosage form can be in a liquid form for nebulization, e.g., for inhalants, in a tablet or liquid, e.g., for oral delivery, or a saline solution, e.g., for injection.

[0121] By “therapeutically effective dose or amount” as used herein is meant a dose that produces effects for which it is administered (e.g. treating or preventing a disease). The exact dose and formulation will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Remington: *The Science and Practice of Pharmacy*, 20th Edition, Gennaro, Editor (2003), and Pickar, *Dosage Calculations* (1999)). For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as “-fold” increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a standard control. A therapeutically effective dose or amount may ameliorate one or more symptoms of a

disease. A therapeutically effective dose or amount may prevent or delay the onset of a disease or one or more symptoms of a disease when the effect for which it is being administered is to treat a person who is at risk of developing the disease.

[0122] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0123] The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, *e.g.*, Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, *e.g.*, Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In embodiments, the formulations of the compositions of the present invention can be delivered

by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0124] As used herein, the term "pharmaceutically acceptable" is used synonymously with "physiologically acceptable" and "pharmacologically acceptable". A pharmaceutical composition will generally comprise agents for buffering and preservation in storage, and can include buffers and carriers for appropriate delivery, depending on the route of administration.

[0125] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0126] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0127] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with

or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0128] The pharmaceutical preparation is optionally in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The unit dosage form can be of a frozen dispersion.

[0129] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

ANTI-ROR2 ANTIBODIES

[0130] Provided herein are, *inter alia*, antibodies (e.g., humanized antibodies, monoclonal antibodies), antibody fragments (e.g., scFvs) and antibody compositions (e.g., chimeric antigen receptors, bispecific antibodies), which bind human tyrosine kinase-like orphan receptor 2 (ROR2) with high efficiency and specificity. The antibodies and antibody compositions provided herein include novel light and heavy chain domain CDRs and framework regions and have been identified to bind extracellular domains of human ROR2. For example, the antibodies provided herein including embodiments thereof, may bind the Kringle or the Ig-like domain of ROR2 with high affinity and specificity. Further, Applicants have characterized the amino acid residues in the ROR2 extracellular domains, which are important for binding of antibodies as described herein including embodiments thereof. Antibodies specifically binding the epitope described herein including embodiments thereof, are useful for binding human ROR2 with high effectivity and affinity and inhibiting ROR2 signaling in cells expressing ROR2. The antibodies provided herein including embodiments thereof, may be used for diagnostic and therapeutic purposes in cancer and other ROR2-related diseases. The variable light chain and the variable heavy chain domains provided herein may, *inter alia*, form part of an anti-ROR2 chimeric antigen receptor or an anti-ROR2 bispecific antibody. Furthermore, due to their internalization

properties, some of the anti-ROR2 antibodies provided herein may be attached to therapeutic moieties and used as antibody-drug conjugates (ADC), or they may be attached to a detectable moiety and used for diagnostic purposes. The antibodies provided herein including
embodiments thereof, have an ability to inhibit migration of ROR2 expressing metastatic cells
5 and therefore are capable of mitigating the risk of metastasis in patients with ROR2-expressing cancer cells

[0131] Exemplary anti-ROR2 antibodies provided herein are referred to by clone names (e.g., 6E6, 4G9, 5C11 and 5G3). In embodiments, the anti-ROR2 antibody is antibody 6E6. In
embodiments, the antibody 6E6 has a heavy chain variable domain of SEQ ID NO:2 and a light
10 variable domain of SEQ ID NO:4. In embodiments, the antibody 6E6 has a heavy chain
variable domain and a light chain variable domain, wherein the heavy chain variable domain
includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and
a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a
CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3
15 as set forth in SEQ ID NO:30. In embodiments, the anti-ROR2 antibody is antibody 4G9. In
embodiments, the antibody 4G9 has a heavy chain variable domain of SEQ ID NO:6 and a light
variable domain of SEQ ID NO:8. In embodiments, the antibody 4G9 has a heavy chain variable
domain and a light chain variable domain, wherein the heavy chain variable domain includes: a
CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3
20 as set forth in SEQ ID NO:33; and wherein said light chain variable domain includes: a CDR L1
as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set
forth in SEQ ID NO:36. In embodiments, the anti-ROR2 antibody is antibody 5C11. In
embodiments, the antibody 5C11 and has a heavy chain variable domain of SEQ ID NO:10 and a
light variable domain of SEQ ID NO:12. In embodiments, the antibody 5C11 has a heavy chain
25 variable domain and a light chain variable domain, wherein the heavy chain variable domain
includes: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and
a CDR H3 as set forth in SEQ ID NO:39; and wherein said light chain variable domain
includes: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and
a CDR L3 as set forth in SEQ ID NO:42. In embodiments, the anti-ROR2 antibody is antibody
30 5G3. In embodiments, the antibody 5G3 has a heavy chain variable domain of SEQ ID NO:14
and a light variable domain of SEQ ID NO:16. In embodiments, the antibody 5G3 has a heavy
chain variable domain and a light chain variable domain, wherein the heavy chain variable
domain includes: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID

NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and wherein said light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0132] In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0133] As described above, a "light chain variable (VL) domain" as provided herein refers to the variable region of the light chain of an antibody, an antibody variant or fragment thereof. Likewise, the "heavy chain variable (VH) domain" as provided herein refers to the variable region of the heavy chain of an antibody, an antibody variant or fragment thereof. The light chain variable domain and the heavy chain variable domain together form the paratope, which binds an antigen (epitope). The paratope or antigen-binding site is formed at the N-terminus of an antibody, an antibody variant or fragment thereof. In embodiments, the light chain variable (VL) domain includes CDR L1, CDR L2, CDR L3 and FR L1, FR L2, FR L3 and FR L4 (framework regions) of an antibody light chain. In embodiments, the heavy chain variable (VH) domain includes CDR H1, CDR H2, CDR H3 and FR H1, FR H2, FR H3 and FR H4 (framework regions) of an antibody heavy chain. In embodiments, the light chain variable (VL) domain and a light chain constant (CL) domain form part of an antibody light chain. In embodiments, the heavy chain variable (VH) domain and a heavy chain constant (CH1) domain form part of an antibody heavy chain. In embodiments, the heavy chain variable (VH) domain and one or more heavy chain constant (CH1, CH2, or CH3) domains form part of an antibody heavy chain. Thus, in embodiments, the light chain variable (VL) domain forms part of an antibody. In embodiments, the heavy chain variable (VH) domain forms part of an antibody. In embodiments, the light chain variable (VL) domain forms part of a therapeutic antibody. In embodiments, the heavy chain variable (VH) domain forms part of a therapeutic antibody. In embodiments, the light chain variable (VL) domain forms part of a human antibody. In embodiments, the heavy chain variable (VH) domain forms part of a human antibody. In embodiments, the light chain variable (VL) domain forms part of a humanized antibody. In embodiments, the heavy chain variable (VH) domain forms part of a humanized antibody. In embodiments, the light chain variable (VL) domain forms part of a chimeric antibody. In

embodiments, the heavy chain variable (VH) domain forms part of a chimeric antibody. In embodiments, the light chain variable (VL) domain forms part of an antibody fragment. In embodiments, the heavy chain variable (VH) domain forms part of an antibody fragment. In embodiments, the light chain variable (VL) domain forms part of an antibody variant. In

5 embodiments, the heavy chain variable (VH) domain forms part of an antibody variant. In embodiments, the light chain variable (VL) domain forms part of a Fab. In embodiments, the heavy chain variable (VH) domain forms part of a Fab. In embodiments, the light chain variable (VL) domain forms part of a scFv. In embodiments, the heavy chain variable (VH) domain forms part of a scFv

10 **[0134]** In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:2. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:2. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:4. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:4.

15 **[0135]** In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:49, a FR H2 as set forth in SEQ ID NO:50, a FR H3 as set forth in SEQ ID NO:51 and a FR H4 as set forth in SEQ ID NO:52. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:53, a FR L2 as set forth in SEQ ID NO:54, a FR L3 as set forth in SEQ ID NO:55 and a FR L4 as set forth in SEQ ID NO:56.

20 **[0136]** In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID
25 NO:22. In embodiments, the extracellular domain is a Kringle domain. In embodiments the Kringle domain includes the amino acid sequence of SEQ ID NO:113.

30 **[0137]** In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 or an aspartic acid at a position corresponding to position 354 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 and an aspartic acid at a position corresponding to position 354 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 or an aspartic acid at a position corresponding to position 354 of SEQ ID NO:18. In

embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 and an aspartic acid at a position corresponding to position 354 of SEQ ID NO:18.

[0138] In embodiments, the antibody does not bind an arginine at a position corresponding to position 349 of SEQ ID NO:20. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:20. In embodiments, the antibody does not bind an arginine at a position corresponding to position 349 of SEQ ID NO:24. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:24.

[0139] The ability of an antibody to bind a specific epitope (e.g., a ROR2 protein, a Kringle domain or Ig-like domain of ROR2) can be described by the equilibrium dissociation constant (K_D). The equilibrium dissociation constant (K_D) as defined herein is the ratio of the dissociation rate (K_{off}) and the association rate (K_{on}) of an antibody to a ROR2 protein. It is described by the following formula: $K_D = K_{\text{off}}/K_{\text{on}}$.

[0140] In embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant (K_D) from 0.01 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.4 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.5 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.6 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.7 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.8 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.9 nM to 1 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant (K_D) from 1.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.4 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.5 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.6 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.7 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.8 nM to 10 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 1.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 2.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
5 from 2.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
2.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 2.4 nM
to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 2.5 nM to 10
nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 2.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2.7 nM to 10 nM. In
10 embodiments, the antibody binds the ROR2 protein with a K_D from 2.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 3 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 4.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
15 from 4.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
4.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 4.4 nM
to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 4.5 nM to 10
nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 4.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4.7 nM to 10 nM. In
20 embodiments, the antibody binds the ROR2 protein with a K_D from 4.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 5.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
25 from 5.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
5.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 5.4 nM
to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 5.5 nM to 10
nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 5.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 5.7 nM to 10 nM. In
30 embodiments, the antibody binds the ROR2 protein with a K_D from 5.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 5.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant

(K_D) from 6.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 6.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 6.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 6.4 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 6.5 nM to 10 nM. In
5 embodiments, the antibody binds the ROR2 protein with a K_D from 6.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6.7 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 7 nM to 10 nM. In
10 embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 7.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
from 7.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
7.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 7.4 nM
to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 7.5 nM to 10
15 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 7.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 7.7 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 7.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 7.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 8 nM to 10 nM. In
20 embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 8.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
from 8.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
8.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 8.4 nM
to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 8.5 nM to 10
25 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 8.6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 8.7 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 8.8 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 8.9 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 9 nM to 10 nM. In
30 embodiments, the antibody binds the ROR2 protein with an equilibrium dissociation constant
(K_D) from 9.1 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D
from 9.2 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from
9.3 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.4 nM

to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.5 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.6 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.7 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.8 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9.9 nM to 10 nM.

[illegible]

[illegible]

[illegible]

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 0.4 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 0.3 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 0.2 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 0.1 nM.

5 **[0142]** In embodiments, the antibody binds the ROR2 protein with a K_D of 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 10 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0143] In embodiments, the antibody binds the ROR2 protein with a K_D of about 0.06 nM. In embodiments, the antibody is antibody 6E6 and binds a ROR2 protein with a K_D of 0.01 nM to 10 nM. In embodiments, the antibody 6E6 binds a ROR2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 15 or 10 nM. In embodiments, the antibody is antibody 6E6 and binds a ROR2 protein with a K_D of 0.06 nM.

[0144] In embodiments, the antibody is attached to a therapeutic agent. In embodiments, the antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable moiety.

20 **[0145]** In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:2 and a light chain variable domain of SEQ ID NO:4. In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26; a CDR H3 as set forth in SEQ ID NO:27; a FR H1 as set forth in SEQ ID NO:49, a FR H2 as set forth in SEQ ID NO:50, a FR H3 as set forth in SEQ ID NO:51 25 and a FR H4 as set forth in SEQ ID NO:52; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, a CDR L3 as set forth in SEQ ID NO:30; a FR L1 as set forth in SEQ ID NO:53, a FR L2 as set forth in SEQ ID NO:54, a FR L3 as set forth in SEQ ID NO:55 and a FR L4 as set forth in SEQ ID NO:56. In one further embodiment, the antibody is antibody 6E6.

30 **[0146]** In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth

in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0147] In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:6. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:6. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:8. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:8.

[0148] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:57, a FR H2 as set forth in SEQ ID NO:58, a FR H3 as set forth in SEQ ID NO:59 and a FR H4 as set forth in SEQ ID NO:60. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:61, a FR L2 as set forth in SEQ ID NO:62, a FR L3 as set forth in SEQ ID NO:63 and a FR L4 as set forth in SEQ ID NO:64.

[0149] In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID NO:22. In embodiments, the extracellular domain is an Ig-like domain. In embodiments, the Ig-like domain includes the amino acid sequence of SEQ ID NO:114.

[0150] In embodiments, the ROR2 protein includes a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a methionine at a position corresponding to position 386 of SEQ ID NO:18.

[0151] In embodiments, the antibody does not bind a valine at a position corresponding to position 349 of SEQ ID NO:20. In embodiments, the antibody does not bind a valine at a position corresponding to position 349 of SEQ ID NO:24.

[0152] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.6 nM to 5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1 nM to 5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.4 nM to 5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1.8 nM to 5 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 2.2 nM to 5 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2.6 nM to 5 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 3 nM to 5 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 3.4 nM to 5 nM. In
5 embodiments, the antibody binds the ROR2 protein with a K_D from 3.8 nM to nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4.2 nM to 5 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4.6 nM to 5 nM.

[0153] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 4.6
nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 4.2 nM.

10 In embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 3.8 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 3.4 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 3 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 2.6 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 2.2 nM. In
15 embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 1.8 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 1.4 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 1 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 0.2 nM to 0.6 nM.

[0154] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 10

20 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 1 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 1.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 2.5 nM to 10 nM. In
25 embodiments, the antibody binds the ROR2 protein with a K_D from 3 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 3.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 4.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 5 nM to 10 nM. In
30 embodiments, the antibody binds the ROR2 protein with a K_D from 5.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 6.5 nM to 10 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 7 nM to 10 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 7.5 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 8 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 8.5 nM to 10 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 9 nM to 10 nM.

- 5 **[0155]** In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 9.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 9 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 8.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 8 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 7.5 nM. In
- 10 embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 7 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 6.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 6 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 5.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 5 nM. In
- 15 embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 4.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 4 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 3.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 3 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 2.5 nM. In
- 20 embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 2 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 1.5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.1 nM to 1 nM.

[0156] In embodiments, the antibody binds the ROR2 protein with a K_D of 0.1, 0.4, 0.8, 1.2, 1.6, 2, 2.4, 2.8, 3.2, 3.6, 4, 4.4, 4.8, 5.2, 5.6, 6, 6.4, 6.8, 7.2, 7.6, 8, 8.4, 8.8, 9.2, 9.6, or 10 nM.

- 25 **[0157]** In embodiments, the antibody binds the ROR2 protein with a K_D of about 1.9 nM. In embodiments, the antibody is antibody 4G9 and binds a ROR2 protein with a K_D of 0.1 nM to 10 nM. In embodiments, the antibody 4G9 binds a ROR2 protein with a K_D of 0.1, 0.4, 0.8, 1.2, 1.6, 2, 2.4, 2.8, 3.2, 3.6, 4, 4.4, 4.8, 5.2, 5.6, 6, 6.4, 6.8, 7.2, 7.6, 8, 8.4, 8.8, 9.2, 9.6, or 10 nM. In embodiments, the antibody is antibody 4G9 and binds a ROR2 protein with a K_D of 1.9 nM.

- 30 **[0158]** In embodiments, the antibody is attached to a therapeutic agent. In embodiments, the antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable moiety.

[0159] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:6 and a light chain variable domain of SEQ ID NO:8. In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32; a CDR H3 as set forth in SEQ ID NO:33; a FR H1 as set forth in SEQ ID NO:57, a FR H2 as set forth in SEQ ID NO:58, a FR H3 as set forth in SEQ ID NO:59 and a FR H4 as set forth in SEQ ID NO:60; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, a CDR L3 as set forth in SEQ ID NO:36; a FR L1 as set forth in SEQ ID NO:61, a FR L2 as set forth in SEQ ID NO:62, a FR L3 as set forth in SEQ ID NO:63 and a FR L4 as set forth in SEQ ID NO:64. In one further embodiment, the antibody is antibody 4G9.

[0160] In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0161] In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:10. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:10. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:12. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:12.

[0162] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:65, a FR H2 as set forth in SEQ ID NO:66, a FR H3 as set forth in SEQ ID NO:67 and a FR H4 as set forth in SEQ ID NO:68. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:69, a FR L2 as set forth in SEQ ID NO:70, a FR L3 as set forth in SEQ ID NO:71 and a FR L4 as set forth in SEQ ID NO:72.

[0163] In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID

NO:22. In embodiments, the extracellular domain is a Kringle domain. In embodiments the Kringle domain includes the amino acid sequence of SEQ ID NO:113.

[0164] In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, and a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position

corresponding to position 349, an aspartic acid at a position corresponding to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:18. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, and a methionine at a position corresponding to position 386 of SEQ ID NO:18.

[0165] In embodiments, the antibody does not bind an arginine at a position corresponding to position 349 of SEQ ID NO:20. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:20. In embodiments, the antibody does not bind a valine at a position corresponding to position 386 of SEQ ID NO:20. In embodiments, the antibody does not bind an arginine at a position corresponding to position 349 of SEQ ID NO:24. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:24. In embodiments, the antibody does not bind a valine at a position corresponding to position 386 of SEQ ID NO:24.

[0166] In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 20 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 30 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 40 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 50 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 60 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 70 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 80 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 90 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 100 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 110 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 120 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 130 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 140 nM to 150 nM.

[0167] In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 140 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 130 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 120 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 110 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 100 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 90 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 80 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 70 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 60 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 50 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 40 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 30 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 20 nM. In embodiments, the antibody binds the ROR2 protein with a K_D of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 nM.

[0168] In embodiments, the antibody is 5C11 and binds a ROR2 protein with a K_D of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 nM.

[0169] In embodiments, the antibody is attached to a therapeutic agent. In embodiments, the antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable moiety.

[0170] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:10 and a light chain variable domain of SEQ ID NO:12. In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38; a CDR H3 as set forth in SEQ ID NO:39; a FR H1 as set forth in SEQ ID NO:65, a FR H2 as set forth in SEQ ID NO:66, a FR H3 as set forth in SEQ ID NO:67 and a FR H4 as set forth in SEQ ID NO:68; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, a CDR L3 as set forth in SEQ ID NO:42; a FR L1 as set forth in SEQ ID NO:69, a FR L2 as set forth in SEQ

ID NO:70, a FR L3 as set forth in SEQ ID NO:71 and a FR L4 as set forth in SEQ ID NO:72.

In one further embodiment, the antibody is antibody 5C11.

[0171] In an aspect is provided an anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0172] In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:14. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:14. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:16. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:16.

[0173] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:73, a FR H2 as set forth in SEQ ID NO:74, a FR H3 as set forth in SEQ ID NO:75 and a FR H4 as set forth in SEQ ID NO:76. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:77, a FR L2 as set forth in SEQ ID NO:78, a FR L3 as set forth in SEQ ID NO:79 and a FR L4 as set forth in SEQ ID NO:80.

[0174] In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID NO:22. In embodiments, the extracellular domain is an Ig-like domain. In embodiments, the Ig-like domain includes the amino acid sequence of SEQ ID NO:114.

[0175] In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 20 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 30 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 40 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 50 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 60 nM to 150 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 70 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 80 nM to 150 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 90 nM to 150 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 100 nM to 150 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 110 nM to 150 nM. In
5 embodiments, the antibody binds the ROR2 protein with a K_D from 120 nM to 150 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 130 nM to 150 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 140 nM to 150 nM.

[0176] In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 140
nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 130 nM.

10 In embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 120 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 110 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 100 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 90 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 80 nM. In
15 embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 70 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 60 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 50 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 40 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 30 nM. In
20 embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 20 nM. In
embodiments, the antibody binds the ROR2 protein with a K_D of 10, 20, 30, 40, 50, 60, 70, 80,
90, 100, 110, 120, 130, 140 or 150 nM.

[0177] In embodiments, the antibody is 5G3 and binds a ROR2 protein with a K_D of 10, 20,
30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 nM.

25 **[0178]** In embodiments, the antibody is attached to a therapeutic agent. In embodiments, the
antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable
moiety.

[0179] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:14
and a light chain variable domain of SEQ ID NO:16. In one embodiment, the antibody includes
30 (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:43, a CDR H2
as set forth in SEQ ID NO:44; a CDR H3 as set forth in SEQ ID NO:45; a FR H1 as set forth in
SEQ ID NO:73, a FR H2 as set forth in SEQ ID NO:74, a FR H3 as set forth in SEQ ID NO:75

and a FR H4 as set forth in SEQ ID NO:76; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, a CDR L3 as set forth in SEQ ID NO:48; a FR L1 as set forth in SEQ ID NO:77, a FR L2 as set forth in SEQ ID NO:78, a FR L3 as set forth in SEQ ID NO:79 and a FR L4 as set forth in SEQ ID NO:80.

5 In one further embodiment, the antibody is antibody 5G3.

[0180] The antibodies provided herein including embodiments thereof (e.g., antibody 6e6, 4G9, 5C11 or 5G3), may be humanized antibodies. Thus, in embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody. In embodiments, antibody is a Fab' fragment. In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG. The anti-ROR2 antibody provided herein may be an IgG1, IgG2, IgG3 or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG2a. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0181] In embodiments, the antibody does not bind a mouse ROR2 protein. In embodiments, the antibody does not bind a mouse ROR2 protein identified by the UniProt reference number Q9Z138. In embodiments, the antibody provided herein does not bind a protein comprising the amino acid sequence of SEQ ID NO:20. In embodiments, the antibody provided herein does not bind a protein comprising the amino acid sequence of SEQ ID NO:24. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:20 or SEQ ID NO:24. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:20. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:24.

[0182] In an aspect is provided the ROR2 protein bound by the antibodies provided herein including embodiments thereof (e.g., antibody 6e6, 4G9, 5C11 or 5G3) may be expressed by a cell (e.g., cancer cell). Thus, in embodiments, the ROR2 protein is expressed on a cell. In embodiments, the cell is a cancer cell. In embodiments, the cancer cell is cancer is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell. In embodiments, the cancer cell is a breast cancer cell. In embodiments, the cancer cell is an ovarian cancer cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is cancer is a cervical cancer cell. In embodiments, the cancer cell is cancer is a gastric cancer cell. In embodiments, the cancer cell is cancer is a renal cancer cell. In embodiments, the cancer cell is cancer is a head and neck cancer cell. In embodiments, the

cancer cell is a cancer is bone cancer cell. In embodiments, the cancer cell is cancer is a skin cancer cell. In embodiments, the cancer cell is cancer is a prostate cancer cell.

[0183] In embodiments, the antibody provided herein (e.g., antibody 6E6, 4G9, 5C11 or 5G3) does not bind a ROR2-negative cell. A “ROR2-negative cell” as provided herein is a cell that
5 does not express a detectable amount of a ROR2 protein relative to a standard control. In embodiments, the expression level of a ROR2-negative cell is undetectable using methods conventionally known in the art to a detect protein expression in a cell (e.g., immunofluorescent detection, protein biochemistry, RNA expression level). In embodiments, the expression level of a ROR2-negative cell is 1000, 500, 100, 50, 25, 20, 10, 5, or 1.5 times lower than the expression
10 level of a standard control (e.g., a cell expressing detectable levels of ROR2 using conventional methods). No limiting examples of ROR2-negative cells include a peripheral blood mononuclear cell (PBMC) from a healthy subject.

[0184] Any of the variable light chain domain or the variable heavy chain of the antibodies provided herein may form part of an scFv. Thus, in embodiments, the antibody is a single chain
15 antibody (scFv). In embodiments, the light chain variable domain and the heavy chain variable domain form part of a scFv. In embodiments, a linker forms part of the scFv. In embodiments, the linker includes the sequence of SEQ ID NO:82. In embodiments, a leader peptide forms part of the scFv. In embodiments, the leader peptide includes the sequence of SEQ ID NO:81. In embodiments, the scFv further includes a heavy chain constant region (CH2-CH3). In
20 embodiments, the heavy chain constant region includes the sequence of SEQ ID NO:84.

[0185] In embodiments, the scFv includes the sequence of SEQ ID NO:85. In embodiments, the scFv is the sequence of SEQ ID NO:85.

[0186] In embodiments, the scFv binds the ROR2 protein with an equilibrium dissociation constant (K_D) from 0.01 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a
25 K_D from 0.1 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.2 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.3 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.4 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.5 nM to 10 nM. In
30 embodiments, the scFv binds the ROR2 protein with a K_D from 0.6 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.7 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.8 nM to 10 nM. In embodiments, the scFv binds the ROR2 protein with a K_D from 0.9 nM to 1 nM. In

[illegible]

[illegible]

embodiments, the scFv binds the ROR2 protein with a K_D from 7.9 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.1 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.2 nM to 10 nM. In
5 embodiments, the scFv binds the ROR2 protein with a K_D from 8.3 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.4 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.5 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.6 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.7 nM to 10 nM. In
10 embodiments, the scFv binds the ROR2 protein with a K_D from 8.8 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 8.9 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.1 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.2 nM to 10 nM. In
15 embodiments, the scFv binds the ROR2 protein with a K_D from 9.3 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.4 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.5 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.6 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.7 nM to 10 nM. In
20 embodiments, the scFv binds the ROR2 protein with a K_D from 9.8 nM to 10 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 9.9 nM to 10 nM.

[0187] In embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.9 nM.

In embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.8 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.7 nM. In
25 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.6 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.5 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.4 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.3 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.2 nM. In
30 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9.1 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 9 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 8.9 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 8.8 nM. In

[illegible]

[illegible]

embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 2.1 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 2 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.9 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.8 nM. In
5 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.7 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.6 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.5 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.4 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.3 nM. In
10 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.2 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 1.1 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.9 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.8 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.7 nM. In
15 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.6 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.5 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.4 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.3 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.2 nM. In
20 embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 0.1 nM.

[0188] In embodiments, the scFv binds the ROR2 protein with a K_D of 0.01, 0.1, 0.2, 0.3, 0.4,
0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7,
2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5,
5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3,
25 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6,
9.7, 9.8, 9.9, or 10 nM.

[0189] In embodiments, the scFv binds the ROR2 protein with a K_D of about 0.07 nM. In
embodiments, the scFv is 6E6 scFv and binds a ROR2 protein with a K_D of 0.01 nM to 10 nM.
In embodiments, the 6E6 scFv binds a ROR2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4,
30 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 nM. In
embodiments, the scFv is 6E6 scFv and binds a ROR2 protein with a K_D of 0.07 nM.

[0190] In one embodiment, the scFv includes from the N-terminus to the C-terminus: a leader peptide of SEQ ID NO:81, a light chain variable domain of SEQ ID NO:4, a linker domain of SEQ ID NO:82, a heavy chain variable domain of SEQ ID NO:2, a spacer of SEQ ID NO:83, and a constant heavy chain domain (CH2-CH3) of SEQ ID NO:84. In one further embodiment, the scFv is the 6E6 scFv.

[0191] In embodiments, the scFv includes the sequence of SEQ ID NO:86. In embodiments, the scFv is the sequence of SEQ ID NO:86.

[0192] In embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 150 nM.

In embodiments, the scFv binds the ROR2 protein with a K_D from 1 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 20 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 30 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 40 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 50 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 60 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 70 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 80 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 90 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 100 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 110 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 120 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 130 nM to 150 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 140 nM to 150 nM.

[0193] In embodiments, the scFv binds the ROR2 protein with a K_D from 0.01 nM to 140 nM.

In embodiments, the scFv binds the ROR2 protein with a K_D from 1 nM to 140 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 140 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 130 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 120 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 110 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 100 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 90 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 80 nM. In

embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 70 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 60 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 50 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 40 nM. In
5 embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 30 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 20 nM. In
embodiments, the scFv binds the ROR2 protein with a K_D of 10, 20, 30, 40, 50, 60, 70, 80, 90,
100, 110, 120, 130, 140 or 150 nM.

[0194] In embodiments, the scFv is 4G9 scFv and binds a ROR2 protein with a K_D of 0.01, 1,
10 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 nM.

[0195] In one embodiment, the scFv includes from the N-terminus to the C-terminus: a leader
peptide of SEQ ID NO:81; a light chain variable domain of SEQ ID NO:8, a linker domain of
SEQ ID NO:82, a heavy chain variable domain of SEQ ID NO:6, a spacer of SEQ ID NO:83,
and and a constant heavy chain domain (CH2-CH3) of SEQ ID NO:84. In one further
15 embodiment, the scFv is 4G9 scFv.

[0196] In embodiments, the scFv is capable of binding a ROR2 protein. In embodiments, the
the ROR2 protein is a human ROR2 protein. In embodiments, the scFv binds a ROR2 protein.
In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In
embodiments, the scFv is capable of binding an extracellular domain of the ROR2 protein. In
20 embodiments, the scFv binds an extracellular domain of the ROR2 protein. In embodiments, the
extracellular domain includes the amino acid sequence of SEQ ID NO:22. In embodiments, the
extracellular domain is a Kringle domain. In embodiments the Kringle domain includes the
amino acid sequence of SEQ ID NO:113. In embodiments, the extracellular domain is an Ig-like
domain. In embodiments the Ig-like domain includes the amino acid sequence of SEQ ID
25 NO:114.

[0197] In embodiments, the scFv does not bind a mouse ROR2 protein. In embodiments, the
scFv does not bind a mouse ROR2 protein identified by the UniProt reference number Q9Z138.
In embodiments, the scFv provided herein does not bind a protein comprising the amino acid
sequence of SEQ ID NO:20. In embodiments, the scFv provided herein does not bind a protein
30 comprising the amino acid sequence of SEQ ID NO:24. In embodiments, the scFv provided
herein does not bind the protein of SEQ ID NO:20 or SEQ ID NO:24. In embodiments, the scFv

provided herein does not bind the protein of SEQ ID NO:20. In embodiments, the scFv provided herein does not bind the protein of SEQ ID NO:24

[0198] In another aspect an anti-ROR2 antibody is provided. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:2. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:4.

[0199] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:2; and a light chain variable domain of SEQ ID NO:4.

[0200] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:1; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:3.

[0201] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID:6. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:8.

[0202] In an aspect an anti-ROR2 antibody is provided. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:6; and a light chain variable domain of SEQ ID NO:8.

[0203] In an aspect an anti-ROR2 antibody is provided. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the

nucleic acid sequence of SEQ ID:5; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:7.

[0204] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:10; and a light chain variable domain of SEQ ID NO:12.

[0205] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:9; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:11.

[0206] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID:14. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:16.

[0207] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain of SEQ ID:14; and a light chain variable domain of SEQ ID NO:16.

[0208] In an aspect is provided an anti-ROR2 antibody. The anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody including a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:13; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:15.

[0209] In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID NO:22. In embodiments, the extracellular domain is a Kringle domain. In embodiments the

Kringle domain includes the amino acid sequence of SEQ ID NO:113. In embodiments, the extracellular domain is an Ig-like domain. In embodiments, the Ig-like domain includes the amino acid sequence of SEQ ID NO:114.

[0210] In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, and a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position

corresponding to position 349, an aspartic acid at a position corresponding to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:18. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, and a methionine at a position corresponding to position 386 of SEQ ID NO:18.

[0211] In embodiments, the ROR2 protein includes a methionine at a position corresponding to position 386 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 of SEQ ID NO:22. In embodiments, the ROR2 protein includes an aspartic acid at a position corresponding to position 354 of SEQ ID NO:22. In embodiments, the ROR2 protein includes a methionine at a position corresponding to position 386 of SEQ ID NO:18. In embodiments, the ROR2 protein includes a histidine at a position corresponding to position 349 of SEQ ID NO:18. In embodiments, the ROR2 protein includes an aspartic acid at a position corresponding to position 354 of SEQ ID NO:18.

[0212] In embodiments, the antibody is capable of binding a ROR2 protein. In embodiments, the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2 protein. In embodiments, the ROR2 protein includes the amino acid sequence of SEQ ID NO:18. In embodiments, the antibody is capable of binding an extracellular domain of the ROR2 protein. In embodiments, the antibody binds an extracellular domain of the ROR2 protein. In embodiments, the extracellular domain includes the amino acid sequence of SEQ ID NO:22. In embodiments, the extracellular domain is an Ig-like domain. In embodiments, the Ig-like domain includes residues corresponding to positions 79 to 147 of SEQ ID NO:22.

[0213] In embodiments, the antibody is attached to a therapeutic agent. In embodiments, the antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable moiety.

[0214] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 150

5 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 20 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 30 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 40 nM to 150 nM. In

10 embodiments, the antibody binds the ROR2 protein with a K_D from 50 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 60 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 70 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 80 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 90 nM to 150 nM. In

15 embodiments, the antibody binds the ROR2 protein with a K_D from 100 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 110 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 120 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 130 nM to 150 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 140 nM to 150 nM.

20 [0215] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 140

nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 140 nM.

In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 130 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 120 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 110 nM. In

25 embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 100 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 90 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 80 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 70 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 60 nM. In

30 embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 50 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 40 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 30 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 20 nM. In

embodiments, the antibody binds the ROR2 protein with a K_D from 10 nM to 20 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 20 nM. In embodiments, the antibody binds the ROR2 protein with a K_D of 0.01, 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 nM.

5 **[0216]** The antibodies binding the epitopes provided herein may be humanized antibodies. Thus, in embodiments, the antibody is a humanized antibody. In embodiments, antibody is a chimeric antibody. In embodiments, antibody is a Fab' fragment. In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG. The anti-ROR2 antibody provided herein may be an IgG1, IgG2, IgG3 or IgG4. In embodiments, the antibody is an IgG1. In
10 embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG2a. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0217] In embodiments, the antibody does not bind a mouse ROR2 protein. In embodiments, the antibody does not bind a mouse ROR2 protein identified by the UniProt reference number Q9Z138. In embodiments, the antibody provided herein does not bind a protein comprising the
15 amino acid sequence of SEQ ID NO:20. In embodiments, the antibody provided herein does not bind a protein comprising the amino acid sequence of SEQ ID NO:24. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:20 or SEQ ID NO:24. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:20. In embodiments, the antibody provided herein does not bind the protein of SEQ ID NO:24.

20 **[0218]** In embodiments, the antibody does not bind an arginine at a position corresponding to position 349 of SEQ ID NO:20. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:20. In embodiments, the antibody does not bind a valine at a position corresponding to position 386 of SEQ ID NO:20. In
embodiments, the antibody does not bind an arginine at a position corresponding to position 349
25 of SEQ ID NO:24. In embodiments, the antibody does not bind a glutamic acid at a position corresponding to position 354 of SEQ ID NO:24. In embodiments, the antibody does not bind a valine at a position corresponding to position 386 of SEQ ID NO:24.

[0219] In embodiments, the antibody provided herein does not bind a ROR2-negative cell. A “ROR2-negative cell” as provided herein is a cell that does not express a detectable amount of a
30 ROR2 protein relative to a standard control. In embodiments, the expression level of a ROR2-negative cell is undetectable using methods conventionally known in the art to detect protein expression in a cell (e.g., immunofluorescent detection, protein biochemistry, RNA expression

level). In embodiments, the expression level of a ROR2-negative cell is 1000, 500, 100, 50, 25, 20, 10, 5, or 1.5 times lower than the expression level of a standard control (e.g., a cell expressing undetectable levels of ROR2 using conventional methods). No limiting examples of ROR2-negative cells include a peripheral blood mononuclear cell (PBMC) from a healthy subject.

5 CHIMERIC ANTIGEN RECEPTOR PROTEINS

[0220] As described above, the heavy chain variable (VH) domain and the light chain variable (VL) domain provided herein including embodiments thereof, may each independently form part of an antibody, a fragment of an antibody, or a chimeric antigen receptor or bispecific antibody. Provided herein are, *inter alia*, chimeric antigen receptors and bispecific antibodies, which include the light chain variable (VL) domain and/or the heavy chain variable (VH) domain as provided herein and are therefore capable of binding human ROR2 effectively and efficiently. The antibody region of the chimeric antigen receptor may include any of the light chain and heavy chain variable domains provided herein including embodiments thereof. The light chain variable (VL) domain and/or the heavy chain variable (VH) domain as provided herein may form part of a chimeric antigen receptor. Thus, in an aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO: 28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID NO:27; and (ii) a transmembrane domain. In one embodiment, the chimeric antigen receptor includes the light chain variable domain of antibody 6E6 and a heavy chain variable domain of antibody 6E6.

[0221] In another aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID NO:33; and (ii) a transmembrane domain. In one embodiment, the chimeric antigen receptor includes the light chain variable domain of antibody 4G9 and a heavy chain variable domain of antibody 4G9.

[0222] In another aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42;

and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38, and a CDR H3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain. In one embodiment, the chimeric antigen receptor includes the light chain variable domain of antibody 5C11 and a heavy chain variable domain of antibody 5C11.

- 5 **[0223]** In an aspect is provided a chimeric antigen receptor including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (b) a heavy chain variable region domain including a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44, and a CDR H3 as set forth in SEQ ID NO:45; and (ii) a
10 transmembrane domain. In one embodiment, the chimeric antigen receptor includes the light chain variable domain of antibody 5G3 and a heavy chain variable domain of antibody 5G3.

- [0224]** An "antibody region" as provided herein refers to a monovalent or multivalent protein moiety that forms part of the recombinant protein (e.g., CAR, bispecific antibody) provided herein including embodiments thereof. A person of ordinary skill in the art will therefore
15 immediately recognize that the antibody region is a protein moiety capable of binding an antigen (epitope). Thus, the antibody region provided herein may include a domain of an antibody (e.g., a light chain variable (VL) domain, a heavy chain variable (VH) domain) or a fragment of an antibody (e.g., Fab). In embodiments, the antibody region is a protein conjugate. A "protein conjugate" as provided herein refers to a construct consisting of more than one polypeptide,
20 wherein the polypeptides are bound together covalently or non-covalently. In embodiments, the polypeptides of a protein conjugate are encoded by one nucleic acid molecule. In embodiments, the polypeptides of a protein conjugate are encoded by different nucleic acid molecules. In embodiments, the polypeptides are connected through a linker. In embodiments, the polypeptides are connected through a chemical linker. In embodiments, the antibody region is an
25 scFv. The antibody region may include a light chain variable (VL) domain and/or a heavy chain variable (VH) domain. In embodiments, the antibody region includes a light chain variable (VL) domain. In embodiments, the antibody region includes a heavy chain variable (VH) domain.

- [0225]** A "transmembrane domain" as provided herein refers to a polypeptide forming part of a biological membrane. The transmembrane domain provided herein is capable of spanning a
30 biological membrane (e.g., a cellular membrane) from one side of the membrane through to the other side of the membrane. In embodiments, the transmembrane domain spans from the intracellular side to the extracellular side of a cellular membrane. Transmembrane domains may

include non-polar, hydrophobic residues, which anchor the proteins provided herein including embodiments thereof in a biological membrane (e.g., cellular membrane of a T cell). Any transmembrane domain capable of anchoring the proteins provided herein including embodiments thereof are contemplated. Non-limiting examples of transmembrane domains
5 include the transmembrane domains of CD28, CD8, CD4 or CD3-zeta. In embodiments, the transmembrane domain is a CD4 transmembrane domain.

[0226] In embodiments, the transmembrane domain is a CD28 transmembrane domain. The term "CD28 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD28, or variants or homologs
10 thereof that maintain CD28 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD28 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50,
100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28
15 transmembrane domain polypeptide. In embodiments, CD28 is the protein as identified by the NCBI sequence reference GI:340545506, homolog or functional fragment thereof.

[0227] In embodiments, the transmembrane domain is a CD8 transmembrane domain. The term "CD8 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD8, or variants or homologs thereof
20 that maintain CD8 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD8 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100,
150 or 200 continuous amino acid portion) compared to a naturally occurring CD8
25 transmembrane domain polypeptide. In embodiments, CD8 is the protein as identified by the NCBI sequence reference GI:225007534, homolog or functional fragment thereof.

[0228] In embodiments, the transmembrane domain is a CD4 transmembrane domain. The term "CD4 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD4, or variants or homologs thereof
30 that maintain CD4 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD4 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino

acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD4 transmembrane domain polypeptide. In embodiments, CD4 is the protein as identified by the NCBI sequence reference GI:303522473, homolog or functional fragment thereof.

- 5 **[0229]** In embodiments, the transmembrane domain is a CD3-zeta (also known as CD247) transmembrane domain. The term "CD3-zeta transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD3-zeta, or variants or homologs thereof that maintain CD3-zeta transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity
- 10 compared to the CD3-zeta transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3-zeta transmembrane domain polypeptide. In embodiments, CD3-zeta is the protein as identified by the NCBI sequence reference
- 15 GI:166362721, homolog or functional fragment thereof.

- [0230]** In embodiments, the chimeric antigen receptor further includes an intracellular T-cell signaling domain. An "intracellular T-cell signaling domain" as provided herein includes amino acid sequences capable of providing primary signaling in response to binding of an antigen to the antibody region provided herein including embodiments thereof. In embodiments, the signaling
- 20 of the intracellular T-cell signaling domain results in activation of the T cell expressing the same. In embodiments, the signaling of the intracellular T-cell signaling domain results in proliferation (cell division) of the T cell expressing the same. In embodiments, the signaling of the intracellular T-cell signaling domain results expression by said T cell of proteins known in the art to characteristic of activated T cell (e.g., CTLA-4, PD-1, CD28, CD69). In embodiments, the
- 25 intracellular T-cell signaling domain is a CD3 ζ intracellular T-cell signaling domain.

- [0231]** In embodiments, the chimeric antigen receptor further includes an intracellular co-stimulatory T-cell signaling domain. An "intracellular co-stimulatory signaling domain" as provided herein includes amino acid sequences capable of providing co-stimulatory signaling in response to binding of an antigen to the antibody region provided herein including embodiments
- 30 thereof. In embodiments, the signaling of the co-stimulatory signaling domain results in production of cytokines and proliferation of the T cell expressing the same. In embodiments, the intracellular co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling

domain, a 4-1BB intracellular co-stimulatory signaling domain, an ICOS intracellular co-stimulatory signaling domain, or an OX-40 intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is a 4-1BB intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is an ICOS intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is an OX-40 intracellular co-stimulatory signaling domain.

[0232] In embodiments, the antibody region includes an Fc domain. In embodiments, the antibody region includes a spacer region. In embodiments, the spacer region is between the transmembrane domain and the antibody region. A "spacer region" as provided herein is a polypeptide connecting the antibody region with the transmembrane domain. In embodiments, the spacer region connects the heavy chain constant region with the transmembrane domain. In embodiments, the spacer region includes an Fc region. In embodiments, the spacer region is an Fc region. Examples of spacer regions contemplated for the compositions provided herein include without limitation, immunoglobulin molecules or fragments thereof (e.g., IgG1, IgG2, IgG3, IgG4) and immunoglobulin molecules or fragments thereof (e.g., IgG1, IgG2, IgG3, IgG4) including mutations affecting Fc receptor binding. In embodiments, the spacer region is a hinge region.

[0233] The term "CTLA-4" as referred to herein includes any of the recombinant or naturally-occurring forms of the cytotoxic T-lymphocyte-associated protein 4 protein, also known as CD152 (cluster of differentiation 152), or variants or homologs thereof that maintain CTLA-4 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CTLA-4). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CTLA-4 protein. In embodiments, the CTLA-4 protein is substantially identical to the protein identified by the UniProt reference number P16410 or a variant or homolog having substantial identity thereto.

[0234] The term "CD28" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 28 protein, or variants or homologs thereof that maintain CD28 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or

100% activity compared to CD28). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28 protein. In embodiments, the CD28 protein is substantially identical to the protein identified by the UniProt reference number P10747 or a variant or homolog having substantial identity thereto.

[0235] The term "CD69" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 69 protein, or variants or homologs thereof that maintain CD69 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD69). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD69 protein. In embodiments, the CD69 protein is substantially identical to the protein identified by the UniProt reference number Q07108 or a variant or homolog having substantial identity thereto.

[0236] The term "4-1BB" as referred to herein includes any of the recombinant or naturally-occurring forms of the 4-1BB protein, also known as tumor necrosis factor receptor superfamily member 9 (TNFRSF9), Cluster of Differentiation 137 (CD137) and induced by lymphocyte activation (ILA), or variants or homologs thereof that maintain 4-1BB activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to 4-1BB). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring EGFR protein. In embodiments, the 4-1BB protein is substantially identical to the protein identified by the UniProt reference number Q07011 or a variant or homolog having substantial identity thereto.

[0237] The chimeric antigen receptors provided herein may include any of the anti-ROR2 antibodies or fragments thereof described herein. Thus, the chimeric antigen receptors may include any of the CDRs, FRs, heavy chain variable domains, or light chain variable domains provided herein. For example, the heavy chain variable domain may include the sequence of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10 or SEQ ID NO:14. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10 or SEQ

ID NO:14. For example, the light chain variable domain may include the sequence of SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, or SEQ ID NO:16. In embodiments, light chain variable domain is the sequence of SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, or SEQ ID NO:16.

[0238] In embodiments, the chimeric antigen receptor further includes a heavy chain constant domain. In embodiments, the chimeric antigen receptor further includes a spacer region. In embodiments, the spacer region is between the transmembrane domain and the antibody region. In embodiments, the spacer region further includes a hinge region. In embodiments, the spacer region includes the sequence of SEQ ID NO:94. In embodiments, the spacer region includes the sequence of SEQ ID NO:95. In embodiments, the spacer region includes the sequence of SEQ ID NO:96.

[0239] In embodiments, the chimeric antigen receptor further includes a linker domain. In embodiments, the linker domain is between the heavy chain variable domain and the light chain variable domain. In embodiments, the linker domain includes the sequence of SEQ ID NO:82. In embodiments, the chimeric antigen receptor further includes a leader peptide. In embodiments, the leader peptide includes the sequence of SEQ ID NO:93.

[0240] In embodiments, the chimeric antigen receptor includes the sequence of SEQ ID NO:100. In embodiments, the chimeric antigen receptor is the sequence of SEQ ID NO:100. In embodiments, the chimeric antigen receptor includes the sequence of SEQ ID NO:101. In embodiments, the chimeric antigen receptor is the sequence of SEQ ID NO:101.

[0241] In one embodiment, the chimeric antigen receptor includes from the N-terminus to the C-terminus: a leader peptide of SEQ ID NO:93, a light chain variable domain of SEQ ID NO:4, a linker domain of SEQ ID NO:82, a heavy chain variable domain of SEQ ID NO:2, a spacer domain of SEQ ID NO:96, a transmembrane domain of SEQ ID NO:97, an intracellular co-stimulatory signaling domain of SEQ ID NO:98, and an intracellular T-cell signaling domain of SEQ ID NO:99.

[0242] In one embodiment, the protein includes from the N-terminus to the C-terminus: a leader peptide of SEQ ID NO:93; a light chain variable domain of SEQ ID NO:8, a linker domain of SEQ ID NO:82, a heavy chain variable domain of SEQ ID NO:6, a spacer domain of SEQ ID NO:96, a transmembrane domain of SEQ ID NO:97, an intracellular co-stimulatory

signaling domain of SEQ ID NO:98, and an intracellular T-cell signaling domain of SEQ ID NO:99.

BISPECIFIC ANTIBODIES

[0243] The light chain variable (VL) domain and the heavy chain variable (VH) domain as provided herein may form part of a bispecific antibody. Thus, the second antibody region may include any of the light chain and/or heavy chain variable domains provided herein including embodiments thereof.

[0244] Thus, in another aspect is provided a bispecific antibody including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and (b) a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0245] In another aspect is provided a bispecific antibody including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and (b) a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0246] In another aspect is provided a bispecific antibody including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and (b) a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0247] In another aspect is provided a bispecific antibody including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and (b) a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0248] The term “effector cell ligand” as provided herein refers to a cell surface molecule expressed on an effector cell of the immune system (e.g., a cytotoxic T cell, a helper T cell, a B cell, a natural killer cell). Upon binding of the first antibody region to the effector cell ligand expressed on the effector cell, the effector cell is activated and able to exert its function (e.g., selective killing or eradication of malignant, infected or otherwise unhealthy cells). In 5 embodiments, the effector cell ligand is a CD3 protein. In embodiments, the effector cell ligand is a CD16 protein. In embodiments, the effector cell ligand is a CD32 protein. In embodiments, the effector cell ligand is a Nkp46 protein. The first antibody region as provided herein may be an antibody, an antibody variant, a fragment of an antibody or a fragment of an antibody variant.

[0249] A "CD3 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 3 (CD3) proteins or variants or homologs thereof that comprise the CD3 complex that mediates signal transduction and maintains CD3 complex activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD3 complex). In some aspects, the variants or homologs have at least 10 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3 proteins in the CD3 complex.

[0250] A "CD16 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 16 (CD16) protein, also known as low affinity immunoglobulin gamma Fc region receptor III-A, or variants or homologs thereof that maintain 20 CD16 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD16). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD16 protein. In embodiments, the CD16 protein is substantially identical to the 25 protein identified by the UniProt reference number P08637 or a variant or homolog having substantial identity thereto.

[0251] A "CD32 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 32 (CD32) protein, also known as low affinity immunoglobulin gamma Fc region receptor II-A, or variants or homologs thereof that maintain 30 CD32 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD32). In some aspects, the variants or homologs have at least 90%, 95%, 96%,

97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD32 protein. In embodiments, the CD32 protein is substantially identical to the protein identified by the UniProt reference number P12318 or a variant or homolog having substantial identity thereto.

[0252] A "NKp46 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the NKp46 protein, also known as natural cytotoxicity triggering receptor 1, or variants or homologs thereof that maintain NKp46 activity (*e.g.* within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to NKp46). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring NKp46 protein. In embodiments, the NKp46 protein is substantially identical to the protein identified by the UniProt reference number O76036 or a variant or homolog having substantial identity thereto.

[0253] The bispecific antibody provided herein may include any of the ROR2 antibodies or fragments thereof described herein. Thus, the second antibody region may include any of the CDRs, FRs, heavy chain variable domains, or light chain variable domains provided herein. In embodiments, the second antibody region includes a heavy chain variable domain including the sequence of SEQ ID NO:2. In embodiments, the second antibody region includes a light chain variable domain includes the sequence of SEQ ID NO:4. In embodiments, the second antibody region includes a heavy chain variable domain with the sequence of SEQ ID NO:2. In embodiments, the second antibody region includes a light chain variable domain with the sequence of SEQ ID NO:4.

[0254] Thus, the heavy chain variable domain of the second antibody region may include, for example, a FR H1 as set forth in SEQ ID NO:49, a FR H2 as set forth in SEQ ID NO:50, a FR H3 as set forth in SEQ ID NO:51, and a FR H4 as set forth in SEQ ID NO:52. The light chain variable domain of the second antibody region may include any of the CDRs or FRs provided herein. For example, the light chain variable domain may include, for example, a FR L1 as set forth in SEQ ID NO:53, a FR L2 as set forth in SEQ ID NO:54, a FR L3 as set forth in SEQ ID NO:55, and a FR L4 as set forth in SEQ ID NO:56.

[0255] In embodiments, the second antibody region includes a heavy chain variable domain including the sequence of SEQ ID NO:6. In embodiments, the second antibody region includes a

light chain variable domain includes the sequence of SEQ ID NO:8. In embodiments, the second antibody region includes a heavy chain variable domain with the sequence of SEQ ID NO:6. In embodiments, the second antibody region includes a light chain variable domain with the sequence of SEQ ID NO:8.

5 **[0256]** The heavy chain variable domain of the second antibody region may include, for example, a FR H1 as set forth in SEQ ID NO:57, a FR H2 as set forth in SEQ ID NO:58, a FR H3 as set forth in SEQ ID NO:59, and a FR H4 as set forth in SEQ ID NO:60. The light chain variable domain of the bispecific antibody provided herein may include, for example, a FR L1 as set forth in SEQ ID NO:61, a FR L2 as set forth in SEQ ID NO:62, a FR L3 as set forth in SEQ
10 ID NO:63, and a FR L4 as set forth in SEQ ID NO:64.

[0257] In embodiments, the second antibody region includes a heavy chain variable domain including the sequence of SEQ ID NO:10. In embodiments, the second antibody region includes a light chain variable domain includes the sequence of SEQ ID NO:12. In embodiments, the second antibody region includes a heavy chain variable domain with the sequence of SEQ ID
15 NO:10. In embodiments, the second antibody region includes a light chain variable domain with the sequence of SEQ ID NO:12.

[0258] The heavy chain variable domain of the second antibody region may include, for example, a FR H1 as set forth in SEQ ID NO:65, a FR H2 as set forth in SEQ ID NO:66, a FR H3 as set forth in SEQ ID NO:67, and a FR H4 as set forth in SEQ ID NO:68. The light chain
20 variable domain of the bispecific antibody provided herein may include, for example, a FR L1 as set forth in SEQ ID NO:69, a FR L2 as set forth in SEQ ID NO:70, a FR L3 as set forth in SEQ ID NO:71, and a FR L4 as set forth in SEQ ID NO:72.

[0259] In embodiments, the second antibody region includes a heavy chain variable domain including the sequence of SEQ ID NO:14. In embodiments, the second antibody region includes
25 a light chain variable domain includes the sequence of SEQ ID NO:16. In embodiments, the second antibody region includes a heavy chain variable domain with the sequence of SEQ ID NO:14. In embodiments, the second antibody region includes a light chain variable domain with the sequence of SEQ ID NO:16.

[0260] The heavy chain variable domain of the second antibody region may include, for
30 example, a FR H1 as set forth in SEQ ID NO:73, a FR H2 as set forth in SEQ ID NO:74, a FR H3 as set forth in SEQ ID NO:75, and a FR H4 as set forth in SEQ ID NO:76. The light chain variable domain of the bispecific antibody provided herein may include, for example, a FR L1 as

set forth in SEQ ID NO:77, a FR L2 as set forth in SEQ ID NO:78, a FR L3 as set forth in SEQ ID NO:79, and a FR L4 as set forth in SEQ ID NO:80.

[0261] In embodiments, the first antibody region is a first Fab' fragment or the second antibody region is a second Fab' fragment. In embodiments, the first antibody region is a single chain variable fragment (scFv) or the second antibody region is a second single chain variable fragment (scFv).

[0262] In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.1 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 1 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 10 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 20 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 30 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 40 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 50 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 60 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 70 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 80 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 90 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 100 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 110 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 120 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 130 nM to 150 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 140 nM to 150 nM.

[0263] In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 140 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 130 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 120 nM. In embodiments,

the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 110 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 100 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 90 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 80 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 70 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 60 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 50 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 40 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 30 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 20 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 10 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D from 0.01 nM to 1 nM.

[0264] In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D of about 0.07 nM. In embodiments, the scFv of the second antibody region binds the ROR2 protein with a K_D of 0.07 nM. In embodiments, the scFv of the second antibody region is the 6E6 scFv and binds the ROR2 protein with a K_D of 0.07 nM.

[0265] The second antibody region may include a light chain variable (VL) domain or a heavy chain variable (VH) domain. In embodiments, the second antibody region includes a light chain variable (VL) domain. In embodiments, the second antibody region includes a heavy chain variable (VH) domain.

[0266] In embodiments, the second antibody region is bound to a ROR2 protein. In embodiments, the ROR2 protein is expressed on a cell. In embodiments, the cell is a cancer cell. In embodiments, the cancer cell is cancer is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell. In embodiments, the cancer cell is a breast cancer cell. In embodiments, the cancer cell is an ovarian cancer cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is cancer is a cervical cancer cell. In embodiments, the cancer cell is cancer is a gastric cancer cell. In embodiments, the cancer cell is cancer is a renal cancer cell. In embodiments, the cancer cell is cancer is a head

and neck cancer cell. In embodiments, the cancer cell is a cancer is bone cancer cell. In embodiments, the cancer cell is cancer is a skin cancer cell. In embodiments, the cancer cell is cancer is a prostate cancer cell.

NUCLEIC ACID COMPOSITIONS

5 [0267] The compositions provided herein include nucleic acid molecules encoding the anti-ROR2 antibodies, CARs and bispecific antibodies or portions thereof provided herein including embodiments thereof. The antibodies, CARs and bispecific antibodies encoded by the isolated nucleic acid are described in detail throughout this application (including the description above and in the examples section). Thus, in an aspect, an isolated nucleic acid encoding an antibody
10 as provided herein including embodiments thereof is provided.

[0268] In embodiments, the isolated nucleic acid encodes a variable heavy chain domain or a variable light chain domain provided herein. In embodiments, the isolated nucleic acid encodes a variable heavy chain domain. In embodiments, the isolated nucleic acid encodes a variable light chain domain. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:1.

15 In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:3. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:5. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:7. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:9. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:11. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:13. In embodiments, the isolated nucleic acid includes the sequence of
20 SEQ ID NO:15.

[0269] In another aspect, an isolated nucleic acid encoding an antibody as provided herein including embodiments thereof is provided. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:91. In embodiments, the isolated nucleic acid includes the sequence
25 of SEQ ID NO:92.

[0270] In another aspect, an isolated nucleic acid encoding a chimeric antigen receptor as provided herein including embodiments thereof is provided. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:111. In embodiments, the isolated nucleic acid includes the sequence of SEQ ID NO:112.

30 PHARMACEUTICAL COMPOSITIONS

[0271] The compositions provided herein include pharmaceutical compositions including the anti anti-ROR2 antibodies, CARs and bispecific antibodies provided herein including

embodiments thereof. Thus, in an aspect is provided a pharmaceutical composition including a therapeutically effective amount of an antibody as provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

[0272] In another aspect is provided a pharmaceutical composition including a therapeutically effective amount of a CAR as provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

[0273] In another aspect is provided a pharmaceutical composition including a therapeutically effective amount of a bispecific antibody as provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

10 METHODS OF TREATMENT

[0274] The compositions (e.g., the anti-ROR2 antibodies CARs and bispecific antibodies) provided herein, including embodiments thereof, are contemplated as providing effective treatments for diseases such as cancer (e.g., breast cancer).

[0275] Thus, in an aspect is provided a method of treating cancer in a subject in need thereof, the method including administering to a subject a therapeutically effective amount of an antibody as provided herein including embodiments thereof. In another aspect is provided a method of inhibiting metastasis of a ROR2 expressing cancer in a subject in need thereof, the method including administering to a subject a therapeutically effective amount of an antibody provided herein including embodiments thereof.

[0276] In another aspect is provided a method of treating cancer in a subject in need thereof, the method including administering a therapeutically effective amount of a chimeric antigen receptor provided herein including embodiments thereof to a subject.

[0277] In embodiments, the cancer is a solid tumor malignancy. In embodiments, the cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer. In embodiments, the cancer is breast cancer. In embodiments, the cancer is ovarian cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is cervical cancer. In embodiments, the cancer is gastric cancer. In embodiments, the cancer is renal cancer. In embodiments, the cancer is head and neck cancer. In embodiments, the cancer is bone cancer. In embodiments, the cancer is skin cancer. In embodiments, the cancer is prostate cancer.

[0278] In an aspect is provided a method of detecting a ROR2 expressing cell, the method including (i) contacting a ROR2-expressing cell with an antibody provided herein including embodiments thereof; (ii) and detecting binding of the antibody to a ROR2 protein expressed by the cell. In embodiments, the antibody is attached to a detectable moiety.

5 [0279] In an aspect is a method of delivering a therapeutic agent to a ROR2 expressing cell, the method including contacting a ROR2 expressing cell with an antibody provided herein including embodiments thereof, wherein the antibody is attached to a therapeutic agent. In embodiments, the therapeutic agent is an anti-cancer agent. Exemplary anti-cancer agent include
10 calicheamicin, duocarmycin, pyrrolbenzodiazepine, (PBD), SN-38, DXd and anti-tubulin. Methods for generating antibody drug conjugates are well known in the art and described for example, by Hafeez, U. et al. Antibody-Drug Conjugates for Cancer Therapy; Molecules 2020, 25, 4764; doi:10.3390/molecules25204764.; Ponziani, S. et al. Antibody-Drug Conjugates; The New Frontier of Chemotherapy. Int. J. Mol. Sci. 2020, 21, 5510; doi:10.3390/ijms21155510. and;
15 Joubert, N. et al. Antibody-Drug Conjugates: The Last Decade. Pharmaceuticals 2020, 13, 245; doi:10.3390/ph13090245.; which are incorporated by reference herein in their entirety and for all purposes.

[0280] For the methods provided herein, in embodiments, the contacting occurs *in vitro*. In embodiments, the ROR2-expressing cell is in a subject. In embodiments, the subject is a healthy
20 subject. In embodiments, the subject is a subject having cancer. In embodiments, the cancer is a solid tumor malignancy. In embodiments, the cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer. In embodiments, the cancer is breast cancer. In embodiments, the cancer is ovarian cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the
25 cancer is cervical cancer. In embodiments, the cancer is gastric cancer. In embodiments, the cancer is renal cancer. In embodiments, the cancer is head and neck cancer. In embodiments, the cancer is bone cancer. In embodiments, the cancer is skin cancer. In embodiments, the cancer is prostate cancer.

[0281] For the methods provided herein, in embodiments, the ROR2 expressing cell is a cancer
30 cell. In embodiments, the cancer cell is cancer is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell. In embodiments, the cancer

cell is a breast cancer cell. In embodiments, the cancer cell is an ovarian cancer cell. In
embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is
cancer is a cervical cancer cell. In embodiments, the cancer cell is cancer is a gastric cancer cell.
In embodiments, the cancer cell is cancer is a renal cancer cell. In embodiments, the cancer cell
5 is cancer is a head and neck cancer cell. In embodiments, the cancer cell is a cancer is bone
cancer cell. In embodiments, the cancer cell is cancer is a skin cancer cell. In embodiments, the
cancer cell is cancer is a prostate cancer cell.

[0282] For the methods provided herein, in embodiments, the antibody is administered at an
amount from about 0.01 nM to about 10 nM. In embodiments, the antibody is administered at an
10 amount from about 0.05 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 0.1 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 0.5 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 1 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 2 nM to about 10 nM. In embodiments, the antibody is administered at an
15 amount from about 4 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 6 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 4 nM to about 10 nM. In embodiments, the antibody is administered at an
amount from about 8 nM to about 10 nM. In embodiments, the antibody is administered at an
amount of about 0.01 nM, 0.05 nM, 0.1 nM, 0.5 nM, 1 nM, 2 nM, 2 nM, 4 nM, 5 nM, 6 nM, 7
20 nM, 8 nM, 9 nM or 10 nM.

[0283] In embodiments, the antibody is administered at an amount from 0.01 nM to 10 nM. In
embodiments, the antibody is administered at an amount from 0.05 nM to 10 nM. In
embodiments, the antibody is administered at an amount from 0.1 nM to 10 nM. In
embodiments, the antibody is administered at an amount from 0.5 nM to 10 nM. In
25 embodiments, the antibody is administered at an amount from 1 nM to 10 nM. In embodiments,
the antibody is administered at an amount from 2 nM to 10 nM. In embodiments, the antibody is
administered at an amount from 4 nM to 10 nM. In embodiments, the antibody is administered at
an amount from 6 nM to 10 nM. In embodiments, the antibody is administered at an amount
from 4 nM to 10 nM. In embodiments, the antibody is administered at an amount from 8 nM to
30 10 nM. In embodiments, the antibody is administered at an amount of 0.01 nM, 0.05 nM, 0.1
nM, 0.5 nM, 1 nM, 2 nM, 2 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM or 10 nM.

[0284] In embodiments, the antibody is administered at an amount from about 0.01 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 0.05 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 0.1 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 0.5 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 1 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 2 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 4 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 6 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 4 nM to about 8 nM.

[0285] In embodiments, the antibody is administered at an amount from 0.01 nM to 8 nM. In embodiments, the antibody is administered at an amount from 0.05 nM to 8 nM. In embodiments, the antibody is administered at an amount from 0.1 nM to 8 nM. In embodiments, the antibody is administered at an amount from 0.5 nM to 8 nM. In embodiments, the antibody is administered at an amount from 1 nM to 8 nM. In embodiments, the antibody is administered at an amount from 2 nM to 8 nM. In embodiments, the antibody is administered at an amount from 4 nM to 8 nM. In embodiments, the antibody is administered at an amount from 6 nM to 8 nM. In embodiments, the antibody is administered at an amount from 4 nM to 8 nM.

[0286] In embodiments, the antibody is administered at an amount from about 0.01 nM to about 6 nM. In embodiments, the antibody is administered at an amount from about 0.05 nM to about 6 nM. In embodiments, the antibody is administered at an amount from about 0.1 nM to about 6 nM. In embodiments, the antibody is administered at an amount from about 0.5 nM to about 8 nM. In embodiments, the antibody is administered at an amount from about 1 nM to about 6 nM. In embodiments, the antibody is administered at an amount from about 2 nM to about 6 nM. In embodiments, the antibody is administered at an amount from about 4 nM to about 6 nM.

[0287] In embodiments, the antibody is administered at an amount from 0.01 nM to 6 nM. In embodiments, the antibody is administered at an amount from 0.05 nM to 6 nM. In embodiments, the antibody is administered at an amount from 0.1 nM to 6 nM. In embodiments, the antibody is administered at an amount from 0.5 nM to 6 nM. In embodiments, the antibody is administered at an amount from 1 nM to 6 nM. In embodiments, the antibody is administered at

an amount from 2 nM to 6 nM. In embodiments, the antibody is administered at an amount from 4 nM to 6 nM.

[0288] In embodiments, the antibody is administered at an amount from about 0.01 nM to about 4 nM. In embodiments, the antibody is administered at an amount from about 0.05 nM to about 4 nM. In embodiments, the antibody is administered at an amount from about 0.1 nM to about 4 nM. In embodiments, the antibody is administered at an amount from about 0.5 nM to about 4nM. In embodiments, the antibody is administered at an amount from about 1 nM to about 4 nM. In embodiments, the antibody is administered at an amount from about 2 nM to about 4 nM.

[0289] In embodiments, the antibody is administered at an amount from 0.01 nM to 4 nM. In embodiments, the antibody is administered at an amount from 0.05 nM to 4 nM. In embodiments, the antibody is administered at an amount from 0.1 nM to 4 nM. In embodiments, the antibody is administered at an amount from 0.5 nM to 4 nM. In embodiments, the antibody is administered at an amount from 1 nM to 4 nM. In embodiments, the antibody is administered at an amount from 2 nM to 4 nM.

[0290] In embodiments, the antibody is administered at an amount from about 0.01 nM to about 2 nM. In embodiments, the antibody is administered at an amount from about 0.05 nM to about 2 nM. In embodiments, the antibody is administered at an amount from about 0.1 nM to about 2 nM. In embodiments, the antibody is administered at an amount from about 0.5 nM to about 2 nM. In embodiments, the antibody is administered at an amount from about 1 nM to about 2 nM.

[0291] In embodiments, the antibody is administered at an amount from 0.01 nM to 2 nM. In embodiments, the antibody is administered at an amount from 0.05 nM to 2 nM. In embodiments, the antibody is administered at an amount from 0.1 nM to 2 nM. In embodiments, the antibody is administered at an amount from 0.5 nM to 2 nM. In embodiments, the antibody is administered at an amount from 1 nM to 2 nM.

[0292] In embodiments, the antibody is administered at an amount from about 0.01nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 1nM.

[0293] In embodiments, the antibody is administered at an amount from 0.01nM to 1nM. In embodiments, the antibody is administered at an amount from 0.05nM to 1nM. In embodiments, the antibody is administered at an amount from 0.1nM to 1nM. In embodiments, the antibody is administered at an amount from 0.5nM to 1nM.

5 [0294] In embodiments, the antibody is administered at an amount of about 3.15nM. In embodiments, the antibody is administered at an amount of 3.15nM. In embodiments, the antibody is administered at an amount of about 1.05nM. In embodiments, the antibody is administered at an amount of 1.05nM.

[0295] It is understood that the the bispecific antibody or the chimeric antigen receptor
10 provided herein including embodiments thereof may be administered at any of the concentrations described herein for the administration of the antibody (e.g., 0.01nM-10nM).

[0296] In embodiments, the antibody is administered at an amount from about 10 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 20 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 30 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 40 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 50 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 60 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 70 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 80 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 90 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 100 µg to about 500 µg.

[0297] In embodiments, the antibody is administered at an amount from about 110 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 120 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 130 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 140 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 150 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 160 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 170 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 180 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 190 µg to about 500 µg.

500 µg. In embodiments, the antibody is administered at an amount from about 470 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 480 µg to about 500 µg. In embodiments, the antibody is administered at an amount from about 490 µg to about 500 µg.

5 **[0301]** In embodiments, the antibody is administered at an amount from about 10 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 20 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 30 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 40 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 50 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 60 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 70 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 80 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 90 µg to about 400 µg. In embodiments, the antibody is administered at an amount from about 100 µg to about 400 µg.

[0302] In embodiments, the antibody is administered at an amount from about 10 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 20 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 30 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 40 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 50 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 60 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 70 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 80 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 90 µg to about 300 µg. In embodiments, the antibody is administered at an amount from about 100 µg to about 300 µg.

[0303] In embodiments, the antibody is administered at an amount from about 10 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 20 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 30 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 40 µg to about 200 µg.

200 µg. In embodiments, the antibody is administered at an amount from about 50 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 60 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 70 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 80 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 90 µg to about 200 µg. In embodiments, the antibody is administered at an amount from about 100 µg to about 200 µg.

[0304] In embodiments, the antibody is administered at an amount from about 10 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 20 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 30 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 40 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 50 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 60 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 70 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 80 µg to about 100 µg. In embodiments, the antibody is administered at an amount from about 90 µg to about 100 µg.

[0305] In embodiments, the antibody is administered at an amount of about 10 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg, 100 µg, 110 µg, 120 µg, 130 µg, 140 µg, 150 µg, 160 µg, 170 µg, 180 µg, 190 µg, 200 µg, 210 µg, 220 µg, 230 µg, 240 µg, 250 µg, 260 µg, 270 µg, 280 µg, 290 µg, 300 µg, 310 µg, 320 µg, 330 µg, 340 µg, 350 µg, 360 µg, 370 µg, 380 µg, 390 µg, 400 µg, 410 µg, 420 µg, 430 µg, 440 µg, 450 µg, 460 µg, 470 µg, 480 µg, 490 µg, or 500 µg.

[0306] In embodiments, the antibody is administered at an amount of 10 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg, 100 µg, 110 µg, 120 µg, 130 µg, 140 µg, 150 µg, 160 µg, 170 µg, 180 µg, 190 µg, 200 µg, 210 µg, 220 µg, 230 µg, 240 µg, 250 µg, 260 µg, 270 µg, 280 µg, 290 µg, 300 µg, 310 µg, 320 µg, 330 µg, 340 µg, 350 µg, 360 µg, 370 µg, 380 µg, 390 µg, 400 µg, 410 µg, 420 µg, 430 µg, 440 µg, 450 µg, 460 µg, 470 µg, 480 µg, 490 µg, or 500 µg.

[0307] It is understood that the bispecific antibody or the chimeric antigen receptor provided herein including embodiments thereof may be administered at any of the concentrations described herein for the administration of the antibody (e.g., 10 µg -500 µg).

METHODS OF INHIBITING CELL MIGRATION

5 [0308] The compositions provided herein, including embodiments thereof, are further contemplated for inhibiting cell migration. Thus, in an aspect is provided a method of inhibiting migration of a ROR2-expressing cell, the method including contacting a ROR2 expressing cell with an antibody provided herein including embodiments thereof. In embodiments, the antibody includes a heavy chain variable domain and a light chain variable domain, wherein the heavy
10 chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0309] For the methods provided herein, in embodiments, the ROR2 expressing cell is a cancer
15 cell. In embodiments, the cancer cell is cancer is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell. In embodiments, the cancer is cancer is breast cancer. In embodiments, the cancer cell is an ovarian cancer cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is
20 cancer is a cervical cancer cell. In embodiments, the cancer cell is cancer is a gastric cancer cell. In embodiments, the cancer cell is cancer is a renal cancer cell. In embodiments, the cancer cell is cancer is a head and neck cancer cell. In embodiments, the cancer cell is a cancer is bone cancer cell. In embodiments, the cancer cell is cancer is a skin cancer cell. In embodiments, the cancer cell is cancer is a prostate cancer cell.

25 [0310] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1:

[0311] Due to its expression in cancer cells, ROR2 has the potential to serve as a diagnostic and therapeutic target. There have been monoclonal antibodies generated that reportedly bind ROR2 and that are available from commercial sources. However, Applicants found that several reacted with cells expressing ROR2 by immunoblot and/or flow cytometry. Further, Applicants discovered that several of these antibodies also unexpectedly reacted with cells that were deleted of ROR2 using CRISPR-Cas9 technology. This unexpected binding revealed that many commercially available antibodies are not specific for ROR2.

[0312] Thus, Applicants generated monoclonal antibodies that specifically target the extracellular portion of human ROR2. For this, mice were immunized with recombinant protein of the extracellular portion (AA 1-403) of the ROR2 protein that include the Ig-like, cysteine rich domain (CRD) and Kringle domains (FIG. 1). Because of the high degree of homology between the murine and human molecules, Applicants co-injected immune stimulatory agents, such as Freund's Complete Adjuvant, to maximize the generation of anti-human ROR2 antibodies.

Hybridomas generated following fusion of splenocytes with a myeloma fusion partner were screened for expression of anti-ROR2 mAb using ELISA and flow cytometry to identify clones that produce antibody that specifically bind to human ROR2. These antibodies are designated in this disclosure as mAbs N-LN or in the more familiar form 6-E6, are listed in Table 1, and the sequences of the heavy and light chain variable regions are depicted in FIG. 2.

[0313] Table 1. Characteristics of anti-human ROR2 monoclonal antibodies

mAb Name	Subclass	Sequence	Human ROR2 binding domain	KD (nM)
6E6	mIgG1	mKappa	Kringle	< 0.1
4G9	mIgG2a	mKappa	Ig-like	~ 1.9
5C11	mIgG1	mKappa	Kringle	> 40
5G3	mIgG2a	mKappa	Ig-like	> 40

[0314] Applicants assessed binding specificity and relative affinities of each mAb using recombinant ROR2-extracellular protein in an ELISA assay, in which binding was measured using decreasing/limiting amounts of ROR2 protein and assessed in combination with decreasing concentrations of each of the four mAb (FIG. 3). Higher absorbance values for 6E6 and 4G9 at both lower ROR2 protein amounts and lower concentrations of mAb, indicate these mAb have higher affinities compared to 5C11 and 5G3. Equilibrium dissociation constants (Kd) were

measured in a kinetic exclusion assay (KinExA) that measures the equilibrium binding affinity and kinetics between unmodified molecules in solution. The 6E6 mAb binds to the target ROR2 extracellular sequence with a K_d of about 0.1 nM. 4G9 binds to the extracellular domain of human ROR2 with a K_d of about 2 nM (FIG.s 4A and 4B). Analysis of the 5C11 and 5G3 mAb
5 determined that each has a K_d greater than about 40 nM, consistent with the results from the ELISA analysis above.

[0315] Applicants developed a series recombinant human/mouse hybrid proteins that isolate specific domains of the human ROR2 protein. These recombinant proteins were used to identify the specific binding domains that each of the four mAb target (FIG. 5). The 6E6 and 5C11 mAb
10 bind to the Kringle domain of human, but not mouse, ROR2. The 4G9 and 5G3 mAb bind within the first 111 aa of human ROR2, which includes the Ig-like domain. None of the four mAb bind mouse ROR2.

[0316] Applicants also refined this procedure to identify specific amino acids that are critical for the binding of the two anti-ROR2 mAbs that bind within the Kringle domain (FIG. 6).

15 Applicants produced several recombinant human ROR2 proteins in which one of the amino acids that differs between human and mouse ROR2 within the Kringle domain was replaced with the corresponding amino acid of mouse ROR2. Assessment of binding of 6E6 and 5C11 mAbs indicates that they require a histidine residue at position 349 and an aspartic acid at position 354 for binding to the Kringle domain of human ROR2, as replacement of these amino acids with the
20 murine molecule's arginine and glutamic acid residues, respectively, the 6E6 and 5C11 mAbs no longer bind the ROR2 protein. Additionally, 5C11 requires a methionine residue at position 386, as binding is lost upon replacement of methionine with the valine of mouse ROR2.

[0317] Binding of each of the mAb to human ROR2 was validated by flow cytometric staining and analysis of several cell lines known to express ROR2 using each mAb conjugated with
25 Alexa647 (FIG. 7 A). Specificity was validated by the absence of binding to HCT116 colorectal cancer cells and HEK293 cells in which ROR2 expression was eliminated using CRISPR-cas9 (FIG. 7B). Validation of the specificity of these mAb sets them apart from many commercially available anti-human ROR2 polyclonal and monoclonal antibodies, as in the last few years several that have been widely used in published studies, have subsequently been recalled and are
30 no longer available, as they were determined to not be specific for ROR2.

[0318] Additionally, the 6E6 and 4G9 mAb have been tested on primary human cells. 6E6 and 4G9 each stain ROR2 on BR1936, but not BR1367 (ROR2 negative), human breast cancer PDX

cells (FIG. 8), compared to staining with equal amounts of isotype matched Alex647-conjugated control antibody. Neither 6E6 nor 4G9 demonstrate binding to peripheral blood mononuclear cells isolated from several healthy donors (FIG. 9).

[0319] Initial functional studies of 6E6 and 4G9, demonstrate that each mAb is internalized, as assessed by increased relative fluorescence with 6E6 and 4G9 mAb conjugated to the pH sensitive dye pHrodo. Following staining with saturating amounts of pHrodo-conjugated mAb, cells were washed, incubated for 2 hours at either 37°C or 4°C, and analyzed by flow cytometry for changes in relative cell fluorescence associated with pHrodo and lower intracellular pH (FIG. 10), indicating that the antibody was internalized into primary endosomes and lysosomes of the treated cells that express ROR2. Both the 6E6 and 4G9 mAb had increased relative fluorescence in K562 cells at 37°C, relative to unstained cells or cells incubated at 4°C, and showed no difference at either temperature for JEKO cells that lacked ROR2 expression. Applicants discovered that 6E6 internalized with greater efficiency than 4G9. Because antibodies that internalize into primary endosomes/lysosomes have been demonstrated to be effective vehicles for delivering drugs or other molecules conjugated to them to the cell that expresses the target antigen, in this case ROR2, Applicants conclude from these data that 6E6 would be very effective as the antibody in antibody-drug conjugates (or ADCs) that then could target cells that express ROR2.

[0320] Thus, antibodies targeting the epitope recognized by 6E6 can be used to deliver drugs or other compounds efficiently to cells that express ROR2 in a fashion that allows for the drug/compound to be internalized into the cell and active within the ROR2 cell. This allows for selective targeting of ROR2 positive cells in vivo. Further, these antibodies may be used for targeting ROR2-expressing cells with agents that can identify the ROR2-expressing cell for diagnostic imaging or fluorescence identification during surgical extraction of ROR2-positive cancer cells.

[0321] Tumor-cell expression of ROR2 may have functional significance. Transfection of the breast-cancer cell line, MCF7 with an expression vector encoding ROR2, generated MCF7-ROR2 cells that expressed surface ROR2. MCF7-ROR2 cells had enhanced motility and tissue invasiveness in response to Wnt5a than parental MCF7 cells, which do not express ROR2. The increased motility and invasiveness are associated with an enhanced capacity to form metastatic tumors in immune-deficient mice, such has been observed using MCF7 cells transfected to express ROR1.¹ Applicants examined whether any one of the specific anti-ROR2 mAb could

inhibit the capacity of Wnt5a to enhance the migration/invasiveness of MCF7-ROR2 cells in vitro. For this Applicants established cell migration assay and invasion assays to evaluate the capacity of cells to migrate or invade Matrigel, respectively. As demonstrated in FIG. 11, MCF7-ROR2 cells treated with Wnt5a had 2-fold greater migration/invasiveness than Wnt5a-treated MCF7 cells; the increased migration MCF7-ROR2 cells was not inhibited when control, non-specific mouse IgG was added to the cultures (FIG. 11A, gray bars). Applicants discovered, 25 ug/ml of 6E6 (white bars), but not 4G9 (black bars), provided for complete inhibition of Wnt5a-induced migration of MCF7-ROR2 cells, such that it no longer had an advantage over MCF7 cells in the migration/invasiveness assay. These data demonstrate that 6E6 can inhibit the function of ROR2 in enhancing tumor cell migration and invasiveness. By extension, this implies that 6E6 reacts with ROR2 in a fashion that inhibits ROR2-signaling, which contributes to enhanced metastases. The fact that 6E6 had such activity, but not 4G9, implies that the epitope recognized by 6E6 is important for inhibition of ROR2 signaling leading to enhanced tumor cell invasion. Thus, antibodies that bind the epitope recognized by 6E6 can inhibit the function of ROR2 and should have activity in mitigating the risk of metastases in patients with tumor cells that express ROR2.

[0322] Applicants have generated single chain Fv (scFv) by combining the variable regions of the light and heavy chains of 6E6 or 4G9 onto the constant regions (CH2-CH3) of human IgG1. The variable regions of these single chain constructs include linker sequences conjoining the light and heavy variable regions of both antibodies. Applicants found that scFv for 6E6 or 4G9 bind to the ROR2 antigen by ELISA and can bind specifically to cells that express the ROR2 surface antigen (FIG. 12). Therefore, the 6E6 or 4G9 scFv retain their specificity and binding activity for the target antigen. Such scFv's also may be used to generate bispecific antibodies that conjoin the scFv of 6E6 or 4G9 with another scFv, such as the scFv that recognizes a surface antigen expressed by T cells (e.g. CD3). These chimeric bispecific molecules may be used for cellular immune activation for the purpose of killing ROR2-expressing cells in patients treated with such bispecific antibodies.

[0323] The capacity of the scFv to bind with high specificity and affinity to the ROR2 protein allows for the generation of chimeric antigen receptors (CARs) that can be transduced into T cells or NK cells for generation of cytotoxic effector cells capable of specifically killing cells that express the ROR2 surface antigen. Applicants have generated CAR constructs using the variable region sequences of either the 6E6 or 4G9 scFv. Applicants find that transfection of cells with these constructs can generate cells that express surface CAR that bind to the

extracellular domain of ROR2. To demonstrate this Applicants generated a recombinant protein called ROR2-Ig, which is comprised of the ROR2 extracellular domain and the CH2-CH3 constant region domains of human IgG1. Applicants also generated a recombinant protein calls ROR1-Ig, comprised of the extracellular domain of ROR1 and the CH2-CH3 constant region domains of human IgG1. This allows for isolation of soluble proteins with the extracellular domain of either ROR2 or ROR1. Applicants found that cells transfected with the ROR2-CAR constructs generated from the scFv of either 6E6 or 4G9 can bind specifically to the ROR2-Ig, but not the highly related ROR1-Ig, demonstrating the specificity of this interaction (FIG. 13). Therefore, the scFv with sequences generated from 6E6 or 4G9, or their humanized counterparts, may be used to generate ROR2-specific CAR T cells or CAR NK cells that are specifically cytotoxic for ROR2-expressing cells.

[0324] Based on these preclinical findings, Applicants believe that these anti-human ROR2 mAb have high affinity and specificity for human ROR2 and could be used to target ROR2 in various human cancers.

EMBODIMENTS

[0325] Embodiment 1. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0326] Embodiment 2. The antibody of embodiment 1, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:2.

[0327] Embodiment 3. The antibody of embodiment 1 or 2, wherein said light chain variable domain comprises the sequence of SEQ ID NO:4.

[0328] Embodiment 4. The antibody of any one of embodiments 1 to 3, wherein said antibody is a humanized antibody.

[0329] Embodiment 5. The antibody of any one of embodiments 1 to 4, wherein said antibody is a Fab' fragment.

[0330] Embodiment 6. The antibody of any one of embodiments 1 to 4, wherein said antibody is a single chain antibody (scFv).

[0331] Embodiment 7. The antibody of any one of embodiments 1 to 3, wherein said antibody is a chimeric antibody.

[0332] Embodiment 8. The antibody of any one of embodiments 1 to 4, wherein said antibody is an IgG.

5 [0333] Embodiment 9. The antibody of any one of embodiments 1 to 4 or 8, wherein said antibody is an IgG1 or an IgG2.

[0334] Embodiment 10. The antibody of any one of embodiments 1 to 9, wherein said antibody is capable of binding a ROR2 protein.

10 [0335] Embodiment 11. The antibody of embodiment 10, wherein said ROR2 protein comprises the amino acid sequence of SEQ ID NO:18.

[0336] Embodiment 12. The antibody of embodiment 10 or 11, wherein said antibody is capable of binding the extracellular domain of said ROR2 protein.

[0337] Embodiment 13. The antibody of embodiment 12, wherein said extracellular domain comprises the amino acid sequence of SEQ ID NO:22.

15 [0338] Embodiment 14. The antibody of embodiment 12, wherein said extracellular domain is a Kringle domain.

[0339] Embodiment 15. The antibody of any one of embodiments 10 to 14, wherein said ROR2 protein comprises a histidine at a position corresponding to position 349 or an aspartic acid at a position corresponding to position 354 of SEQ ID NO:22.

20 [0340] Embodiment 16. The antibody of any one of embodiments 10 to 15, wherein said ROR2 protein is expressed on a cell.

[0341] Embodiment 17. The antibody of embodiment 16, wherein said cell is a cancer cell.

25 [0342] Embodiment 18. The antibody of embodiment 17, wherein said cancer cell is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

[0343] Embodiment 19. The antibody of any one of embodiments 10 to 18, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 1 nM.

[0344] Embodiment 20. The antibody of any one of embodiments 10 to 19, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) of about 0.06 nM.

5 [0345] Embodiment 21. The antibody of any one of embodiments 1 to 20, wherein said antibody is attached to a therapeutic agent.

[0346] Embodiment 22. The antibody of any one of embodiments 1 to 20, wherein said antibody is attached to a diagnostic agent.

10 [0347] Embodiment 23. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

15 [0348] Embodiment 24. The antibody of embodiment 23, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:6.

[0349] Embodiment 25. The antibody of embodiment 23 or 24, wherein said light chain variable domain comprises the sequence of SEQ ID NO:8.

[0350] Embodiment 26. The antibody of any one of embodiments 23 to 25, wherein said antibody is a humanized antibody.

20 [0351] Embodiment 27. The antibody of any one of embodiments 23 to 26, wherein said antibody is a Fab' fragment.

[0352] Embodiment 28. The antibody of any one of embodiments 23 to 26, wherein said antibody is a single chain antibody (scFv).

25 [0353] Embodiment 29. The antibody of any one of embodiments 23 to 25, wherein said antibody is a chimeric antibody.

[0354] Embodiment 30. The antibody of any one of embodiments 23 to 26, wherein said antibody is an IgG.

[0355] Embodiment 31. The antibody of any one of embodiments 23 to 26 or 30, wherein said antibody is an IgG1 or an IgG2.

[0356] Embodiment 32. The antibody of any one of embodiments 23 to 31, wherein said antibody is capable of binding a ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

5 [0357] Embodiment 33. The antibody of embodiment 32, wherein said antibody is capable of binding an extracellular domain of said ROR2 protein.

[0358] Embodiment 34. The antibody of embodiment 33, wherein said extracellular domain comprises the amino acid sequence of SEQ ID NO:22.

[0359] Embodiment 35. The antibody of embodiment 33, wherein said extracellular domain is an Ig-like domain.

10 [0360] Embodiment 36. The antibody of any one of embodiments 32 to 35, wherein said ROR2 protein comprises a methionine at a position corresponding to position 386 of SEQ ID NO:22.

[0361] Embodiment 37. The antibody of any one of embodiments 32 to 36, wherein said ROR2 protein is expressed on a cell.

15 [0362] Embodiment 38. The antibody of embodiment 37, wherein said cell is a cancer cell.

[0363] Embodiment 39. The antibody of embodiment 38, wherein said cancer cell is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

20 [0364] Embodiment 40. The antibody of any one of embodiments 32 to 39, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.2 nM to about 5 nM.

[0365] Embodiment 41. The antibody of any one of embodiments 32 to 40, wherein said antibody is capable of binding a ROR2 protein with an equilibrium dissociation constant (K_D) of
25 about 1.9 nM.

[0366] Embodiment 42. The antibody of any one of embodiments 23 to 41, wherein said antibody is conjugated to a therapeutic agent.

[0367] Embodiment 43. The antibody of any one of embodiments 23 to 41, wherein said antibody is conjugated to a diagnostic agent.

[0368] Embodiment 44. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0369] Embodiment 45. The antibody of embodiment 44, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:10.

[0370] Embodiment 46. The antibody of embodiment 44 or 45, wherein said light chain variable domain comprises the sequence of SEQ ID NO:12.

[0371] Embodiment 47. The antibody of any one of embodiments 44 to 46, wherein said antibody is a humanized antibody.

[0372] Embodiment 48. The antibody of any one of embodiments 44 to 47, wherein said antibody is a Fab' fragment.

[0373] Embodiment 49. The antibody of any one of embodiments 44 to 47, wherein said antibody is a single chain antibody (scFv).

[0374] Embodiment 50. The antibody of any one of embodiments 44 to 46, wherein said antibody is a chimeric antibody.

[0375] Embodiment 51. The antibody of any one of embodiments 44 to 47, wherein said antibody is an IgG.

[0376] Embodiment 52. The antibody of any one of embodiments 44 to 47 or 51, wherein said antibody is an IgG1.

[0377] Embodiment 53. The antibody of any one of embodiments 44 to 52, wherein said antibody is capable of binding a ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

[0378] Embodiment 54. The antibody of embodiment 53, wherein said antibody is capable of binding an extracellular domain of a ROR2 protein.

[0379] Embodiment 55. The antibody of embodiment 54, wherein said extracellular domain comprises the amino acid sequence of SEQ ID NO:22.

[0380] Embodiment 56. The antibody of embodiment 54, wherein said extracellular domain is a Kringle domain.

[0381] Embodiment 57. The antibody of any one of embodiments 53 to 56, wherein said ROR2 protein comprises a histidine at a position corresponding to position 349, an aspartic acid at a position corresponding to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:22.

[0382] Embodiment 58. The antibody of any one of embodiments 43 to 57, wherein said ROR2 protein is expressed on a cell.

[0383] Embodiment 59. The antibody of embodiment 58, wherein said cell is a cancer cell.

[0384] Embodiment 60. The antibody of embodiment 59, wherein said cancer cell is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

[0385] Embodiment 61. The antibody of any one of embodiments 44 to 50, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150 nM.

[0386] Embodiment 62. The antibody of any one of embodiments 44 to 61, wherein said antibody is conjugated to a therapeutic agent.

[0387] Embodiment 63. The antibody of any one of embodiments 44 to 61, wherein said antibody is conjugated to a diagnostic agent.

[0388] Embodiment 64. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0389] Embodiment 65. The antibody of embodiment 64, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:14.

[0390] Embodiment 66. The antibody of embodiment 64 or 65, wherein said light chain variable domain comprises the sequence of SEQ ID NO:16.

[0391] Embodiment 67. The antibody of any one of embodiments 64 to 66, wherein said antibody is a humanized antibody.

[0392] Embodiment 68. The antibody of any one of embodiments 64 to 67, wherein said antibody is a Fab' fragment.

5 [0393] Embodiment 69. The antibody of any one of embodiments 64 to 67, wherein said antibody is a single chain antibody (scFv).

[0394] Embodiment 70. The antibody of any one of embodiments 64 to 66, wherein said antibody is a chimeric antibody.

10 [0395] Embodiment 71. The antibody of any one of embodiments 64 to 67, wherein said antibody is an IgG.

[0396] Embodiment 72. The antibody of any one of embodiments 64 to 66 or 71, wherein said antibody is an IgG1.

15 [0397] Embodiment 73. The antibody of any one of embodiments 64 to 67, wherein said antibody is capable of binding a ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

[0398] Embodiment 74. The antibody of embodiment 73, wherein said antibody is capable of binding an extracellular domain of said ROR2 protein.

[0399] Embodiment 75. The antibody of embodiments 74, wherein said extracellular domain comprises the amino acid sequence of SEQ ID NO:22.

20 [0400] Embodiment 76. The antibody of embodiment 72, wherein said extracellular domain is an Ig-like domain.

[0401] Embodiment 77. The antibody of any one of embodiments 74 to 76, wherein said ROR2 protein is expressed on a cell.

[0402] Embodiment 78. The antibody of embodiment 77, wherein said cell is a cancer cell.

25 [0403] Embodiment 79. The antibody of embodiment 78, wherein said cancer cell is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

[0404] Embodiment 80. The antibody of any one of embodiments 64 to 79, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150 nM.

5 [0405] Embodiment 81. The antibody of any one of embodiments 64 to 80, wherein said antibody is conjugated to a therapeutic agent.

[0406] Embodiment 82. The antibody of any one of embodiments 64 to 80, wherein said antibody is conjugated to a diagnostic agent.

10 [0407] Embodiment 83. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 1 to 82.

[0408] Embodiment 84. A method of inhibiting metastasis of a ROR2 expressing cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 1 to 82.

15 [0409] Embodiment 85. The method of embodiments 83 or 84, wherein said cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer.

[0410] Embodiment 86. A method of detecting a ROR2 expressing cell, said method comprising (i) contacting a ROR2-expressing cell with an antibody of any one of embodiments 1 to 82; and (ii) detecting binding of said antibody to a ROR2 protein expressed by said cell.

20 [0411] Embodiment 87. The method of embodiment 86, wherein said antibody is attached to a detectable moiety.

[0412] Embodiment 88. The method of embodiment 86 or 87, wherein said ROR2-expressing cell is in a subject.

25 [0413] Embodiment 89. The method of embodiment 88, wherein said subject is a subject having cancer.

[0414] Embodiment 90. The method of embodiment 89, wherein said cancer is cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer.

[0415] Embodiment 91. The method of embodiment 86 or 87, wherein said contacting occurs *in vitro*.

[0416] Embodiment 92. A method of delivering a therapeutic agent to a ROR2 expressing cell, said method comprising contacting a ROR2 expressing cell with an antibody of any one of
5 embodiments 1-82, wherein said antibody is attached to a therapeutic agent.

[0417] Embodiment 93. The method of embodiment 92, wherein said therapeutic agent is an anti-cancer agent.

[0418] Embodiment 94. The method of embodiment 92 or 93, wherein said ROR2-expressing cell is in a subject.

10 [0419] Embodiment 95. The method of embodiment 94, wherein said subject is a subject having cancer.

[0420] Embodiment 96. The method of embodiment 95, wherein said cancer is cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer.

15 [0421] Embodiment 97. The method of embodiment 93 or 94, wherein said contacting occurs *in vitro*.

[0422] Embodiment 98. A method of inhibiting migration of a ROR2-expressing cell, said method comprising contacting a ROR2 expressing cell with an antibody of any one of embodiments 1-80.

20 [0423] Embodiment 99. The method of embodiment 98, wherein said ROR2 expressing cell is in a subject having cancer.

[0424] Embodiment 100. The method of embodiment 99, wherein said cancer is cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer.

25 [0425] Embodiment 101. The method of embodiment 98, wherein said contacting occurs *in vitro*.

[0426] Embodiment 102. The method of any one of embodiments 86 to 101, wherein said ROR2 expressing cell is a cancer cell.

[0427] Embodiment 103. The method of embodiment 102, wherein said cancer cell is a breast cancer cell, ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

5 [0428] Embodiment 104. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in
10 SEQ ID NO:30

[0429] Embodiment 105. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain of SEQ ID:2; and a light chain variable domain of SEQ ID NO:4.

[0430] Embodiment 106. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the
15 same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:1; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:3.

[0431] Embodiment 107. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising: a
20 CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0432] Embodiment 108. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the
25 same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain of SEQ ID:6; and a light chain variable domain of SEQ ID NO:8.

[0433] Embodiment 109. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:5; and a light chain variable domain encoded by the nucleic
30 acid sequence of SEQ ID:7.

[0434] Embodiment 110. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42

[0435] Embodiment 111. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain of SEQ ID:10; and a light chain variable domain of SEQ ID NO:12.

[0436] Embodiment 112. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:9; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:11.

[0437] Embodiment 113. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0438] Embodiment 114. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain of SEQ ID:14; and a light chain variable domain of SEQ ID NO:16.

[0439] Embodiment 115. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same epitope as an anti-ROR2 antibody comprising a heavy chain variable domain encoded by the nucleic acid sequence of SEQ ID:13; and a light chain variable domain encoded by the nucleic acid sequence of SEQ ID:15.

[0440] Embodiment 116. A chimeric antigen receptor comprising: (i) an antibody region comprising: (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO: 28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30; and (b) a heavy chain variable region domain comprising a CDR H1 as set forth in SEQ ID NO:25, a

CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID NO:27; and (ii) a transmembrane domain.

[0441] Embodiment 117. A chimeric antigen receptor comprising: (i) an antibody region comprising: (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36; and (b) a heavy chain variable region domain comprising a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID NO:33; and (ii) a transmembrane domain.

[0442] Embodiment 118. A chimeric antigen receptor comprising: (i) an antibody region comprising: (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and (b) a heavy chain variable region domain comprising a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38, and a CDR H3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain

[0443] Embodiment 119. A chimeric antigen receptor comprising: (i) an antibody region comprising: (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (b) a heavy chain variable region domain comprising a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44, and a CDR H3 as set forth in SEQ ID NO:45; and (ii) a transmembrane domain.

[0444] Embodiment 120. The chimeric antigen receptor of any one of embodiments 116 to 119, further comprising an intracellular T-cell signaling domain.

[0445] Embodiment 121. The chimeric antigen receptor of embodiments 116 to 120, wherein the intracellular T-cell signaling domain is a CD3 ζ intracellular T-cell signaling domain.

[0446] Embodiment 122. The chimeric antigen receptor of any one of embodiments 116 to 121, further comprising an intracellular co-stimulatory T-cell signaling domain.

[0447] Embodiment 123. The chimeric antigen receptor of embodiment 122, wherein said intracellular co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain, a 4-1BB intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling domain, or an OX-40 intracellular co-stimulatory signaling domain.

[0448] Embodiment 124. The chimeric antigen receptor of any one of embodiments 116 to 123, further comprising a spacer region.

[0449] Embodiment 125. The chimeric antigen receptor of embodiment 124, wherein the spacer region further comprises a hinge region.

5 [0450] Embodiment 126. The chimeric antigen receptor of any one of embodiments 116 to 125, further comprising a linker domain.

[0451] Embodiment 127. The chimeric antigen receptor of any one of embodiments 116 to 126, further comprising a heavy chain constant domain.

10 [0452] Embodiment 128. A method of treating cancer in a subject in need thereof said method comprising, administering a therapeutically effective amount of a chimeric antigen receptor of any one of embodiments 116 to 127 to a subject.

[0453] Embodiment 129. The method of embodiment 126, wherein said cancer is cancer is breast cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer, bone cancer, skin cancer or prostate cancer.

15 INFORMAL SEQUENCE LISTING

[0454] SEQ ID NO:1; 6E6 VH SEQ

20 GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCC
TGAAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAATTATGGCATGTCTT
GGGTTCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCGCAACCATTAGTAG
TGGTGGTGGTTACACTCACTATGTAGACAGTGTGAAGGGGCGATTACCATTT
CCAGAGACAATGCCAACCATATCCTGTACCTGCAAATGAGCAGTCTGAACTCT
GAGGACACAGCCATGTATTATTGTGCAAGACACCCGAGGGATTTTTCCTATGC
TATGGACTACTGGGGTCAGGGAACCTCAGTCACCGTCTCCTCA

25 [0455] SEQ ID NO:2; 6E6 VH SEQ

EVQLVESGGDLVKPGGSLKLSCAASGFTFSNYGMSWVRQTPDKRLEWVATISSG
GGYTHYVDSVKGRFTISRDNANHILYLQMSSLNSEDAMYYCARHPRDFSAMD
YWGQGTSTVTVSS

30 [0456] SEQ ID NO:3; 6E6 VK SEQ

35 GACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAATAGGAGACAG
GGTCAGCATCACCTGCAAGGCCAGTCAGGATGTGGGTCATTATGTGGCCTGGT
ATCAACAGAAACCAGGTCAATCTCCTAACTACTGATTACTGGGCATCCACC
CGGCACACTGGAGTCCCTGATCGCTTCACAGGTAGTGGATCTGGGACAGATTT

CACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTGTC
AGCAATATAACATCTATCCGTGGACGTTCCGGTGGAGGCTCCAAGCTGGCAATC
AAA

5 [0457] SEQ ID NO:4; 6E6 VL SEQ

DIVMTQSHKFMSTSIGDRV SITCKASQDVGHYVAWYQQKPGQSPKLLIYWASTR
HTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNIYPWTFGGGSKLAIK

10 [0458] SEQ ID NO:5; 4G9 VH SEQ

CAGGTTCAACTGCAACAGTCTGGGGCTGAGCTGGTGAGGCCTGGGGCTTCAGT
GAAGCTGTCCTGCAAGGCTTTGGGCTACACATTTACTGACTATGAAATGCACT
GGGTGAAGCAGACACCTGTGCATGGCCTGGAATGGATTGGAGCTATTCATCCA
GGAAGTGGTGGTACTGCCTATAATCAGAAGTTCAAGGGCAAGGCCACACTGA
15 CTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGGCTGACATCT
GAGGACTCTGCTGTCTATTACTGTACAAGAAGGAGGCCTAGGTTCTATGGTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

[0459] SEQ ID NO:6; 4G9 VH SEQ

20 QVQLQQSGAELVRPGASVKLSCKALGYTFTDYEMHWVKQTPVHGLEWIGAIHPG
SGGTAYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTRRRPRFYGMDY
WGQGTSVTVSS

25 [0460] SEQ ID NO:7; 4G9 VL SEQ

GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTC
AGTATCCATCTCCTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACA
CTTACTTGTATTGGTTCCTGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATAT
ATCGGATGTCCAACCTTGCTCAGGAGTCCCAGACAGGTTTCAGTGGCAGTGGG
30 TCAGGAAGTGTTCACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGTGG
GTGTTTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGTCTGGG
ACCAAGCTGGAGCTGAAA

[0461] SEQ ID NO:8; 4G9 VL SEQ

35 DIVMTQAAPSPVPTPGESVSISCRSSKSLLSNNGNTYLYWFLQRPQGQSPQLLIYRM
SNLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTVGAGTKLEL
K

[0462] SEQ ID NO:9; 5C11 VH SEQ

40 GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGCCTGGAGGGTCCC
TGAAACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAACTATGGCATGTCTT
GGGTTCCGACAGACTCCAGACAAGAGGCTGGAGTGGGTCGCAACCATTAGTAG

TGGTGGTGGTTCCACCTACTATCCAGACAGTGTGAAGGGGCGATTACCATCT
CCAGAGACAATGCCAAGAACTCCCTGTACCTGCAAATGAGCAGTCTGAAGTCT
GAGGACACAGCCATGTATTACTGTGCAAGACATCCCTATGATTACGGGTACTA
CTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

5

[0463] SEQ ID NO:10; 5C11 VH SEQ

EVQLVESGGDLVKPGGSLKLSCAASGFTFSNYGMSWVRQTPDKRLEWVATISSG
GGSTYYPD SVKGRFTISRDN AKNSLYLQMSSLKSEDTAMYYCARHPYDYGYYFD
YWGQGTTLTVSS

10

[0464] SEQ ID NO:11; 5C11 VL SEQ

GACATCTTGCTGACTCAGTCTCCAGACATCCTGTCTGTGAGTCCAGGAGAAAG
AGTCAGTTTCTCCTGCAGGGCCAGTCAGAGCATTGGCACAAGCATACACTGGT
ATCAGCAGAGAACAATGGTTCTCCAAGGCTTCTCATAAAATATGCTTCTGAG
TCTATCTCTGGGATCCCTTCCAGGTTTAGTGGCAGTGGATCAGGGACAGATTT
TACTCTTAGCATCAACAGTGTGGAGTCTGAAGATATTGCAGATTATTACTGTC
AACAAAGTGATAGCTGGCCATTCCCGTTCTGGCTCGGGGACAAAATTGGAAAA
AAAA

15

20

[0465] SEQ ID NO:12; 5C11 VL SEQ

DILLTQSPDILSVSPGERVSFSCRASQSIGTSIHWYQRTNGSPRLLIKYASESISGIP
SRFSGSGSGTDFTLINSVESEDIADYYCQQSDSWPFPFGSGTKLEKK

25

[0466] SEQ ID NO:13; 5G3 VH SEQ

GAGGTGCAGCTTGTTGAGTCTGGTGGAGGATTGGTGCAGCCTAAAGGGTCATT
GAAGCTCTCATGTGCAGCCTCTGGATTACCTTCAATACCTACGCCATGAACT
GGGTCCGCCAGGCTCCAGGAAAGGGTTTGGAATGGGTTGCTCGCATAAGAAG
TAAAAGTAATAATTATGCAACATATTATGCCGATTTCAGTGAAAGACAGGTTCA
CCATCTCCAGAGATGATTCACAAAGCATGCTCCATCTGCAAATGAACAACTTG
AAAAGTGAAGACACAGCCATGTATTACTGTGTGAGACACGGTAGTAGCCTCTA
CTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

30

35

[0467] SEQ ID NO:14; 5G3 VH SEQ

EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRS
KSNYYATYYADSVKDRFTISRDDSQSMHLQMNNLKTEDTAMYYCVRHGSSLY
YAMDYWGQGTSVTV
SS

40

[0468] SEQ ID NO:15; 5G3 VL SEQ

GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTGCCTCTCTGGGAGAAAG
AGTCAGTCTCACTTGTCTGGGCAAGTCAGGAAATTAGTGGTTACTTAGGCTGGC
TTCAGCAGAAACCAGATGGAAC TATTAACGCCTGATCTACGCCGCATCCACT
TTAGATTCTGGTGTCCCAAAAAGGTTTCAGTGGCAGTAGGTCTGGGTCAGCTTA
5 TTCTCTCACCATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATTACTGTCT
ACAATATGCTAGTTATCCGTACACGTTTCGGAGGGGGGACCAAGCTGGAAATA
AAA

[0469] SEQ ID NO:16; 5G3 VL SEQ

10 DIQMTQSPSSLASLGERVSLTCRASQEISGYLGWLQQKPDGTIKRLIYAASLTDSG
VPKRFSGRSGSAYSLSLTISSLESEDFADYYCLQYASYPTYTFGGGKLEIK

[0470] SEQ ID NO:17; HUMAN ROR2 FULL LENGTH

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15 CTGGGCGGCCGCGCGCTTCTGCTCTCAGTGTCCCGGACTTCAGGTGAAGTGG
AGGTTCTGGATCCGAACGACCCTTTAGGACCCCTTGATGGGCAGGACGGCCCG
ATTCCAAC TCTGAAAGGTTACTTTCTGAATTTTCTGGAGCCAGTAAACAATAT
CACCATTGTCCAAGGCCAGACGGCAATTCTGCACTGCAAGGTGGCAGGAAAC
CCACCCCTAACGTGCGGTGGCTAAAGAATGATGCCCCGGTGGTGCAGGAGC
20 CGCGGCGGATCATCATCCGGAAGACAGAATATGGTTCACGACTGCGAATCCA
GGACCTGGACACGACAGACACTGGCTACTACCAGTGCGTGGCCACCAACGGG
ATGAAGACCATTACCGCCACTGGCGTCCTGTTTGTGCGGCTGGGTCCAACGCA
CAGCCCAAATCATAACTTTACGGATGATTACCACGAGGATGGGTTCTGCCAGC
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25 GACTCGCTTCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCGGCCTTCA
CCATGATCGGCACGTCTACGCACCTGTCCGACCAGTGCTCACAGTTCCGCCATC
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AAGCCGCGTGAGCTGTGCCGCGACGAGTGCGAGGTGCTGGAGAGCGACCTGT
GCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCTT
30 CAGCTGCCCAAGTGTGAGGCGCTGCCCATGCCTGAGAGCCCCGACGCTGCCA
ACTGCATGCGCATTGGCATCCCAGCCGAGAGGCTGGGCGCTACCATCAGTGC
TATAACGGCTCAGGCATGGATTACAGAGGAACGGCAAGCACCACCAAGTCAG
GCCACCAGTGCCAGCCGTGGGCCCTGCAGCACCCCCACAGCCACCACCTGTCC
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35 GAGGCCAGATGGAGGGCCCCCTGGTGCTTTACGCAGAATAAAAACGTACGCAT
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ATTCTGTACATCTTGGTCCCCAGCATCGCAATTCCACTGGTCATCGCTTGCCTT
TTCTTCTTGGTTTGCATGTGCCGGAATAAGCAGAAGGCATCTGCGTCCACACC
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40 ATTAACCAGCACAAACAGGCCAAACTCAAAGAGATCAGCCTGTCTGCGGTGA
GGTTCATGGAGGAGCTGGGAGAGGACCGGTTTGGGAAAGTCTACAAAGGTCA
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CTGAAGGACAAAGCGGAGGGGGCCCTGCGGGAGGAGTTCCGGCATGAGGCTA
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45 ACCAAGGACCAGCCCCTGAGCATGATCTTCAGCTACTGTTCCGACGGCGACCT
CCACGAATTCCTGGTCATGCGCTCGCCGCACTCGGACGTGGGCAGCACCGATG
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GCACAGATCGCGGCGGGGATGGAGTACCTATCCAGCCACCACGTGGTTCACA

AGGACCTGGCCACCCGCAATGTGCTAGTGTACGACAAGCTGAACGTGAAGAT
 CTCAGACTTGGGCCTCTTCCGAGAGGTGTATGCCGCCGATTACTACAAGCTGC
 TGGGGAACCTCGCTGCTGCCTATCCGCTGGATGGCCCCAGAGGCCATCATGTAC
 GGCAAGTTCTCCATCGACTCAGACATCTGGTCTACGGTGTGGTCTGTGGGA
 5 GGTCTTCAGCTACGGCCTGCAGCCCTACTGCGGGTACTCCAACCAGGATGTGG
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 TGGGTGTATGCCCTCATGATCGAGTGCTGGAACGAGTTCCCCAGCCGGCGGCC
 CCGCTTCAAGGACATCCACAGCCGGCTCCGAGCCTGGGGCAACCTTTCCAAC
 ACAACAGCTCGGCGCAGACCTCGGGGGCCAGCAACACCACGCAGACCAGCTC
 10 CCTGAGCACCAGCCAGTGAGCAATGTGAGCAACGCCCGCTACGTGGGGGCC
 AAGCAGAAGGCCCCGCCCTTCCCACAGCCCCAGTTCATCCCCATGAAGGGCCA
 GATCAGACCCATGGTGCCCCCGCCGCAGCTCTACGTCCCCGTCAACGGCTACC
 AGCCGGTGCCGGCCTATGGGGCCTACCTGCCCAACTTCTACCCGGTGCAGATC
 CCAATGCAGATGGCCCCGCAGCAGGTGCCTCCTCAGATGGTCCCCAAGCCCAG
 15 CTCACACCACAGTGGCAGTGGCTCCACCAGCACAGGCTACGTCACCACGGCCC
 CCTCCAACACATCCATGGCAGACAGGGCAGCCCTGCTCTCAGAGGGCGCTGAT
 GACACACAGAACGCCCCAGAAGATGGGGCCCAGAGCACCGTGCAGGAAGCA
 GAGGAGGAGGAGGAAGGCTCTGTCCCAGAGACTGAGCTGCTGGGGGACTGTG
 ACACTCTGCAGGTGGACGAGGCCCAAGTCCAGCTGGAAGCTTGA

[0471] SEQ ID NO:18; HUMAN ROR2 FULL LENGTH

MARGSALPRRPLLCIPAVWAAAALLSVSRTSGEVEVLDPNDPLGPLDQGDIPT
 LKGYFLNFLEPVNNITIVQGQTALHCKVAGNPPPNVRWLKNDAPVVQEPRRIIR
 KTEYGSRLRIQDLDTTDTGYQCVATNGMKTTITATGVLFVRLGPTHSPNHNFDQD
 25 YHEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTHLSQCS
 QFAIPSFCHFVPLCDARSRTPKPRELCRDECEVLESDLCRQEYTIARSNPLILMRL
 QLPKCEALPMPESPDAAANCMRIGIPAERLGRYHQCYNHSGMDYRGTAATTKSGH
 QCQPWALQHPHSHHLSSTDFPELGGGHAYCRNPQQMEGPWCFTQNKVNRME
 CDVPSCSPRDSKMGILYILVPSIAIPLVIACFLFLVCMCRNKQKASASTPQRRQLM
 30 ASPSQDMEMPLINQHKQAKLKEISLSAVRFMEELGEDRFGKVYKGHLFGPAPGEQ
 TQAVAIKTLKDKAEGPLREEFRHEAMLRARLQHPNVVCLLGVVTKDQPLSMIFS
 YCSHGDLEHFLVMRSPHSDVGSTDDDRTVKSALEPPDFVHLVAQIAAGMEYLSSH
 HVVHKDLATRNVLVYDKLNVKISDLGLFREYVYAADYYKLLGNSLLPIRWMAP
 EAIMYGKFSIDSDIWSYGVVLWEVFSYGLQPYCGYSNQDVVEMIRNRQVLPCPDDCP
 35 AWVYALMIECWNEFPSRRPRFKDIHSRLRAWGNLSNYNSSAQTSGASNTTQTSSL
 STSPVSNVSNARYVGPQKQAPFPQPPQFIPMKGQIRPMVPPQLYVPVNGYQPVPA
 YGAYLPNFYYPVQIPMQMAPQQVPPQMPKPKSSHSGSGSTSTGYVTTAPSNTSMA
 DRAALLSEGADDTQNAPEDGAQSTVQEAEEEEEGSVPETELLGDCDTLQVDEAQ
 VQLEA

[0472] SEQ ID NO:19; MOUSE ROR2 FULL LENGTH

ATGGCTCGGGGCTGGGTGCGGCCGAGCCGTGTGCCTCTGTGCGCCCGGGCCGT
 CTGGACGGCTGCGGCGCTCCTGCTCTGGACACCCTGGACGGCAGGTGAAGTG
 GAAGATTTCGGAGGCAATCGACACCTTGGGACAACCTGATGGACCGGACAGCC
 45 CACTTCCCCTCTGAAAGGCTACTTTCTGAATTTTCTGGAGCCAGTCAACAAT
 ATCACCATTGTTTCAGGGCCAGACGGCAATCCTGCACTGCAAGGTGGCGGGAA
 ACCCACCTCCCAATGTGCGGTGGCTGAAGAATGATGCCCCGGTTGTGCAAGAG
 CCACGAAGGGTCGTCATCCGGAAGACAGAATACGGCTCCCGGCTGCGGATCC

AAGACCTGGACACAACAGACACAGGCTACTACCAGTGTGTGGCTACCAACGG
GCTGAAGACCATCACTGCCACTGGGGTTCTATATGTGCGGCTCGGTCCGACGC
ACAGCCCGAACCACAATTTTCAGGATGACGATCAGGAAGATGGCTTCTGCCA
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5 TGGACTCCCTCCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCTGCCTTC
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CAAGCCTCGCGAACTGTGCCGGGATGAATGTGAGGTGCTGGAGAACGACCTG
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10 CCAGCTGCCCCAAGTGCGAAGCGCTGCCCATGCCCCGAGAGCCCGGATGCTGCG
AACTGCATGCGCATCGGGATCCCCGCGGAGAGGCTGGGTGCTACCACCAGT
GCTACAACGGCTCCGCGCGCCGATTACAGGGGGATGGCCAGTACCACCAAGTC
AGGCCACCAGTGTGACGCTTGGGCTCTGCAGCACCCCCACAGCCATCGCCTAT
CCAGCACGGAATTCCCTGAGCTGGGAGGAGGCCATGCCTACTGCCGGAACCC
15 CGGGGGCCAGATGGAAGGCCCGTGGTGCTTTACGCAGAATAAAAACGTACGC
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20 CATCAGCCAGCACAAACAGGCCAAACTCAAAGAGATCAGCTTGTCCACAGTG
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GCTGAAAGACAAGGCTGAGGGGGCCCTGCGGGAGGAGTTCCGGCAAGAGGCG
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25 GACCAAGGACCAACCCTTGAGCATGATCTTCAGCTACTGTTCCCATGGCGACC
TTCATGAATTCCTGGTCATGCGCTCGCCGCACTCCGATGTGGGCAGCACCGAT
GACGACCGCACAGTGAAGTCAGCCCTGGAGCCCCCGGACTTCGTGCACGTGG
TGGCGCAGATCGCTGCGGGGATGGAGTTCCTGTCCAGCCACCACGTGTGCCAT
AAGGACCTGGCCACACGCAATGTGCTGGTGTACGACAAGCTGAACGTGAGGA
30 TCTCAGACTTGGGCCTCTTCCGTGAGGTATACTCCGCAGATTACTACAACTC
ATGGGCAATTCACTGCTGCCCATCCGCTGGATGTCCCCCGAGGCCGTCATGTA
TGGAAGTTCTCCATCGACTCTGACATCTGGTCCTACGGTGTGGTCCTCTGGG
AGGTCTTTAGCTACGGCCTGCAGCCCTACTGTGGGTACTCCAACCAGGACGTG
GTGGAGATGATCCGGAGCCGGCAGGTGCTGCCCTGCCCGGATGACTGCCCCG
35 CCTGGGTCTATGCCCTCATGATTGAATGCTGGAATGAGTTCCCAAGCCGGAGG
CCCCGCTTTAAGGACATCCACAGCCGGCTCCGGTCTGGGGCAACCTATCCAA
CTATAATAGTTCCGCGCAGACCTCAGGAGCCAGCAACACCACACAGACCAGC
TCCCTGAGCACCAGCCCCGTAAGCAATGTGAGCAATGCCCGCTATATGGCCCC
CAAGCAGAAGGCCCAGCCCTTCCCACAGCCTCAGTTCATCCCCATGAAGGGTC
40 AGATCAGACCCTTGGTGCCCCCGCACAGCTGTACATCCCGGTGAACGGCTAT
CAGCCGGTACCGGCATACGGGGCCTACCTGCCCAACTTCTACCCAGTCCAGAT
CCCCATGCAGATGGCCCCACAGCAGGTGCCCCCTCAGATGGTCCCCAAGCCGA
GCTCACACCACAGTGGCAGCGGCTCCACCAGCACTGGCTACGTCAACACGGC
GCCCTCCAATACATCTGTGGCGGACAGGGCGGCCCTACTCTCTGAGGGCACCG
45 AGGATGTACAGAACATCGCGGAAGACGTGGCCCAGAGCCCTGTGCAGGAAGC
AGAGGAGGAGGAGGAGGGGTCTGTCCCTGAGACTGAACTCCTGGGAGACAAT
GACACGCTCCAGGTGACCGAGGCGGCTCATGTCCAGCTTGAAGCCTGA

[0473] SEQ ID NO:20; MOUSE ROR2 FULL LENGTH

MARGWVRPSRVPLCARAVWTAALLLWTPWTAGEVEDSEAIDTLGQPDGPDSP
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 VVIRKTEYGSRLRIQDLDTTDTGYYQCVATNGLKTITATGVLYVRLGPTHSPNHN
 FQDDDQEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTQL
 5 SDQCSQFAIPSFCHFVFPLCDACSRAPKPRELCRDECEVLENDLCRQEYTIARSNPL
 ILMRLQLPKCEALPMPESPDAAANCMRIGIPAERLGRYHQCYNGSGADYRGMASST
 KSGHQCPWALQHPHSHRLSSTEFPELGGGHAYCRNPGGQMEGPWCFTQNKNV
 RVELCDVPPCSPRYGSKMGILYILVPSIAIPLVIACLFLLVCMCRNKQKASASTPQR
 RQLMASPSQDMEMPLISQHKQAKLKEISLSTVRFMEELGEDRFGKVYKGHFLGPA
 10 PGEPTQAVAIKTLKDKAEGPLREEFRQEAMLRARLQHPNIVCLLGVVTKDQPLSM
 IFSYCSHGLDHEFLVMRSPHSDVGSTDDDRTVKSALEPPDFVHVVAQIAAGMEFL
 SSHHVCHKDLATRNVLVYDKLNVRISDLGLFREYVSADYYKLMGNSLLPIRWMS
 PEAVMYGKFSIDSDIWSYGVVLWEVFSYGLQPYCGYSNQDVVEMIRSRQVLPCP
 DDCPAWVYALMIECWNEFPSRRPRFKDIHSRLRSWGNLSNYNSSAQTSGASNTTQ
 15 TSSLSTSPVSNVSNARYMAPKQKAQFPQPQFIPMKGQIRPLVPPAQLYIPVNGYQ
 PVPAYGAYLPNFYPVQIPMQMAPQQVPPQMVPKPSSHSGSGSTSTGYVTTAPSN
 TSVADRAALLSEGTEVDQNI AEDVAQSPVQEAEEEEEGSVPETELLGDNNDTLQVT
 EAAHVQLEA

20 **[0474]** SEQ ID NO:21; HUMAN ROR2 Extracellular Region

ATGGCCCCGGGGCTCGGCGCTCCCGCGGGCGGCCGCTGCTGTGCATCCCGGCCGT
 CTGGGCGGGCCGCGCGCTTCTGCTCTCAGTGTCCCGGACTTCAGGTGAAGTGG
 AGGTTCTGGATCCGAACGACCCTTTAGGACCCCTTGATGGGCAGGACGGCCCCG
 25 ATTCCAACCTCTGAAAGGTTACTTTCTGAATTTCTGGAGCCAGTAAACAATAT
 CACCATTGTCCAAGGCCAGACGGCAATTCTGCACTGCAAGGTGGCAGGAAAC
 CCACCCCTAACGTGCGGTGGCTAAAGAATGATGCCCCGGTGGTGCAGGAGC
 CGCGGCGGATCATCATCCGGAAGACAGAATATGGTTCACGACTGCGAATCCA
 GGACCTGGACACGACAGACACTGGCTACTACAGTGCGTGGCCACCAACGGG
 ATGAAGACCATTACCGCCACTGGCGTCTGTTTGTGCGGCTGGGTCCAACGCA
 30 CAGCCCAAATCATAACTTTACGGATGATTACCACGAGGATGGGTCTGCCAGC
 CTTACCGGGGAATTGCCTGTGCACGCTTCATTGGCAACCGGACCATTATGTG
 GACTCGCTTCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCGGCCTTCA
 CCATGATCGGCACGTCTACGCACCTGTGCGGACCAGTGCTCACAGTTCGCCATC
 CCATCCTTCTGCCACTTCGTGTTTCTCTGTGCGACGCGCGCTCCCGGGCACCC
 35 AAGCCGCGTGAGCTGTGCCGCGACGAGTGCGAGGTGCTGGAGAGCGACCTGT
 GCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCTT
 CAGCTGCCCAAGTGTGAGGCGCTGCCCATGCCTGAGAGCCCCGACGCTGCCA
 ACTGCATGCGCATTGGCATCCCAGCCGAGAGGCTGGGCCGCTACCATCAGTGC
 TATAACGGCTCAGGCATGGATTACAGAGGAACGGCAAGCACCACCAAGTCAG
 40 GCCACCAGTGCCAGCCGTGGGCCCTGCAGCACCCCCACAGCCACCACCTGTCC
 AGCACAGACTTCCCTGAGCTTGGAGGGGGGACGCCTACTGCCGGAACCCCG
 GAGGCCAGATGGAGGGCCCTGGTGCTTTACGCAGAATAAAAACGTACGCAT
 GGAAGTGTGTGACGTACCTCGTG TAGTCCCCGAGACAGCAGCAAGATGGGG

45 **[0475]** SEQ ID NO:22; HUMAN ROR2 Extracellular Region

MARGSALPRRPLLCIPAVWAAAALLLSVSRTSGEVEVLDPNDPLGPLDGQDGIPT
 LKGYFLNFLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIR
 KTEYGSRLRIQDLDTTDTGYYQCVATNGMKTITATGVLFVRLGPTHSPNHNFQDD

YHEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTHLSQCS
 QFAIPSFCHFVPLCDARSRTPKPRELCRDECEVLESDLCRQEYTIARSNPLILMRL
 QLPKCEALPMPESPDAAANCMRIGIPAERLGRYHQCYNNGSGMDYRGTAATTKSGH
 QCQPWALQHPHSHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQNKNVRMEL
 5 CDVPSCSPRDSSKMG

[0476] SEQ ID NO:23; MOUSE ROR2 Extracellular Region

ATGGCTCGGGGCTGGGTGCGGCCGAGCCGTGTGCCTCTGTGCGCCCGGGCCGT
 CTGGACGGCTGCGGCGCTCCTGCTCTGGACACCCTGGACGGCAGGTGAAGTG
 10 GAAGATTCGGAGGCAATCGACACCTTGGGACAACCTGATGGACCGGACAGCC
 CACTTCCCCTCTGAAAGGCTACTTTCTGAATTTTCTGGAGCCAGTCAACAAT
 ATCACCATTGTTTCAGGGCCAGACGGCAATCCTGCACTGCAAGGTGGCGGGAA
 ACCCACCTCCCAATGTGCGGTGGCTGAAGAATGATGCCCCGGTTGTGCAAGAG
 CCACGAAGGGTCGTCATCCGGAAGACAGAATACGGCTCCCGGCTGCGGATCC
 15 AAGACCTGGACACAACAGACACAGGCTACTACCAGTGTGTGGCTACCAACGG
 GCTGAAGACCATCACTGCCACTGGGGTTCTATATGTGCGGCTCGGTCCGACGC
 ACAGCCCGAACCACAATTTTCAGGATGACGATCAGGAAGATGGCTTCTGCCA
 GCCGTACCGAGGGATCGCTTGTGCGCGCTTCATTGGGAACCGGACTATTTATG
 TGGACTCCCTCCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCTGCCTTC
 20 ACCATGATCGGCACCTCCACGCAACTGTCAGACCAGTGTTACAGTTTGCCAT
 CCCATCCTTCTGCCACTTCGTCTTCCCTCTGTGCGACGCATGCTCCCGGGCGCC
 CAAGCCTCGCGAACTGTGCCGGGATGAATGTGAGGTGCTGGAGAACGACCTG
 TGCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCT
 CCAGCTGCCCAAGTGCGAAGCGCTGCCCATGCCCGAGAGCCCGGATGCTGCG
 25 AACTGCATGCGCATCGGGATCCCCGCGGAGAGGCTGGGTGCTACCACCAAGT
 GCTACAACGGCTCCGGCGCCGATTACAGGGGGATGGCCAGTACCACCAAGTC
 AGGCCACCAGTGTACGCTTGGGCTCTGCAGCACCCCCACAGCCATCGCCTAT
 CCAGCACGGAATTCCCTGAGCTGGGAGGAGGCCATGCCTACTGCCGGAACCC
 CGGGGGCCAGATGGAAGGCCCGTGGTGCTTTACGCAGAATAAAAACGTACGC
 30 GTGGAAGTGTGTGACGTACCCCCGTGTAGTCCCCGATATGGCAGCAAGATGGG
 G

[0477] SEQ ID NO:24; MOUSE ROR2 Extracellular Region

MARGWVRPSRVPLCARAVWTAALLLWTPWTAGEVEDSEAIDTLGQPDGPDSP
 35 LPTLKGYFLNFLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRR
 VVIRKTEYGSRLRIQDLDTDTGYYQCVATNGLKTITATGVLYVRLGPTHSPNHN
 FQDDDQEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTQL
 SDQCSQFAIPSFCHFVPLCDACSRAPKPRELCRDECEVLENDLCRQEYTIARSNPL
 ILMRLQLPKCEALPMPESPDAAANCMRIGIPAERLGRYHQCYNNGSGADYRGMASTT
 40 KSGHQCPWALQHPHSHRLSSTEFPELGGGHAYCRNPGGQMEGPWCFTQNKNV
 RVELCDVPPCSPRYGSKMG

[0478] SEQ ID NO:25; 6E6 CDR H1

GFTFSNYG

45 [0479] SEQ ID NO:26; 6E6 CDR H2

ISSGGGYT

[0480] SEQ ID NO:27; 6E6 CDR H3

HPRDFSAMDY

[0481] SEQ ID NO:28; 6E6 CDR L1

5 QDVGHY

[0482] SEQ ID NO:29; 6E6 CDR L2

WAS

[0483] SEQ ID NO:30; 6E6 CDR L3

QQYNIYPWT

10 [0484] SEQ ID NO:31; 4G9 CDR H1

GYTF TDYE

[0485] SEQ ID NO:32; 4G9 CDR H2

IHPGSGGT

[0486] SEQ ID NO:33; 4G9 CDR H3

15 RRPRFYGMDY

[0487] SEQ ID NO:34; 4G9 CDR L1

KSLHLSNGNTY

[0488] SEQ ID NO:35; 4G9 CDR L2

RMS

20 [0489] SEQ ID NO:36; 4G9 CDR L3

MQHLEYPLT

[0490] SEQ ID NO:37; 5C11 CDR H1

GFTFSNYG

[0491] SEQ ID NO:38; 5C11 CDR H2

25 ISSGGGST

[0492] SEQ ID NO:39; 5C11 CDR H3

HPYDYGYYFDY

[0493] SEQ ID NO:40; 5C11 CDR L1

QSIGTS

5 **[0494]** SEQ ID NO:41; 5C11 CDR L2

YAS

[0495] SEQ ID NO:42; 5C11 CDR L3

QQSDSWPFP

[0496] SEQ ID NO:43; 5G3 CDR H1

10 GFTFNTYA

[0497] SEQ ID NO:44; 5G3 CDR H2

IRSKSNNYAT

[0498] SEQ ID NO:45; 5G3 CDR H3

HGSSLIYAMDY

15 **[0499]** SEQ ID NO:46; 5G3 CDR L1

QEISGY

[0500] SEQ ID NO:47; 5G3 CDR L2

AAS

[0501] SEQ ID NO:48; 5G3 CDR L3

20 LQYASYPYT

[0502] SEQ ID NO:49; 6E6 VH FR1

EVQLVESGGDLVKPGGSLKLSAAS

[0503] SEQ ID NO:50; 6E6 VH FR2

MSWVRQTPDKRLEWVAT

[0504] SEQ ID NO:51; 6E6 VH FR3

HYVDSVKGRFTISRDNANHILYLQMSSLNSEDAMYYCAR

[0505] SEQ ID NO:52; 6E6 VH FR4

WGQGTSVTVSS

5 [0506] SEQ ID NO:53; 6E6 VL FR1

DIVMTQSHKFMSTSIGDRVSITCKAS

[0507] SEQ ID NO:54; 6E6 VL FR2

VAWYQQKPGQSPKLLIY

[0508] SEQ ID NO:55; 6E6 VL FR3

10 TRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFC

[0509] SEQ ID NO:56; 6E6 VL FR4

FGGGSKLAIK

[0510] SEQ ID NO:57; 4G9 VH FR1

QVQLQQSGAELVRPGASVKLSCKAL

15 [0511] SEQ ID NO:58; 4G9 VH FR2

MHWVKQTPVHGLEWIGA

[0512] SEQ ID NO:59; 4G9 VH FR3

AYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTR

[0513] SEQ ID NO:60; 4G9 VH FR4

20 WGQGTSVTVSS

[0514] SEQ ID NO:61; 4G9 VL FR1

DIVMTQAAPSVPTPGESVSISCRSS

[0515] SEQ ID NO:62; 4G9 VL FR2

LYWFLQRPQGSPQLLIY

[0516] SEQ ID NO:63; 4G9 VL FR3

NLASGVDPDRFSGSGSGTAFTLRISRVEAEDVGVYYC

[0517] SEQ ID NO:64; 4G9 VL FR4

VGAGTKLELK

5 [0518] SEQ ID NO:65; 5C11 VH FR1

EVQLVESGGDLVKPGGSLKLSKAAS

[0519] SEQ ID NO:66; 5C11 VH FR2

MSWVRQTPDKRLEWVAT

[0520] SEQ ID NO:67; 5C11 VH FR3

10 YYPDSVKGRFTISRDNKNSLYLQMSLKSSEDAMYYCAR

[0521] SEQ ID NO:68; 5C11 VH FR4

WGQGTTLTVSS

[0522] SEQ ID NO:69; 5C11 VL FR1

DILLTQSPDILSVSPGERVSFSCRAS

15 [0523] SEQ ID NO:70; 5C11 VL FR2

IHWYQQRTNGSPRLLIK

[0524] SEQ ID NO:71; 5C11 VL FR3

ESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYC

[0525] SEQ ID NO:72; 5C11 VL FR4

20 FGSGTKLEKK

[0526] SEQ ID NO:73; 5G3 VH FR1

EVQLVESGGGLVQPKGSLKLSKAAS

[0527] SEQ ID NO:74; 5G3 VH FR2

MNWVRQAPGKGLEWVAR

[0528] SEQ ID NO:75; 5G3 VH FR3

YYADSVKDRFTISRDDSQSMLHLQMNNLKTEDTAMYYCVR

[0529] SEQ ID NO:76; 5G3 VH FR4

WGQGTSVTVSS

5 **[0530]** SEQ ID NO:77; 5G3 VH FR1

DIQMTQSPSSLSASLGERSVSLTCRAS

[0531] SEQ ID NO:78; 5G3 VL FR2

LGWLQQKPDGTIKRLIY

[0532] SEQ ID NO:79; 5G3 VL FR3

10 TLDSGVPKRFSGSRSGSAYSLSLTISSEDFADYYC

[0533] SEQ ID NO:80; 5G3 VL FR4

FGGGTKLEIK

[0534] SEQ ID NO:81; ScFv Leader peptide

ATMGWSCIILFLVATATGVHS

15 **[0535]** SEQ ID NO:82; ScFv and CAR linker

GSTSGSGKPGSGEGSTKG

[0536] SEQ ID NO:83; scFv Spacer

EF

[0537] SEQ ID NO:84; ScFv CH2/CH3

20 LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDSESRWQQGNVFSQSVMEALH
NHYTQKSLSLSPGK

[0538] SEQ ID NO:85; 6E6 scFv amino acid sequence

25 ATMGWSCIILFLVATATGVHSDIVMTQSHKFMSTSIGDRVSITCKASQDVGHYVAWYQQKPGQS
PKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNIYPWTFGGGSKLAIK
GSTSGSGKPGSGEGSTKGEVQLVESGGDLVKPGGSLKLSAASGFTFSNYGMSWVRQTPDKRLE
WVATISSGGGYTHYVDSVKGRFTISRDNANHILYLQMSSLSNSEDAMYYCARHPRDFSYAMDYW

GQGTSVTVSSEFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDESRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

5 **[0539]** SEQ ID NO:86; 4G9 scFv amino acid sequence

ATMGWSCIILFLVATATGVHSDIVMTQAAPSPVPTPGESVSI SCRSSKSLLSNGNTYLYWFLQ
RPGQSPQLLIYRMSNLASGVPDRFSGSGGTAFTLRISRVEAEDVGVYYCMQHLEYPLTVGAGT
KLELKGSTSGSGKPGSGEGSTKGQVQLQQSGAELVRPGASVKLSCKALGYTFTDYEMHWVKQTP
VHGLEWIGAIHPGSGGTAYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTRRRPRFYG
10 MDYWGGQTSVTVSSEFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDESRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0540] SEQ ID NO:87; scFv Leader peptide nucleic acid

15 GCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCC

[0541] SEQ ID NO:88; scFv and CAR Linker nucleic acid

GGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCCACCAAGGGC

[0542] SEQ ID NO:89; scFv Spacer nucleic acid

GAATTC

20 **[0543]** SEQ ID NO:90; scFv CH2/CH3 nucleic acid

CTCTTCCCCCAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGG
TGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTC
CTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
25 CCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
ACAAGACCACGCCTCCCGTGGTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTCACCGT
GGACGAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
30 AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0544] SEQ ID NO:91; 6E6 scFv Full-length Nucleotide Sequence

GCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCG
ACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAATAGGAGACAGGGTCAGCATCAC
CTGCAAGGCCAGTCAGGATGTGGGTATTATGTGGCCTGGTATCAACAGAAACCAGGTCAATCT
35 CCTAACTACTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCTTCACAGGTA
GTGGATCTGGGACAGATTTCACTCTACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTA
TTTCTGTGAGCAATATAACATCTATCCGTGGACGTTCCGGTGGAGGCTCCAAGCTGGCAATCAA
GGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCTACCAAGGGCGAGGTGCAGC
TGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC

TGGATTCACTTTCAGTAATTATGGCATGTCTTGGGTTCGCCAGACTCCAGACAAGAGGCTGGAG
 TGGGTCGCAACCATTAGTAGTGGTGGTGGTTAACTCACTACTATGTAGACAGTGTGAAGGGGCGAT
 TCACCATTTCCAGAGACAATGCCAACCATATCCTGTACCTGCAAATGAGCAGTCTGAACTCTGA
 GGACACAGCCATGTATTATTGTGCAAGACACCCGAGGGATTTTTCTATGCTATGGACTACTGG
 5 GGTCAAGGGAACCTCAGTCACCGTCTCCTCAGAATTCCTCTTCCCCCCTCAAGGACACCC
 TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTGA
 GGTCAAGTTCACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAG
 GAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCCTGCTGCACCAGGACTGGCTGA
 ATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCAT
 10 CTCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAG
 ATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCG
 TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTC
 CGACGGCTCCTTCTTCTCTATAGCAAGCTCACCGTGGACGAGAGCAGGTGGCAGCAGGGGAAC
 GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
 15 TGTCTCCGGGTAAATGA

[0545] SEQ ID NO:92; 4G9 scfv Full-length Nucleotide Sequence

GCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCG
 ATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATCTC
 CTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCCTGCAG
 20 AGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGAGTCCCAG
 ACAGGTTCAGTGGCAGTGGGTGAGGAACTGCTTTCACACTGAGAATCAGTAGAGTGGAGGCTGA
 GGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGCTGGGACC
 AAGCTGGAGCTGAAAGGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCTACCA
 AGGGCCAGGTTCAACTGCAACAGTCTGGGGCTGAGCTGGTGAGGCCTGGGGCTTCAGTGAAGCT
 25 GTCCTGCAAGGCTTTGGGCTACACATTTACTGACTATGAAATGCACTGGGTGAAGCAGACACCT
 GTGCATGGCCTGGAATGGATTGGAGCTATTCATCCAGGAAGTGGTGGTACTGCCTATAATCAGA
 AGTTCAAGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAG
 CAGGCTGACATCTGAGGACTCTGCTGTCTATTACTGTACAAGAAGGAGGCCTAGGTTCTATGGT
 ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCAGAATTCCTCTTCCCCCCTAAAC
 30 CCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
 CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA
 AAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCCTGCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCAGCCCCCAT
 CGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCA
 35 TCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCA
 GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCC
 CGTGCTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTCACCGTGGACGAGAGCAGGTGG
 CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA
 AGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0546] SEQ ID NO:93; CAR Leader peptide

MGWSCIIILFLVATATGVHS

[0547] SEQ ID NO:94; CAR Spacer hIgG4 Hinge Only

VDESKYGPPCPPCP

[0548] SEQ ID NO:95; CAR hIgG4 + CH3

VDESKYGPPCPPCPGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
TCLVKGIFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH
EALHNHYTQKSLSLGLGKM

[0549] SEQ ID NO:96; CAR hIgG4 + CH2/CH3

5 VDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQLDNLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGIFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGKM

[0550] SEQ ID NO:97; CAR hCD28

10 FWVLVVVGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYPYAPPRDFA
AYRS

[0551] SEQ ID NO:98; CAR hCD137

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL

[0552] SEQ ID NO:99; CAR hCD3z

15 RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

[0553] SEQ ID NO:100; 6E6 CAR

MGWSCIILFLVATATGVHSDIVMTQSHKFMSTSIGDRVSITCKASQDVGHYVAWYQQKPGQSPK
LLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNIYPWTFGGGSKLAIKGS
20 TSGSGKPGSGEGSTKGEVQLVESGGDLVKPGGSLKLSAASGFTFSNYGMSWVRQTPDKRLEWV
ATISSGGGYTHYVDSVKGRFTISRDNANHILYLQMSSLSNSEDAMYYCARHPRDFSYAMDYWGQ
GTSVTVSSVDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQLDNLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGIFYPSDIAVEWESNGQPENNYKTTPPVLD
25 DGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGKMFWVLVVVGVLACYS
LLVTVAFIIFWVRSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLLYIFK
QPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYD
LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT
KDTYDALHMQALPPR

30 **[0554]** SEQ ID NO:101; 4G9 CAR

MGWSCIILFLVATATGVHSDIVMTQAAPSPVPTPGESVSI SCRSSKSLLSNNGNTYLYWFLQRP
GQSPQLLIYRMSNLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTVGAGTKL
ELKGSTSGSGKPGSGEGSTKGQVQLQQSGAELVRPGASVKLSCKALGYTFTDYEMHWVKQTPVH
GLEWIGAIHPGSGGTAYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTRRRPRFYGMD
35 YWGQGTSTVTVSSVDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQLDNLNGKEYKCKVSNKGLPSSI
EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGIFYPSDIAVEWESNGQPENNYKTTP
VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGKMFWVLVVVGVLAC
CYSLLVTVAFIIFWVRSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLL
40 YIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRRE

EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDLGYQGLS
TATKDTYDALHMQALPPR

[0555] SEQ ID NO:102; ROR2-IG

MARGSALPRRPLLCIPAVWAAAALLLSVSRTSGEVEVLDPNDPLGPLDGDGPIPTLKGYFLNF
5 LEFVNNTITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRIIRKTEYGSRLRIQDLDTT
DTGYYQCVATNGMKTITATGVL FVRLGPTHSPNHNFDQDDYHEDGFCQPYRGIACARFIGNRTIY
VDSLQMQGEIENRITAAFTMIGTSTHLSQCSQFAIPSFCHFVFPLCDARSRTPKPRELCRDEC
EVLES DCRQEYTIARSNPLILMRLQLPKCEALPMPESPDAANCMRIGIPAERLGRYHQCYNGS
GMDYRGTA STTKSGHQCPWALQHPHSHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQKNV
10 RMELCDVPSCSPRDSSKMGPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[0556] SEQ ID NO:103; ROR1-Ig

MHRPRRRGTRPPLLALLAALLLAARGAAQETELSVSAELVPTSSWNISSELNKDSYLTLDPEM
15 NNITTS LGQTAE LHKVSGNPPPTIRWFKNDAPVVQEPRLSFRSTIYGSRLRIRNLDTTDTGY
FQCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYEEDGFCQPYRGIACARFIGNRTVYMESL
HMQGEIENQITAAFTMIGTSSHLSDKCSQFAIPSLCHYAFPYCDETSSVPKPRDLRDECEILE
NVLCQTEYIFARSNPMILMRLKLPCEDLPQESPEAANCIRIGIPMADPINKNHKCYNSTGVD
20 YRGTVSVTKSGRQCQPWNSQYPHTHTFTALRFPELNGGHSYCRNPGNQKEAPWCFTLDENFKSD
LCDIPACDSKDSKEKNKMEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

25 [0557] SEQ ID NO:104; CAR leader peptide nucleic acid

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCC

[0558] SEQ ID NO:105; CAR Spacer hIgG4 Hinge Only nucleic acid

GTCGACGAGTCCAAATATGGTCCCCCATGCCCACCATGCCCCA

[0559] SEQ ID NO:106; CAR hIgG4 + CH3 nucleic acid

30 GTCGACGAGTCCAAATATGGTCCCCCATGCCCACCATGCCCAGGCAAGGAGTACAAGTGCAAGG
TCTCCAACAAAGGCCTCCCGTCTCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCG
AGAGCCACAGGTGTACACCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAAC TACAAGACCACGCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCTACAG
35 CAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCCCTAGGTAAATG

[0560] SEQ ID NO:107; CAR hIgG4 + CH2/CH3 nucleic acid

GTCGACGAGTCCAAATATGGTCCCCCATGCCCACCATGCCCAGCACCTGAGTTCTGGGGGGAC
CATCAGTCTTCTGTTCCCCCAAACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGT
40 CACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGAT

GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTG
 TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT
 CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
 GAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGA
 5 CCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC
 GGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC
 AGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG
 AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCCCTAGGTAAAATG

[0561] SEQ ID NO:108; CAR hCD28 nucleic acid

10 TTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGTGGCCT
 TTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGAC
 TCCCCGCCGCCCGGGCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCA
 GCCTATCGCTCC

[0562] SEQ ID NO:109; CAR hCD137 nucleic acid

15 AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAAACTA
 CTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAGGAGGATGTGAACTG

[0563] SEQ ID NO:110; CAR hCD3z nucleic acid

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATA
 ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCC
 20 TGAGATGGGGGGAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAA
 GATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGAGGGGGCAAGGGGC
 ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCA
 GGCCCTGCCCCCTCGCTGA

[0564] SEQ ID NO:111; 6E6 CAR nucleic acid

25 ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCGACATTG
 TGATGACCCAGTCTCACAAATTCATGTCCACATCAATAGGAGACAGGGTCAGCATCACCTGCAA
 GGCCAGTCAGGATGTGGGTCATTATGTGGCCTGGTATCAACAGAAACCAGGTCAATCTCCTAAA
 CTACTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCTTCACAGGTAGTGGAT
 CTGGGACAGATTTCACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTG
 30 TCAGCAATATAACATCTATCCGTGGACGTTCCGGTGGAGGCTCCAAGCTGGCAATCAAAGGCTCC
 ACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCCACCAAGGGCGAGGTGCAGCTGGTGG
 AGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATT
 CACTTTCAGTAATTATGGCATGTCTTGGGTTCCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTC
 GCAACCATTAGTAGTGGTGGTGGTTACACTCACTATGTAGACAGTGTGAAGGGGCGATTACCA
 35 TTTCCAGAGACAATGCCAACCATATCCTGTACCTGCAATGAGCAGTCTGAACTCTGAGGACAC
 AGCCATGTATTATTGTGCAAGACACCCGAGGGATTTTTCTATGCTATGGACTACTGGGGTCAG
 GGAACCTCAGTCACCGTCTCCTCAGTCGACGAGTCCAAATATGGTCCCCCATGCCACCATGCC
 CAGCACCTGAGTTCTTGGGGGACCATCAGTCTTCTGTCCCCCCTCAAGGACACTCT
 CATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCGAG
 40 GTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
 AGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAA
 CGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCATCGAGAAAACCATC
 TCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGA
 TGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGT

GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCC
 GACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATG
 TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT
 GTCCCTAGGTAAAATGTTTTGGGTGCTGGTGGTGGTGGTGGAGTCCTGGCTTGCTATAGCTTG
 5 CTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGGGCGGACACAGTG
 ACTACATGAACATGACTCCCCGCCGCCCTGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCC
 ACCACGCGACTTCGCAGCCTATCGCTCCAAACGGGGCAGAAAGAACTCCTGTATATATTCAA
 CAACCATTTATGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAG
 AAGAAGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTA
 10 CCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTT
 TTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAGCCGAGAAGGAAGAACCCTCAGG
 AAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAA
 AGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAG
 GACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA

15 **[0565]** SEQ ID NO:112; 4G9 CAR nucleic acid

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCGATATTG
 TGATGACTCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATCTCCTGCAG
 GTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCTGCAGAGGCCA
 GGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGAGTCCAGACAGGT
 20 TCAGTGGCAGTGGGTGAGGAAGTCTTTCACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGT
 GGGTGTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGTGGGACCAAGCTG
 GAGCTGAAAGGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCCACCAAGGGCC
 AGGTTCAACTGCAACAGTCTGGGGCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGCTGTCTTG
 CAAGGCTTTGGGCTACACATTTACTGACTATGAAATGCACTGGGTGAAGCAGACACCTGTGCAT
 25 GGCCTGGAATGGATTGGAGCTATTCATCCAGGAAGTGGTGGTACTGCCTATAATCAGAAGTTCA
 AGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGGCT
 GACATCTGAGGACTCTGCTGTCTATTACTGTACAAGAAGGAGGCCTAGGTTCTATGGTATGGAC
 TACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCAGTCGACGAGTCCAATATGGTCCCCCAT
 GCCCACCATGCCCAGCACCTGAGTTCCTGGGGGACCATCAGTCTTCCTGTTCCCCCCTAAACC
 30 CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCCTGGTGGTGGACGTGAGCCAG
 GAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAA
 AGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCCTGCACCA
 GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCTCCATC
 GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT
 35 CCCAGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCTACCCAG
 CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCC
 GTGCTGGACTCCGACGGCTCCTTCTTCTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGC
 AGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAA
 GAGCCTCTCCCTGTCCCTAGGTAAAATGTTTTGGGTGCTGGTGGTGGTGGTGGAGTCCTGGCT
 40 TGCTATAGCTTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGG
 GCGGACACAGTGACTACATGAACATGACTCCCCGCCGCCCTGGGCCCACCCGCAAGCATTACCA
 GCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCCAAACGGGGCAGAAAGAACTCCTG
 TATATATTCAAACAACCATTTATGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCT
 GCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTCAGCAGGAGCGCAGA
 45 CGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAG
 GAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAGCCGAGAAGGA
 AGAACCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGA
 GATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGT
 ACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA

[0566] SEQ ID NO:113; Human ROR2 Kringle domain

HQCYNGSGMDYRGTA STTKSGHQCPWALQHPHSHHLSSTDFPELGGGHAYCRNPGG
QMEGPWCFTQNKNVRMELCDVPSCS

[0567] SEQ ID NO:114; Human ROR2 Ig-like domain

5 AILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIRKTEYGSRLRIQDLDTTDTGYYQCVAT
NGMKTITAT

1 WHAT IS CLAIMED IS

2 1. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
3 comprising a heavy chain variable domain and a light chain variable domain,
4 wherein said heavy chain variable domain comprises:
5 a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID
6 NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and
7 wherein said light chain variable domain comprises:
8 a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID
9 NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

1 2. The antibody of claim 1, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:2.

1 3. The antibody of claim 1, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:4.

1 4. The antibody of claim 1, wherein said antibody is a humanized antibody, a
2 Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 5. The antibody of claim 1, wherein said antibody is an IgG1 or an IgG2.

1 6. The antibody of claim 1, wherein said antibody is capable of binding a
2 ROR2 protein.

1 7. The antibody of claim 6, wherein said ROR2 protein comprises the amino
2 acid sequence of SEQ ID NO:18.

1 8. The antibody of claim 6, wherein said antibody is capable of binding the
2 extracellular domain of said ROR2 protein.

1 9. The antibody of claim 8, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.

- 1 10. The antibody of claim 8, wherein said extracellular domain is a Kringle
2 domain.
- 1 11. The antibody of claim 6, wherein said ROR2 protein comprises a histidine
2 at a position corresponding to position 349 or an aspartic acid at a position corresponding to
3 position 354 of SEQ ID NO:22.
- 1 12. The antibody of claim 6, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 1 nM.
- 1 13. The antibody of claim 6, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) of about 0.06 nM.
- 1 14. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID
5 NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and
6 wherein said light chain variable domain comprises:
7 a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR
8 L3 as set forth in SEQ ID NO:36.
- 1 15. The antibody of claim 14, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:6.
- 1 16. The antibody of claim 14, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:8.
- 1 17. The antibody of claim 14, wherein said antibody is a humanized antibody,
2 a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.
- 1 18. The antibody of claim 14, wherein said antibody is an IgG1 or an IgG2.

1 19. The antibody of claim 14, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

1 20. The antibody of claim 19, wherein said antibody is capable of binding an
2 extracellular domain of said ROR2 protein.

1 21. The antibody of claim 20, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.

1 22. The antibody of claim 20, wherein said extracellular domain is an Ig-like
2 domain.

1 23. The antibody of claim 19, wherein said ROR2 protein comprises a
2 methionine at a position corresponding to position 386 of SEQ ID NO:22.

1 24. The antibody of claim 19, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.2 nM to about 5 nM.

1 25. The antibody of claim 19, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) of about 1.9 nM.

1 26. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID
5 NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and
6 wherein said light chain variable domain comprises:
7 a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID
8 NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

1 27. The antibody of claim 26, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:10.

1 28. The antibody of claim 26, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:12.

1 29. The antibody of claim 26, wherein said antibody is a humanized antibody,
2 a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 30. The antibody claim 26, wherein said antibody is an IgG1 or an IgG2.

1 31. The antibody of claim 26, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

1 32. The antibody of claim 31, wherein said antibody is capable of binding an
2 extracellular domain of a ROR2 protein.

1 33. The antibody of claim 32, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.

1 34. The antibody of claim 32, wherein said wherein said extracellular domain
2 is a Kringle domain.

1 35. The antibody of claim 31, wherein said ROR2 protein comprises a
2 histidine at a position corresponding to position 349, an aspartic acid at a position corresponding
3 to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:22.

1 36. The antibody of claim 31, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150
3 nM.

1 37. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID
5 NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and
6 wherein said light chain variable domain comprises:

7 a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID
8 NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

1 38. The antibody of claim 37, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:14.

1 39. The antibody of claim 37, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:16.

1 40. The antibody of claim 37, wherein said antibody is a humanized antibody,
2 a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 41. The antibody of claim 37, wherein said antibody is an IgG1 or an IgG2.

1 42. The antibody of claim 37, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

1 43. The antibody of claim 42, wherein said antibody is capable of binding an
2 extracellular domain of said ROR2 protein.

1 44. The antibody of claim 43, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.

1 45. The antibody of claim 41, wherein said extracellular domain is an Ig-like
2 domain.

1 46. The antibody of claim 42, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150
3 nM.

1 47. The antibody of any one of claims 6, 19, 31 or 42, wherein said ROR2
2 protein is expressed on a cell.

1 48. The antibody of claim 47, wherein said cell is a cancer cell.

1 49. The antibody of claim 48, wherein said cancer cell is a breast cancer cell,
2 ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer
3 cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

1 50. The antibody of any one of claims 1, 14, 26 or 37, wherein said antibody
2 is attached to a therapeutic agent.

1 51. The antibody of any one of claims 1, 14, 26 or 37, wherein said antibody
2 is attached to a diagnostic agent.

1 52. A method of treating cancer in a subject in need thereof, said method
2 comprising administering to a subject a therapeutically effective amount of an antibody of any
3 one of claims 1, 14, 26 or 37.

1 53. A method of inhibiting metastasis of a ROR2-expressing cancer in a
2 subject in need thereof, said method comprising administering to a subject a therapeutically
3 effective amount of any one of claims 1, 14, 26 or 37.

1 54. The method of claim 52, wherein said cancer is breast cancer, ovarian
2 cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck cancer,
3 bone cancer, skin cancer or prostate cancer.

1 55. A method of detecting a ROR2-expressing cell, said method comprising
2 (i) contacting a ROR2-expressing cell with an antibody of any one of claims 1,
3 14, 26 or 37; and
4 (ii) detecting binding of said antibody to a ROR2 protein expressed by said cell.

1 56. The method of claim 55, wherein said antibody is attached to a detectable
2 moiety.

1 57. The method of claim 55, wherein said ROR2-expressing cell is in a
2 subject.

1 58. The method of claim 57, wherein said subject is a subject having cancer.

1 59. The method of claim 58, wherein said cancer is cancer is breast cancer,
2 ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck
3 cancer, bone cancer, skin cancer or prostate cancer.

1 60. The method of claim 55, wherein said contacting occurs *in vitro*.

1 61. A method of delivering a therapeutic agent to a ROR2-expressing cell,
2 said method comprising contacting a ROR2-expressing cell with an antibody of any one of
3 claims 1, 14, 26 or 37, wherein said antibody is attached to a therapeutic agent.

1 62. The method of claim 61, wherein said therapeutic agent is an anti-cancer
2 agent.

1 63. The method of claim 61, wherein said ROR2-expressing cell is in a
2 subject.

1 64. The method of claim 63, wherein said subject is a subject having cancer.

1 65. The method of claim 64, wherein said cancer is cancer is breast cancer,
2 ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck
3 cancer, bone cancer, skin cancer or prostate cancer.

4 66. The method of claim 62, wherein said contacting occurs *in vitro*.

1 67. A method of inhibiting migration of a ROR2-expressing cell, said method
2 comprising contacting a ROR2-expressing cell with an antibody of any one of claims 1, 14, 26 or
3 37.

1 68. The method of claim 67, wherein said ROR2-expressing cell is in a
2 subject having cancer.

1 69. The method of claim 68, wherein said cancer is cancer is breast cancer,
2 ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck
3 cancer, bone cancer, skin cancer or prostate cancer.

1 70. The method of claim 67, wherein said contacting occurs in vitro.

1 71. The method of claim 67, wherein said ROR2-expressing cell is a cancer
2 cell.

1 72. The method of claim 71, wherein said cancer cell is a breast cancer cell,
2 ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer
3 cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.

1 73. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID
4 NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID
7 NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

1 74. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID
4 NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID
7 NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

1 75. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID
4 NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID
7 NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

1 76. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID
4 NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID
7 NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

1 77. A chimeric antigen receptor comprising:
2 (i) an antibody region comprising:
3 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
4 NO: 28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30;
5 and
6 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
7 SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID
8 NO:27; and
9 (ii) a transmembrane domain.

10 78. A chimeric antigen receptor comprising:
11 (i) an antibody region comprising:
12 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
13 NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36;
14 and
15 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
16 SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID
17 NO:33; and
18 (ii) a transmembrane domain.

19 79. A chimeric antigen receptor comprising:
20 (i) an antibody region comprising:

- 21 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
22 NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42;
23 and
24 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
25 SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38, and a CDR H3 as set forth in SEQ ID
26 NO:39; and
27 (ii) a transmembrane domain.

1 80. A chimeric antigen receptor comprising:

2 (i) an antibody region comprising:

3 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
4 NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48;
5 and

6 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
7 SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44, and a CDR H3 as set forth in SEQ ID
8 NO:45; and

9 (i) (ii) a transmembrane domain.

1 81. The chimeric antigen receptor of any one of claims 77, 78, 79 or 80,
2 further comprising an intracellular T-cell signaling domain.

1 82. The chimeric antigen receptor of claim 81, wherein the intracellular T-cell
2 signaling domain is a CD3 ζ intracellular T-cell signaling domain.

1 83. The chimeric antigen receptor of claim 81, further comprising an
2 intracellular co-stimulatory T-cell signaling domain.

1 84. The chimeric antigen receptor of claim 83, wherein said intracellular co-
2 stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain, a 4-1BB
3 intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling
4 domain, or an OX-40 intracellular co-stimulatory signaling domain.

1 85. A method of treating cancer in a subject in need thereof said method
2 comprising, administering a therapeutically effective amount of a chimeric antigen receptor of
3 any one of claims 77, 78, 79 or 80 to a subject.

1 86. The method of claim 85, wherein said cancer is cancer is breast cancer,
2 ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck
3 cancer, bone cancer, skin cancer or prostate cancer.

1/20

FIG. 1

		Leader					
		10	20	30	40	50	60
hROR2	MARGSALPRRPLLCPAVWAAAALLSVSR	TSGEVEVLDPNDPLGPLDGQDGFIFTL	KGY				
mROR2	WVL.S.VP..AR...T.....WTFW.A....DSEAI.T..QP..P.S.L.....						
		Ig-Like Domain					
		70	80	90	100	110	120
hROR2	FLNFLEPVNNITIVQCQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRIIIRKTEYGSRL						
mROR2	VV.....						
		130	140	150	160	170	180
hROR2	RIQDLDTTDTGYQCVATNGMKTITATGVLFVRLGPTHSPNHNFDQDYHEDGFCQPYRGI						
mROR2	L.....Y.....DQ.....						
		CRD					
		190	200	210	220	230	240
hROR2	ACARFIGNRTIYVDSLQMQGEIENRITAFTMIGTSTHLSHQCSQFAIPSFCHFVFPFLCD						
mROR2	Q.....						
		250	260	270	280	290	300
hROR2	ARSRTPKPRELCRDECEVLES DLCRQEYTIARSNFLILMRLQLPKCEALPMPESPDAANC						
mROR2	.C..A.....N.....						
		Kringle					
		310	320	330	340	350	360
hROR2	MRIGIPAERLGRYHQCYNGSGMDYRGTA	STTKSGHQCPWALQHPHSHLSSTDFPELGG					
mROR2	A....M.....R....E.....						
		370	380	390	400		
hROR2	GHAYCRNPGGQMEGPWCFTQNKVRELCDVPSCSPRDSKMG						
mROR2	V.....P....YG....						

	FRI-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	
6E6_VH AC090887 MIGHV5-6*01	1 10 20 30 40 50 EVQLVESGG.DLVKPGSELISCAAS GFTF....SNYG NSWVRQTPERLEWVAT EVQLVESGG.DLVKPGSELISCAAS GFTF....SSYG NSWVRQTPERLEWVAT			N
	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	CDR3	FR4
6E6_VH AC090887 MIGHV5-6*01	60 70 80 90 100 ISSG..GGYT HYVDSEK.GFTISRDNANHILYLQMSGLNSEDITAMNYCAR HFRDPSYANDY NGQGTSTVTVER ISSG..GGYT YYPDSVK.GFTISRDNANHILYLQMSGLNSEDITAMNYCAR			N
	Q H V	NH1	N	
6E6_VK AJ235961 MIGHV6-23*01	1 10 20 30 40 50 DIVMTQSHKFNSTSGDREVSITCKAS QDV.....GHY VANVQGFQGSFKLLIY DIVMTQSHKFNSTSGDREVSITCKAS QDV.....GTA VANVQGFQGSFKLLIY			NY
	I			
	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	CDR3	FR4
6E6_VK AJ235961 MIGHV6-23*01	60 70 80 90 100 WA.....S TRHTGVP.DRFTGSG..SGDTFTLIENVQSEDLAIDFC QQNNIYFWT FCGGSLAIKR WA.....S TRHTGVP.DRFTGSG..SGDTFTLIENVQSEDLAIDFC QQYSSYE			NI

FIG. 2A

	FR1-IMGT (1-26)			CDR1-IMGT (27-38)			FR2-IMGT (39-55)		
	1	10	20	30	40	50			
409 VH	QVQLQESG	ELVRPGASVLSCKAL	GYTF...	TDYE	MHWVKQTFVHGLEWICA				
AC090843 MICHV1-15*01	QVQLQESG	ELVRPGASVLSCKAS	GYTF...	TDYE	MHWVKQTFVHGLEWICA				
	K L								
	CDR2-IMGT (56-65)			FR3-IMGT (66-104)			CDR3 FR4		
	60	70	80	90	100				
409 VH	YHPC...	SGGY	AYNQKFK	GKATLTADKSS	STAYMELSLHSEDS	SAVYYCTR	RRPRFYCMDY	WQVQTSVPVPS	
AC090843 MICHV1-15*01	IDEF...	TCGT	AYNQKFK	GKATLTADKSS	STAYMELSLHSEDS	SAVYYCTR			
	H G S T SR								
	FR1-IMGT (1-26)			CDR1-IMGT (27-38)			FR2-IMGT (39-55)		
	1	10	20	30	40	50			
409 VK	DIWMTQAAPS	VPVTGEGSVSISCRSS	KSLLSH	NGNTY	LYWFLQRPQSPQLLIY				
AJ231263 MICKV2-137*01	DIWMTQAAPS	VPVTGEGSVSISCRSS	KSLLSH	NGNTY	LYWFLQRPQSPQLLIY				
	CDR2-IMGT (56-65)			FR3-IMGT (66-104)			CDR3 FR4		
	60	70	80	90	100				
409 VK	RM...	S	MLASGVP	DRFSGSG	SGTAFTLRISERVEAED	VGVIYC	MOHLEYPLT	VGACTKLELR	
AJ231263 MICKV2-137*01	RM...	S	MLASGVP	DRFSGSG	SGTAFTLRISERVEAED	VGVIYC	MOHLEYP		

FIG. 2B

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)
1	10	20	30 40 50
EVOLVESGG.DLVKPGGSLKLSCAAS GFTF.....SNYG MSWVRQTPDKRLWEVAT			
EVOLVESGG.DLVKPGGSLKLSCAAS GFTF.....SSYG MSWVRQTPDKRLWEVAT			
N			
CDR2-IMGT (56-65)	FR3-IMGT (66-104)	CDR3	FR4
60 70 80 90 100			
ISSC..CGST YYPDSVK.CFTISRDNAKNSLYLQMSSLKSEDTAMYICAR HPDYGYFYUY WQQCTTLTVSS			
ISSC..GSYT YYPDSVK.CFTISRDNAKNTLYLQMSSLKSEDTAMYICAR			
S			
FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	
1	20	30 40 50	
DILLTQSFDILSVKSGEVSFSCRAS QSI.....GTS IHWYQORTNGSPRLLIK			
DILLTQSFAILSVKSGEVSFSCRAS QSI.....GTS IHWYQORTNGSPRLLIK			
D			
CDR2-IMGT (56-65)	FR3-IMGT (66-104)	CDR3	FR4
60 70 80 90 100			
YA.....S ESISGIP.SRFSGSG..SGTDFTLSINVESEDIADYYC QQSDSWFP FCSGTKLEKK			
YA.....S ESISGIP.SRFSGSG..SGTDFTLSINVESEDIADYYC QQGN6WP			

FIG. 2C

	FR1-IMGT (1-26)				CDR1-IMGT (27-38)				FR2-IMGT (39-55)			
	1	10	20	30	40	50						
5G3_VH	EVOLVESGG	GLVQPKGSLKLS	CAAS	QPTF	...NTYA	MMWVQAPGKGLEW	VAR					
AF064445	EVOLVESGG	GLVQPKGSLKLS	CAAS	QPTF	...NTYA	MMWVQAPGKGLEW	VAR					
	CDR2-IMGT (56-65)				FR3-IMGT (66-104)				CDR3			
	60	70	80	90	100							
5G3_VH	IRSKSNYYAT	YIADSVK	DRFTISRDD	QSEMLH	LQNNLKT	EUTAMYYCV	HGSSLIY	AMDY	WGQGT	SVTVSS		
AF064445	IRSKSNYYAT	YIADSVK	DRFTISRDD	QSEMLY	LQNNLKT	EUTAMYYCV	HGSSLIY	AMDY	WGQGT	SVTVSS		
	FR1-IMGT (1-26)				CDR1-IMGT (27-38)				FR2-IMGT (39-55)			
	1	10	20	30	40	50						
5G3_VK	DIQNTQSP	SSLSASLGER	VELTCRAS	QEI	...SGY	LQWLQK	PDGTIKRLIY					
AF003294	DIQNTQSP	SSLSASLGER	VELTCRAS	QEI	...SGY	LQWLQK	PDGTIKRLIY					
	CDR2-IMGT (56-65)				FR3-IMGT (66-104)				CDR3			
	60	70	80	90	100							
5G3_VK	AA...S	TLDSGV	KRFSGSR	..SGS	YSLTIS	SSLESD	FADYYC	LQYAS	YPT	FGG	TKLEIK	
AF003294	AA...S	TLDSGV	KRFSGSR	..SGS	YSLTIS	SSLESD	FADYYC	LQYAS	YPT	FGG	TKLEIK	

FIG. 2D

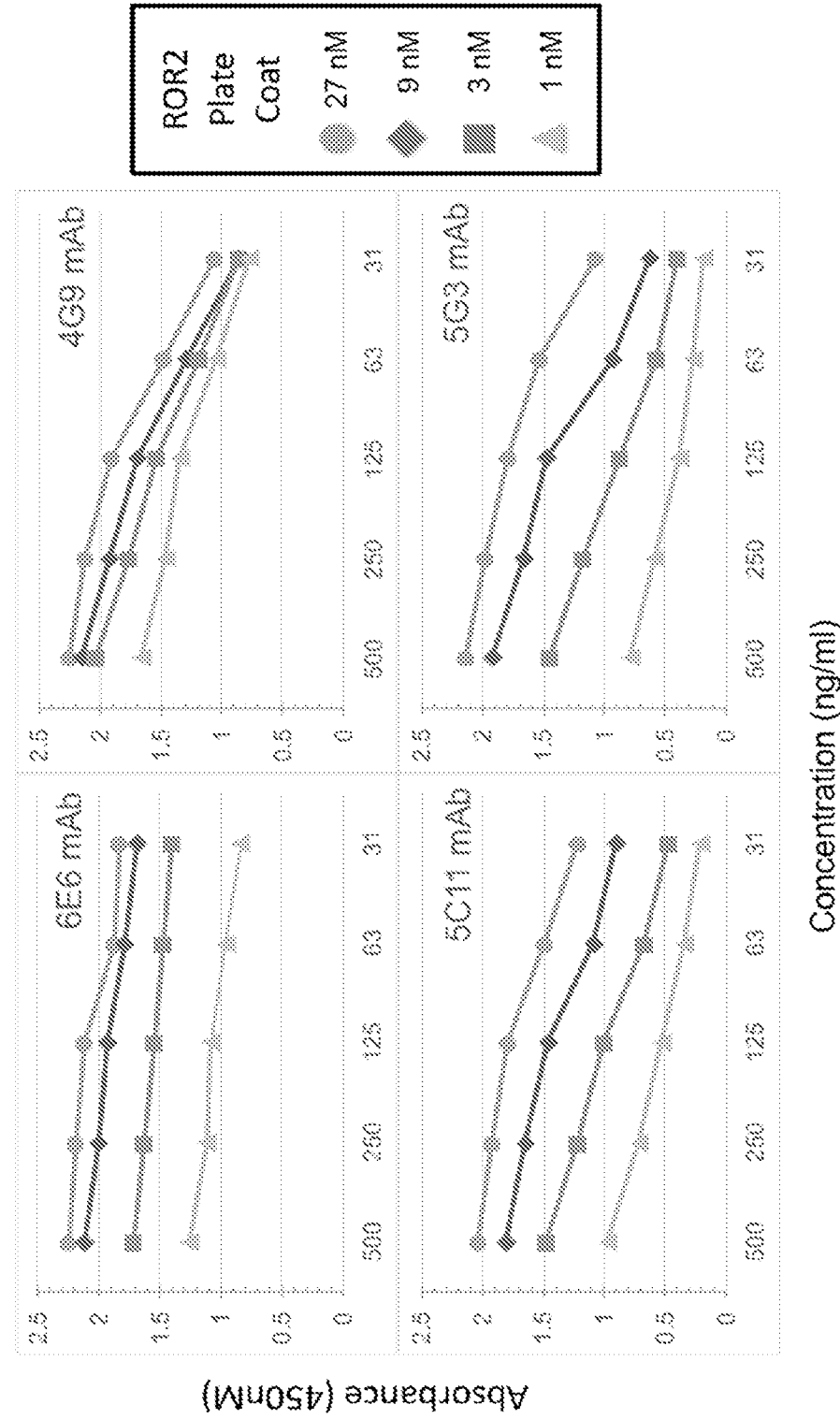
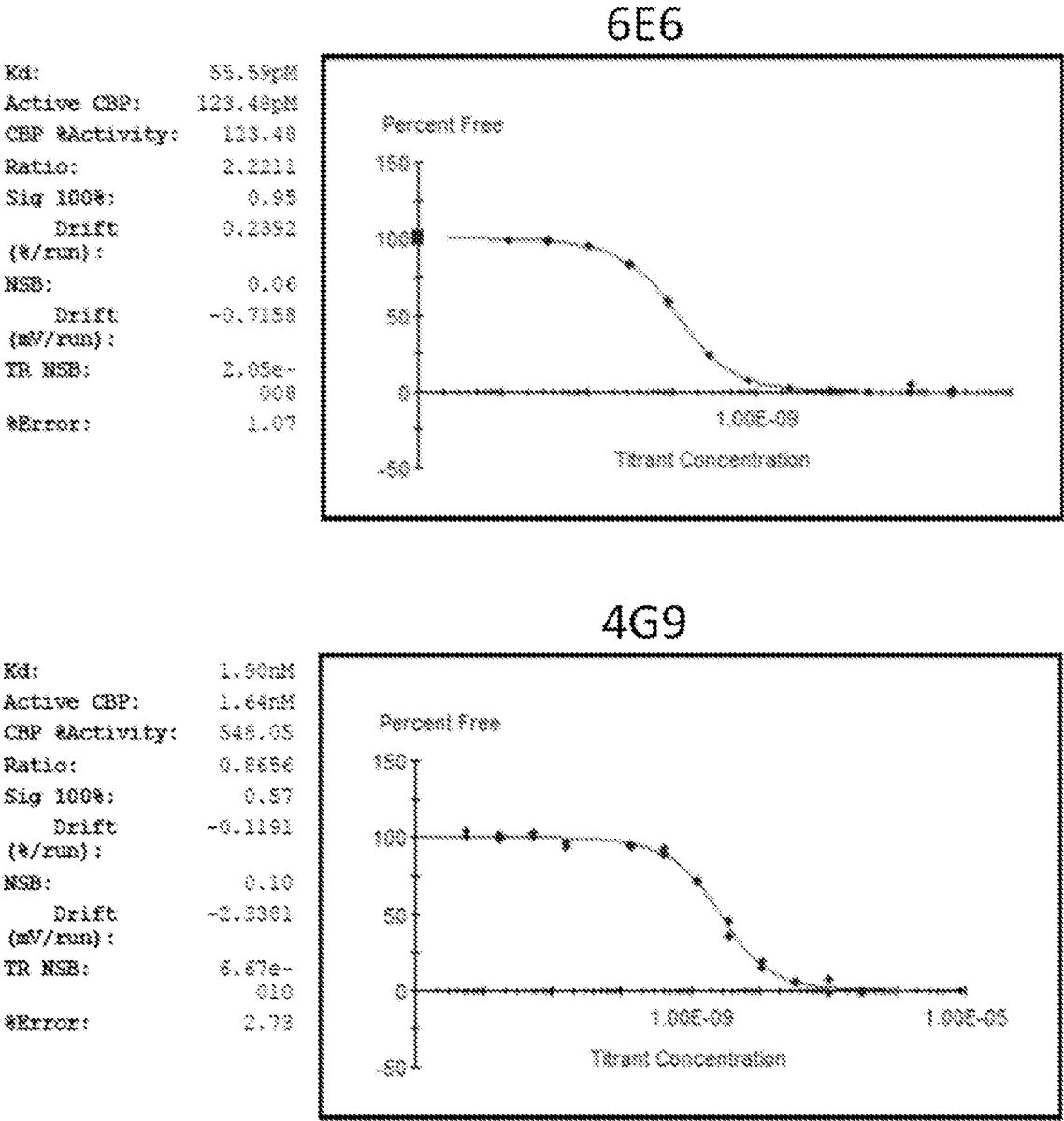


FIG. 3

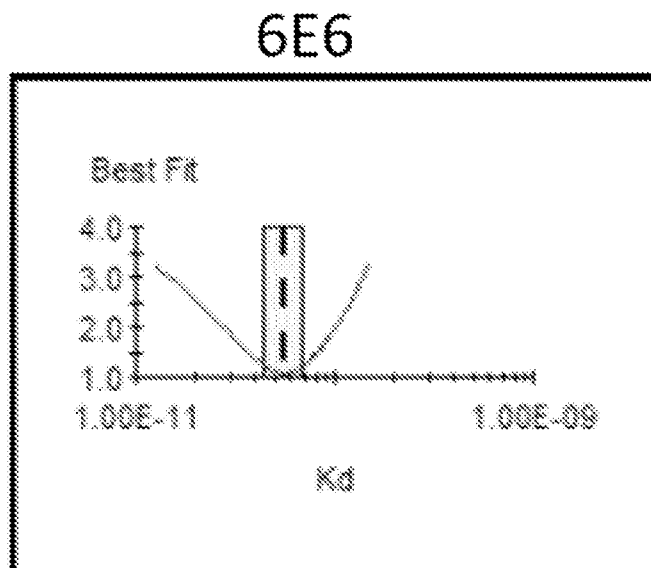
FIG. 4A



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FIG. 4B

Kd: 55.59pM
95% confidence interval
Kd High: 69.01pM
Kd Low: 44.53pM



Kd: 1.90nM
95% confidence interval
Kd High: 3.24nM
Kd Low: 1.02nM

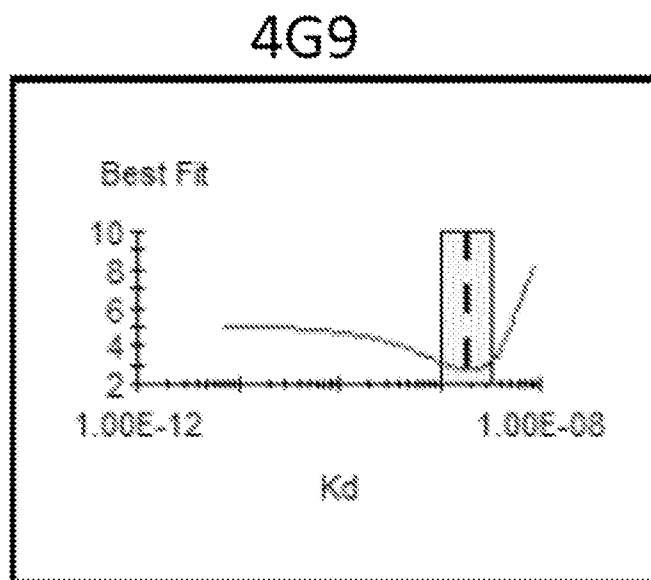
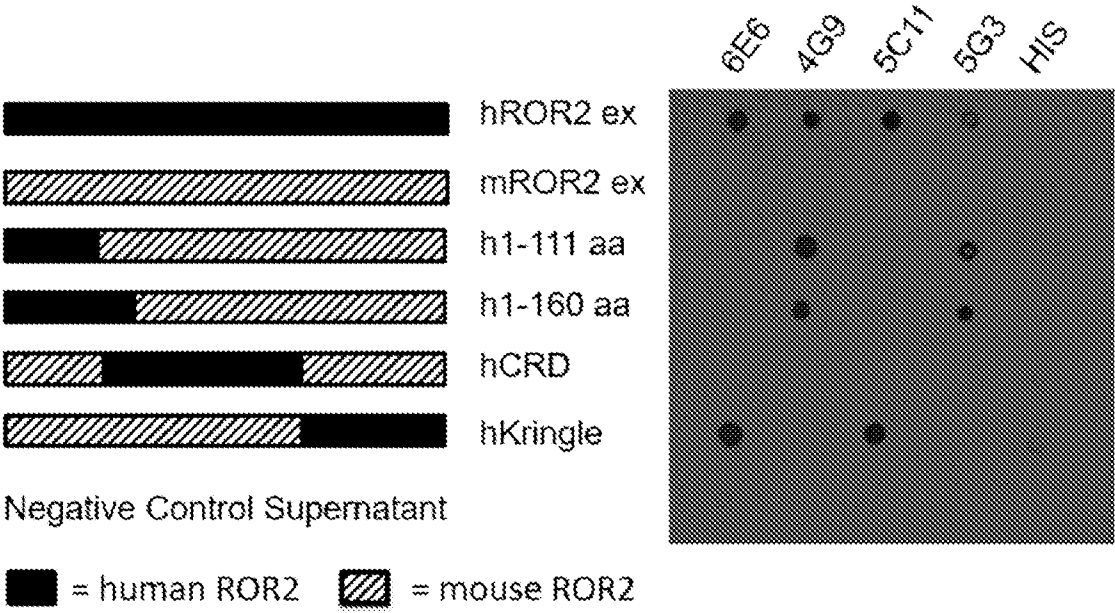


FIG. 5



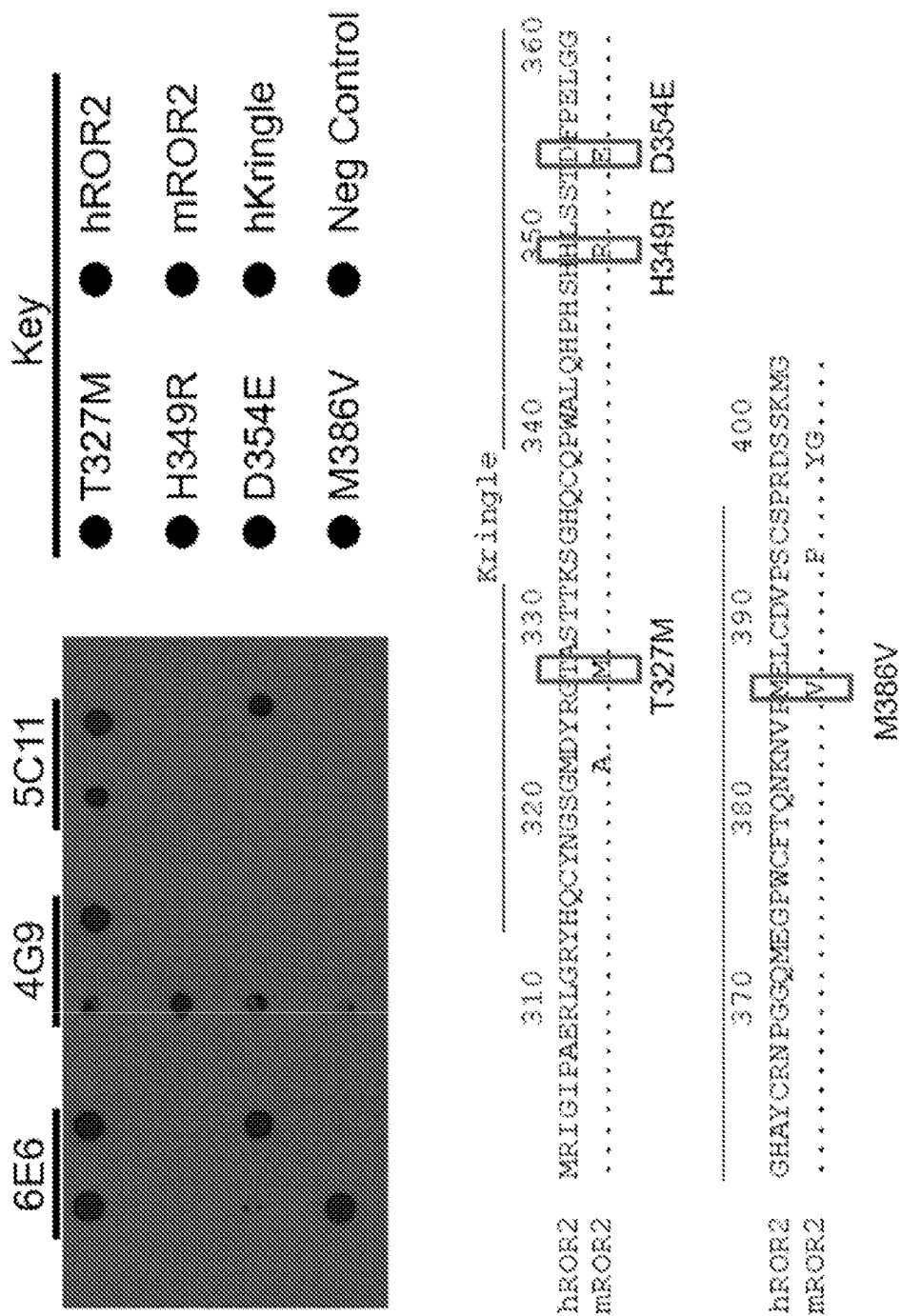


FIG. 6

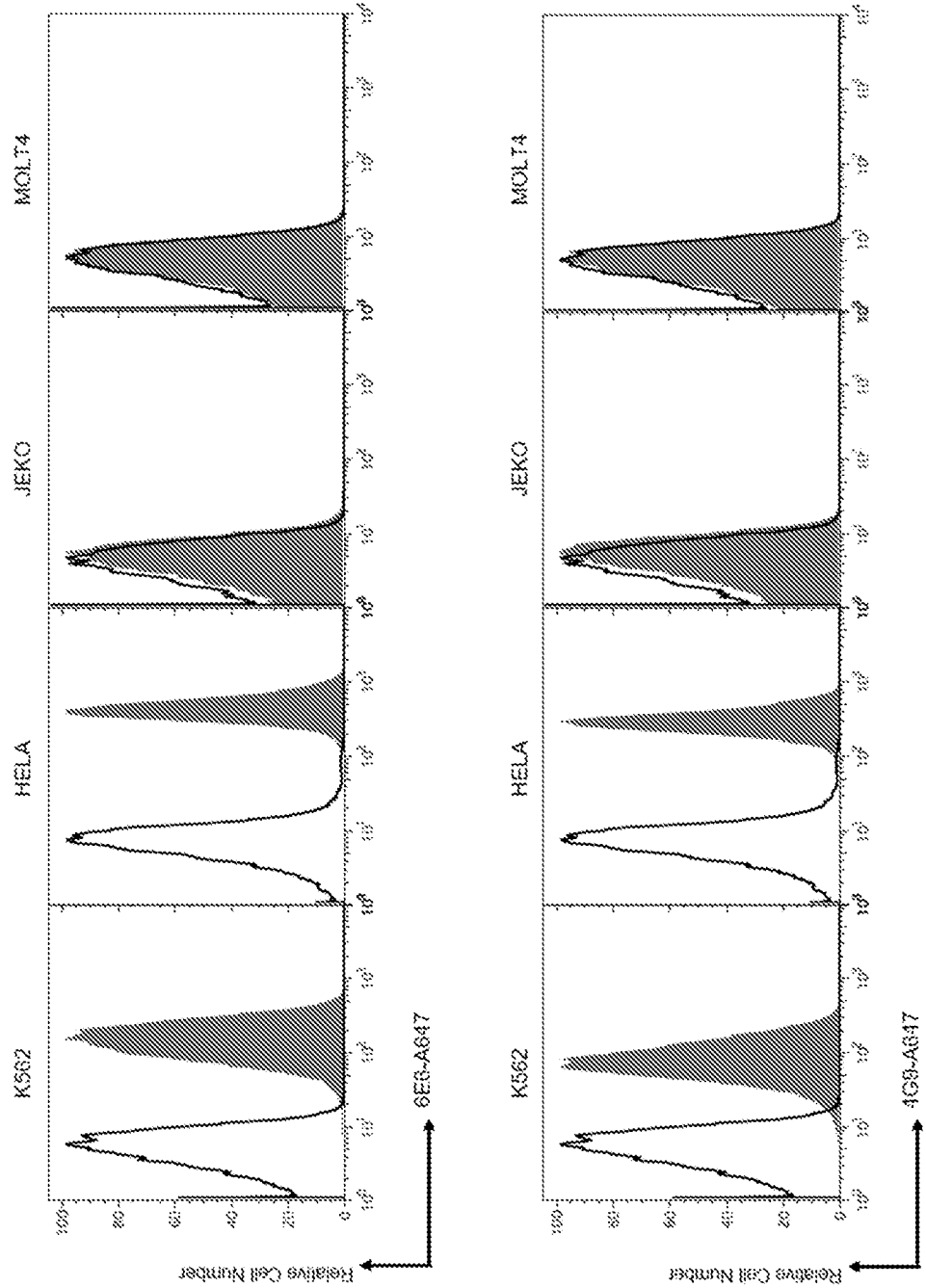


FIG. 7A

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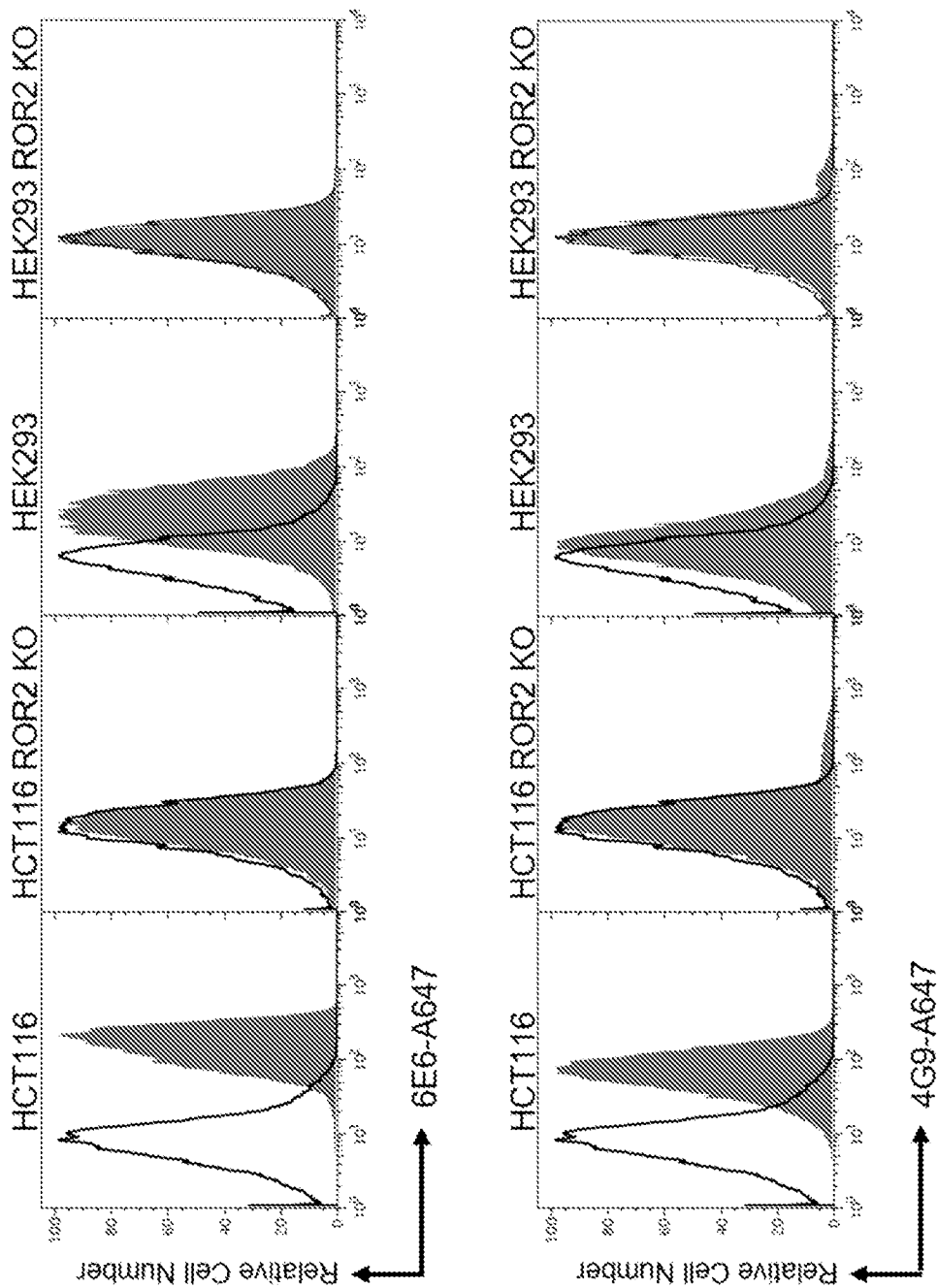
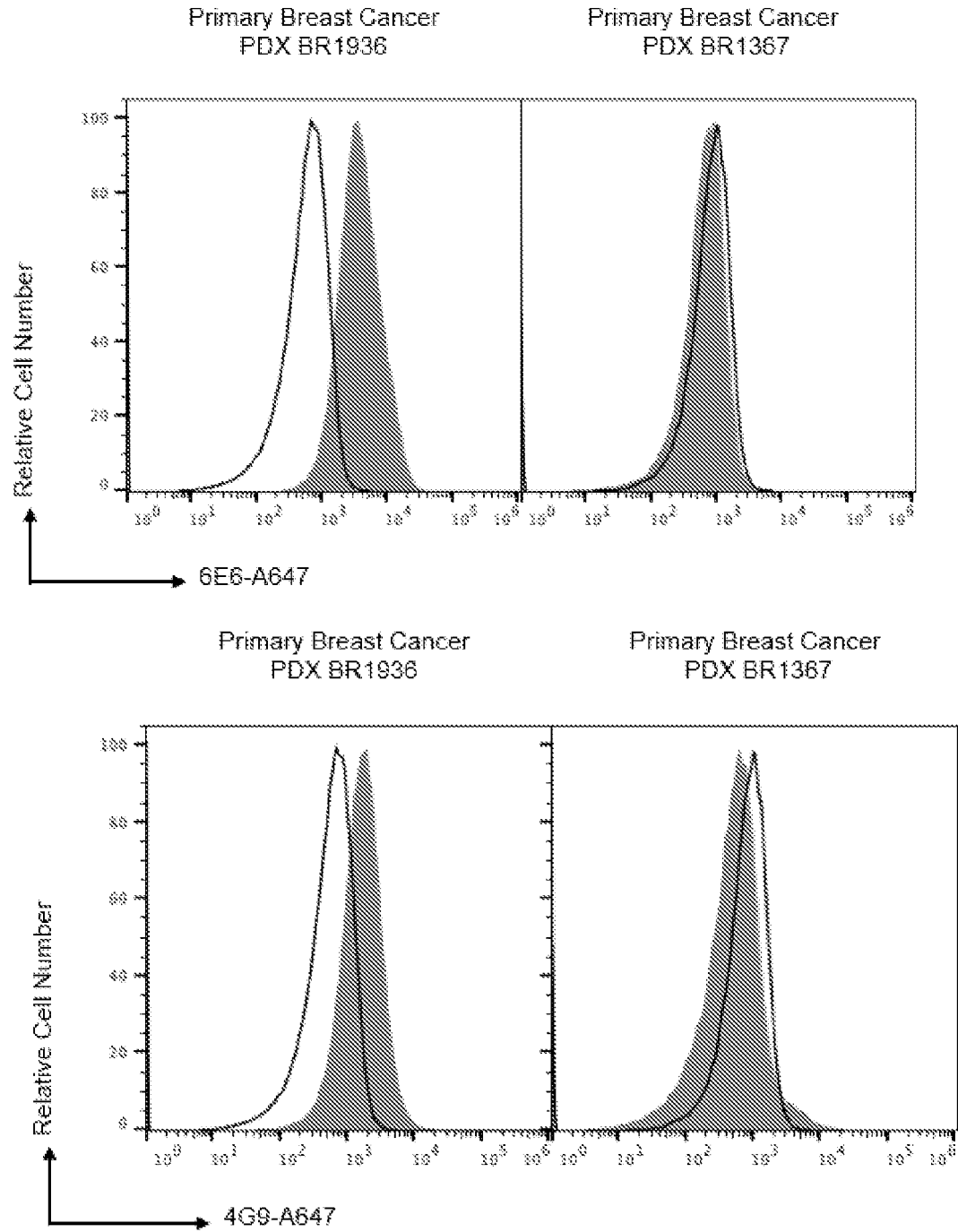


FIG. 7B

FIG. 8



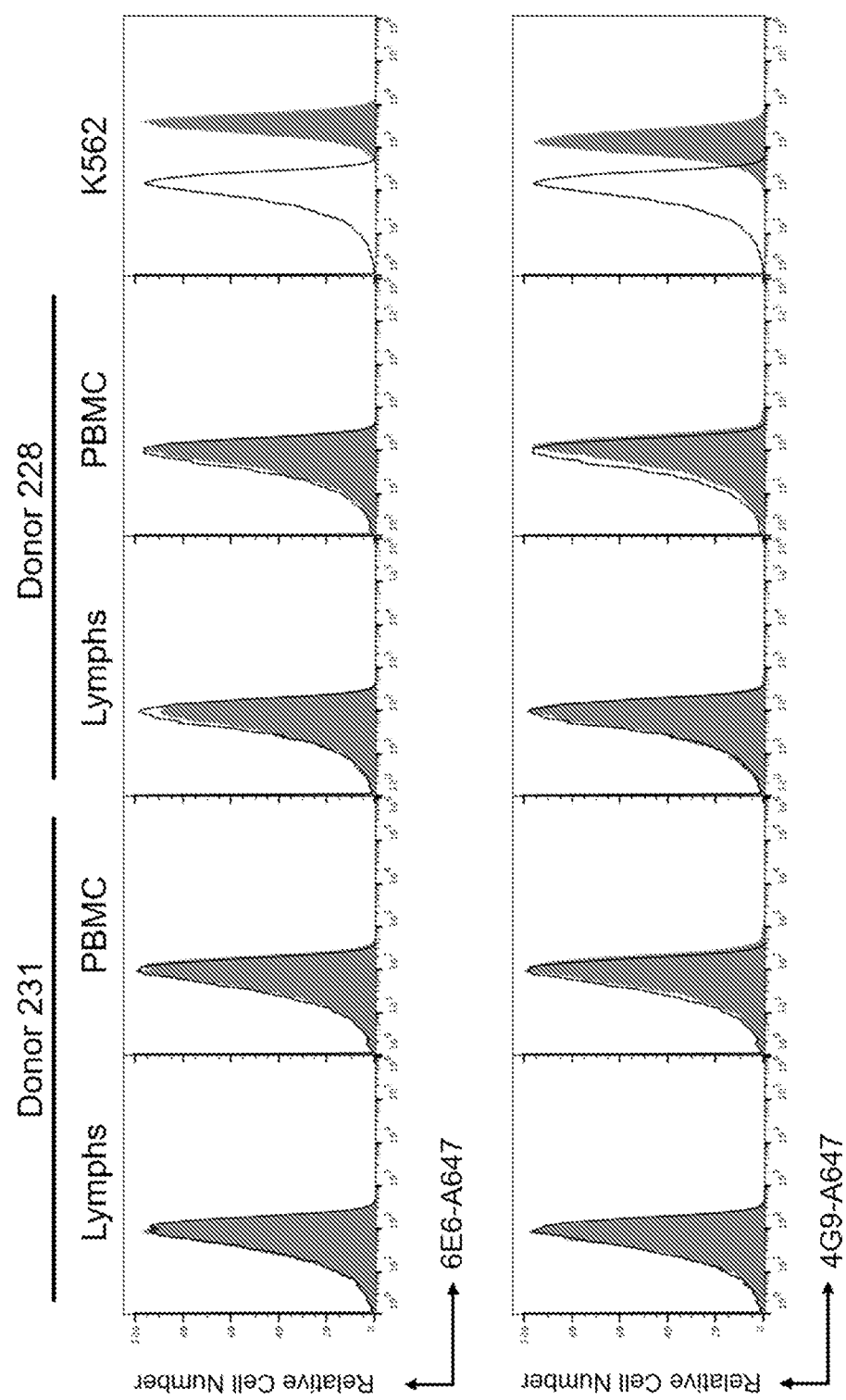


FIG. 9

FIG. 10A

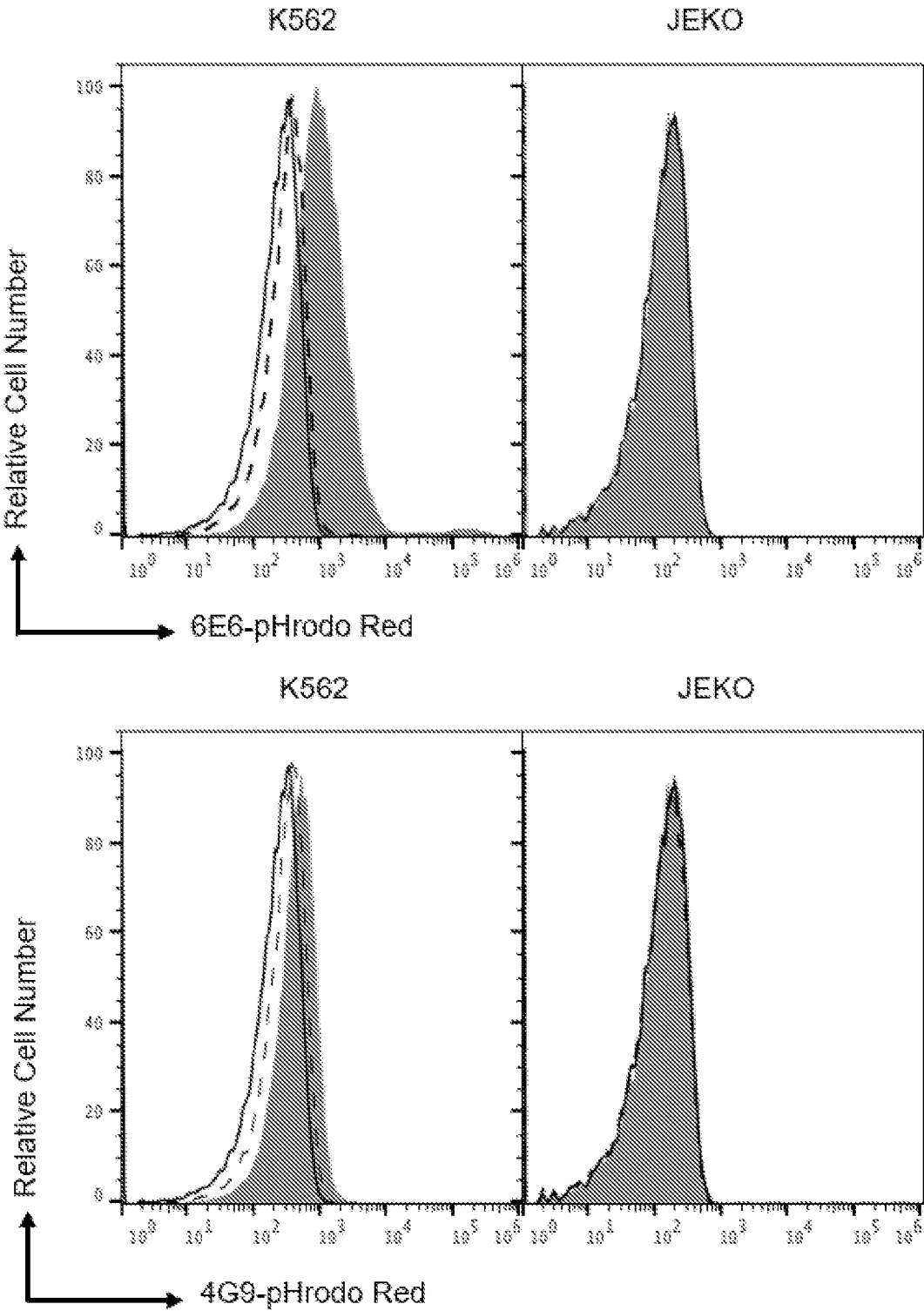


FIG. 10B

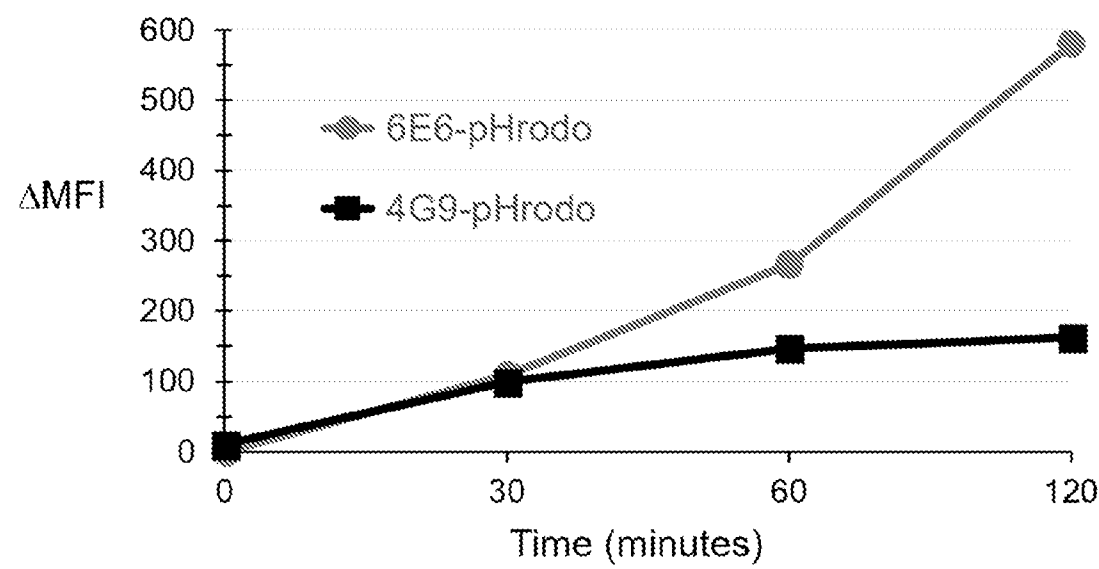


FIG. 11A

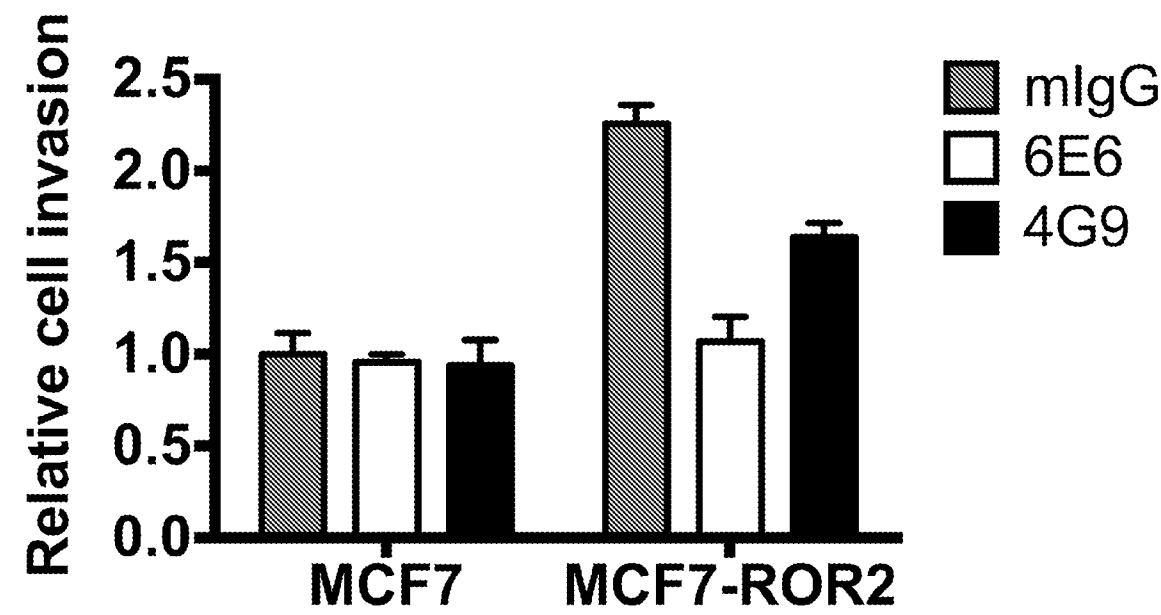


FIG. 11B

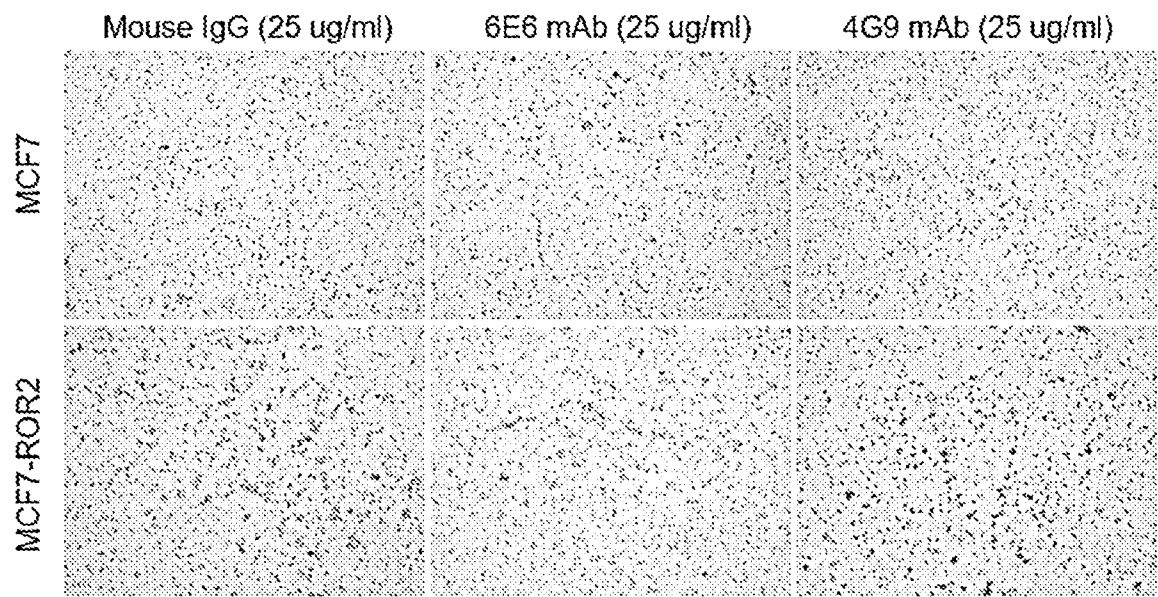
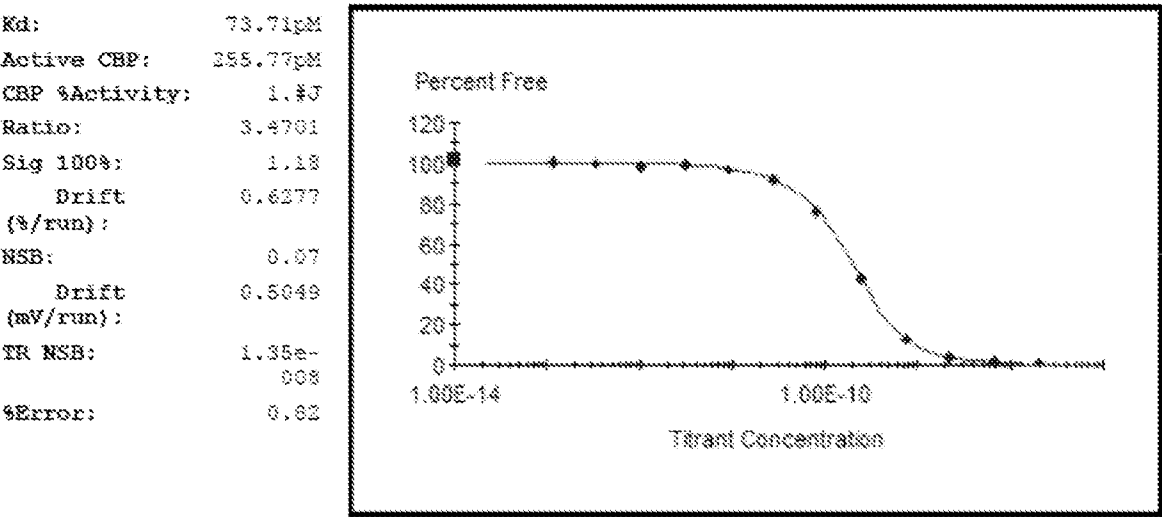


FIG. 12A



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FIG. 12B

Kd: 73.71pM
95% confidence interval
Kd High: 102.03pM
Kd Low: 58.45pM

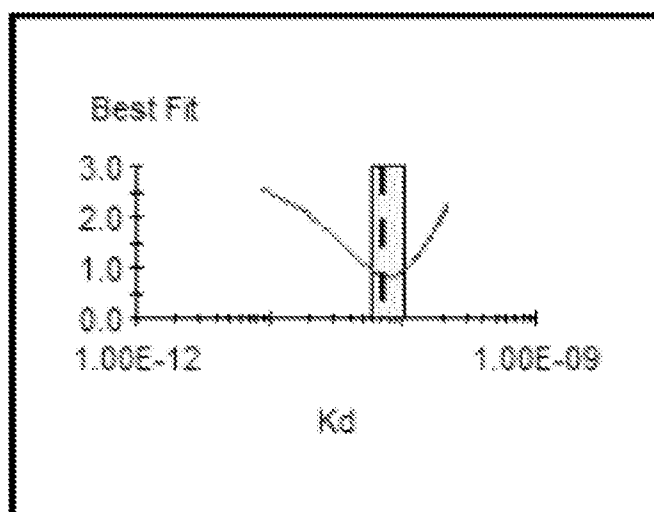
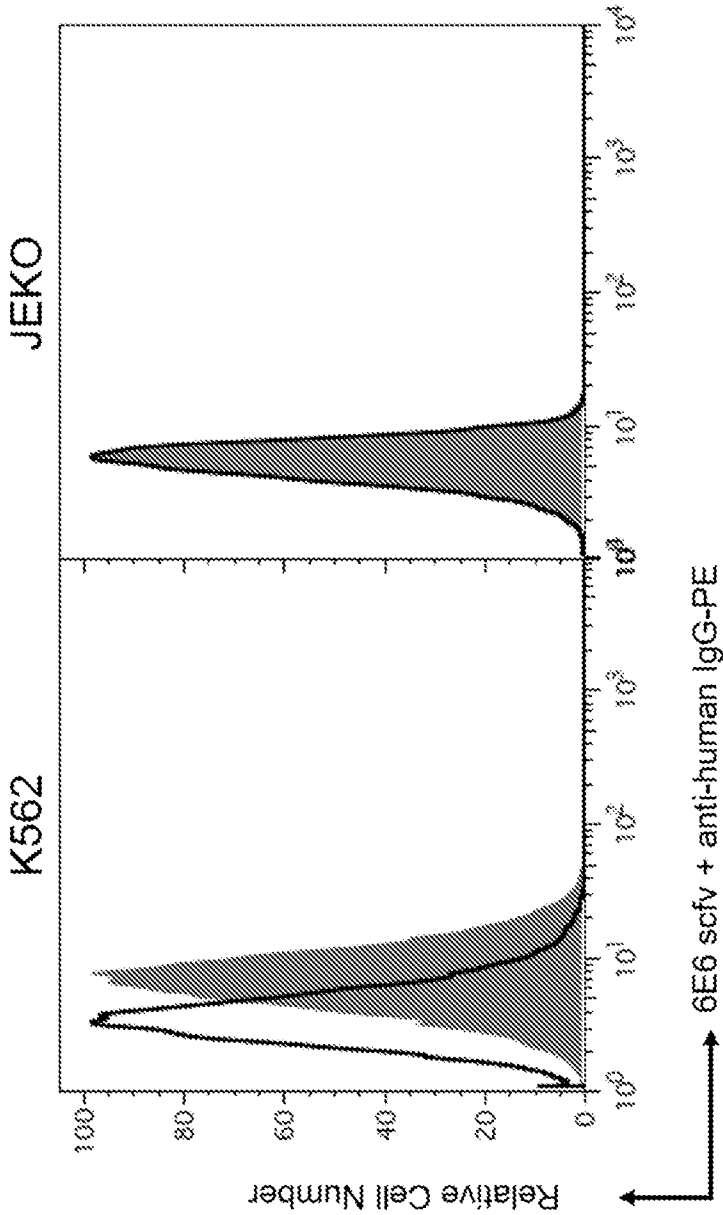


FIG. 12C



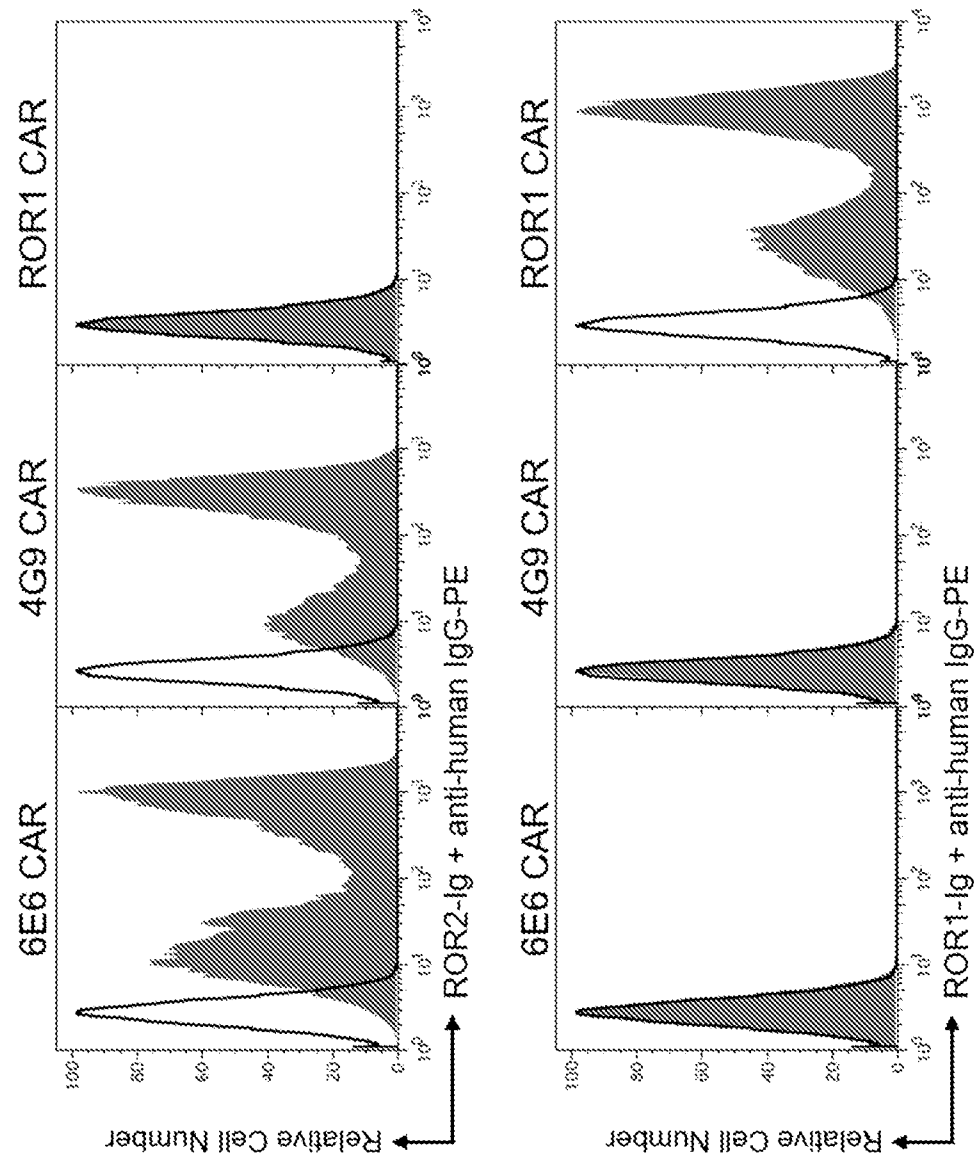


FIG. 13

SEQUENCE LISTING

<110> The Regents of the University of California

<120> Anti-ROR-2 Antibodies and Methods of Use

<130> 048537-632001W0

<150> US 62/936,900

<151> 2019-11-18

<160> 114

<170> PatentIn version 3.5

<210> 1

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<213> Artificial Sequence

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ccagacaaga ggctggagtg ggtcgcaacc attagtagtg gtggtggtta cactcactat	180
gtagacagtg tgaaggggcg attcaccatt tccagagaca atgccaacca tctcctgtac	240
ctgcaaatga gcagtctgaa ctctgaggac acagccatgt attattgtgc aagacaccgc	300
agggattttt cctatgctat ggactactgg ggtcaggga cctcagtcac cgtctcctca	360

<210> 2

<211> 120

<212> PRT

<213> Artificial Sequence

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<400> 2

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly	
1 5 10 15	
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr	
20 25 30	
Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val	
35 40 45	
Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr His Tyr Val Asp Ser Val	
50 55 60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn His Ile Leu Tyr	
65 70 75 80	
Leu Gln Met Ser Ser Leu Asn Ser Glu Asp Thr Ala Met Tyr Tyr Cys	

85

90

95

Ala Arg His Pro Arg Asp Phe Ser Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Ser Val Thr Val Ser Ser
 115 120

<210> 3
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
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 ggtcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat 180
 cgcttcacag gtagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 240
 gaagacttgg cagattatct ctgtcagcaa tataacatct atccgtggac gttcgggtgga 300
 ggctccaagc tggcaatcaa a 321

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 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 4

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Ile Gly
 1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly His Tyr
 20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
 35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
 65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Ile Tyr Pro Trp
 85 90 95

Thr Phe Gly Gly Gly Ser Lys Leu Ala Ile Lys
 100 105

<210> 5
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

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cctgtgcatg gcctggaatg gattggagct attcatccag gaagtgggtg tactgcctat 180
aatcagaagt tcaagggcaa ggccacactg actgcagaca aatcctccag cacagcctac 240
atggagctca gcaggctgac atctgaggac tctgctgtct attactgtac aagaaggagg 300
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<210> 6
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 6
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Lys Leu Ser Cys Lys Ala Leu Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45
Gly Ala Ile His Pro Gly Ser Gly Gly Thr Ala Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Thr Arg Arg Arg Pro Arg Phe Tyr Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Ser Val Thr Val Ser Ser
115

<210> 7
<211> 336
<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 7

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ttcctgcaga ggccaggcca gtctcctcag ctctgatata atcggatgtc caaccttgcc      180
tcaggagtcc cagacaggtt cagtggcagt gggtcaggaa ctgctttcac actgagaatc      240
agtagagtgg aggctgagga tgtgggtgtt tattactgta tgcaacatct agaatatcct      300
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<210> 8

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 8

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Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1           5           10          15
```

```
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
          20          25          30
```

```
Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
          35          40          45
```

```
Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
          50          55          60
```

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65          70          75          80
```

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
          85          90          95
```

```
Leu Glu Tyr Pro Leu Thr Val Gly Ala Gly Thr Lys Leu Glu Leu Lys
          100          105          110
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<210> 9

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 9

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tcctgtgcag cctctggatt cactttcagt aactatggca tgtcttgggt tcgccagact      120
```

ccagacaaga	ggctggagtg	ggtcgcaacc	attagtagtg	gtggtggttc	cacctactat	180
ccagacagtg	tgaaggggcg	attcaccatc	tccagagaca	atgccaaagaa	ctccctgtac	240
ctgcaaatga	gcagtctgaa	gtctgaggac	acagccatgt	attactgtgc	aagacatccc	300
tatgattacg	ggtactactt	tgactactgg	ggccaaggca	ccactctcac	agtctcctca	360

<210>	10
<211>	120
<212>	PRT
<213>	Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 10

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Pro Tyr Asp Tyr Gly Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210>	11
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<212>	DNA
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<220>
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ttctcctgca gggccagtc gagcattggc acaagcatac actggtatca gcagagaaca      120
aatggttctc caaggcttct cataaaatat gcttctgagt ctatctctgg gatcccttcc      180
aggtttagtg gcagtggatc agggacagat tttactctta gcatcaacag tgtggagtct      240
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gaagatattg cagattatta ctgtcaacaa agtgatagct ggccattccc gttcggctcg 300

gggacaaaat tggaaaaaaa a 321

<210> 12

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 12

Asp Ile Leu Leu Thr Gln Ser Pro Asp Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asp Ser Trp Pro Phe
85 90 95

Pro Phe Gly Ser Gly Thr Lys Leu Glu Lys Lys
100 105

<210> 13

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

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ccaggaaagg gtttggaatg ggttgctcgc ataagaagta aaagtaataa ttatgcaaca 180

tattatgccg attcagtga agacaggttc accatctcca gagatgattc acaaagcatg 240

ctccatctgc aaatgaacaa cttgaaaact gaggacacag ccatgtatta ctgtgtgaga 300

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tcctca 366

<210> 14

<211> 122

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 14

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
65 70 75 80

Leu His Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
85 90 95

Tyr Cys Val Arg His Gly Ser Ser Leu Tyr Tyr Ala Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 15
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<213> Artificial Sequence

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<223> Synthetic polynucleotide

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gatggaacta ttaaacgcct gatctacgcc gcatccactt tagattctgg tgtcccaaaa 180
aggttcagtg gcagtaggtc tgggtcagct tattctctca ccatcagcag ccttgagtct 240
gaagattttg cagactatta ctgtctacaa tatgctagtt atccgtacac gttcggaggg 300
gggaccaagc tggaataaaa a 321

<210> 16
<211> 107
<212> PRT
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<220>
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<400> 16

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Gly Trp Leu Gln Gln Lys Pro Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Ala Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 17

<211> 2832

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

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<211> 943
<212> PRT
<213> Homo sapiens

<400> 18

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Gly Glu Val Glu Val Leu Asp Pro Asn Asp Pro Leu Gly Pro Leu Asp
35 40 45

Gly Gln Asp Gly Pro Ile Pro Thr Leu Lys Gly Tyr Phe Leu Asn Phe
50 55 60

Leu Glu Pro Val Asn Asn Ile Thr Ile Val Gln Gly Gln Thr Ala Ile
65 70 75 80

Leu His Cys Lys Val Ala Gly Asn Pro Pro Pro Asn Val Arg Trp Leu
85 90 95

Lys Asn Asp Ala Pro Val Val Gln Glu Pro Arg Arg Ile Ile Ile Arg
100 105 110

Lys Thr Glu Tyr Gly Ser Arg Leu Arg Ile Gln Asp Leu Asp Thr Thr
115 120 125

Asp Thr Gly Tyr Tyr Gln Cys Val Ala Thr Asn Gly Met Lys Thr Ile
130 135 140

Thr Ala Thr Gly Val Leu Phe Val Arg Leu Gly Pro Thr His Ser Pro
145 150 155 160

Asn His Asn Phe Gln Asp Asp Tyr His Glu Asp Gly Phe Cys Gln Pro
165 170 175

Tyr Arg Gly Ile Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Ile Tyr
180 185 190

Val Asp Ser Leu Gln Met Gln Gly Glu Ile Glu Asn Arg Ile Thr Ala
195 200 205

Ala Phe Thr Met Ile Gly Thr Ser Thr His Leu Ser Asp Gln Cys Ser
210 215 220

Gln Phe Ala Ile Pro Ser Phe Cys His Phe Val Phe Pro Leu Cys Asp
225 230 235 240

Ala Arg Ser Arg Thr Pro Lys Pro Arg Glu Leu Cys Arg Asp Glu Cys
245 250 255

Glu Val Leu Glu Ser Asp Leu Cys Arg Gln Glu Tyr Thr Ile Ala Arg
260 265 270

Ser Asn Pro Leu Ile Leu Met Arg Leu Gln Leu Pro Lys Cys Glu Ala
275 280 285

Leu Pro Met Pro Glu Ser Pro Asp Ala Ala Asn Cys Met Arg Ile Gly
290 295 300

Ile Pro Ala Glu Arg Leu Gly Arg Tyr His Gln Cys Tyr Asn Gly Ser
305 310 315 320

Gly Met Asp Tyr Arg Gly Thr Ala Ser Thr Thr Lys Ser Gly His Gln
325 330 335

Cys Gln Pro Trp Ala Leu Gln His Pro His Ser His His Leu Ser Ser
340 345 350

Thr Asp Phe Pro Glu Leu Gly Gly Gly His Ala Tyr Cys Arg Asn Pro
355 360 365

Gly Gly Gln Met Glu Gly Pro Trp Cys Phe Thr Gln Asn Lys Asn Val
370 375 380

Arg Met Glu Leu Cys Asp Val Pro Ser Cys Ser Pro Arg Asp Ser Ser
385 390 395 400

Lys Met Gly Ile Leu Tyr Ile Leu Val Pro Ser Ile Ala Ile Pro Leu
405 410 415

Val Ile Ala Cys Leu Phe Phe Leu Val Cys Met Cys Arg Asn Lys Gln
420 425 430

Lys Ala Ser Ala Ser Thr Pro Gln Arg Arg Gln Leu Met Ala Ser Pro
435 440 445

Ser Gln Asp Met Glu Met Pro Leu Ile Asn Gln His Lys Gln Ala Lys
450 455 460

Leu Lys Glu Ile Ser Leu Ser Ala Val Arg Phe Met Glu Glu Leu Gly
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Glu Asp Arg Phe Gly Lys Val Tyr Lys Gly His Leu Phe Gly Pro Ala
485 490 495

Pro Gly Glu Gln Thr Gln Ala Val Ala Ile Lys Thr Leu Lys Asp Lys
500 505 510

Ala Glu Gly Pro Leu Arg Glu Glu Phe Arg His Glu Ala Met Leu Arg
515 520 525

Ala Arg Leu Gln His Pro Asn Val Val Cys Leu Leu Gly Val Val Thr
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Lys Asp Gln Pro Leu Ser Met Ile Phe Ser Tyr Cys Ser His Gly Asp
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Leu His Glu Phe Leu Val Met Arg Ser Pro His Ser Asp Val Gly Ser
565 570 575

Thr Asp Asp Asp Arg Thr Val Lys Ser Ala Leu Glu Pro Pro Asp Phe
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Val His Leu Val Ala Gln Ile Ala Ala Gly Met Glu Tyr Leu Ser Ser
595 600 605

His His Val Val His Lys Asp Leu Ala Thr Arg Asn Val Leu Val Tyr
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Asp Lys Leu Asn Val Lys Ile Ser Asp Leu Gly Leu Phe Arg Glu Val
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Tyr Ala Ala Asp Tyr Tyr Lys Leu Leu Gly Asn Ser Leu Leu Pro Ile
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Arg Trp Met Ala Pro Glu Ala Ile Met Tyr Gly Lys Phe Ser Ile Asp
660 665 670

Ser Asp Ile Trp Ser Tyr Gly Val Val Leu Trp Glu Val Phe Ser Tyr
675 680 685

Gly Leu Gln Pro Tyr Cys Gly Tyr Ser Asn Gln Asp Val Val Glu Met
690 695 700

Ile Arg Asn Arg Gln Val Leu Pro Cys Pro Asp Asp Cys Pro Ala Trp
705 710 715 720

Val Tyr Ala Leu Met Ile Glu Cys Trp Asn Glu Phe Pro Ser Arg Arg
725 730 735

Pro Arg Phe Lys Asp Ile His Ser Arg Leu Arg Ala Trp Gly Asn Leu
740 745 750

Ser Asn Tyr Asn Ser Ser Ala Gln Thr Ser Gly Ala Ser Asn Thr Thr
755 760 765

Gln Thr Ser Ser Leu Ser Thr Ser Pro Val Ser Asn Val Ser Asn Ala
770 775 780

Arg Tyr Val Gly Pro Lys Gln Lys Ala Pro Pro Phe Pro Gln Pro Gln
785 790 795 800

Phe Ile Pro Met Lys Gly Gln Ile Arg Pro Met Val Pro Pro Pro Gln

805

810

815

Leu Tyr Val Pro Val Asn Gly Tyr Gln Pro Val Pro Ala Tyr Gly Ala
820 825 830

Tyr Leu Pro Asn Phe Tyr Pro Val Gln Ile Pro Met Gln Met Ala Pro
835 840 845

Gln Gln Val Pro Pro Gln Met Val Pro Lys Pro Ser Ser His His Ser
850 855 860

Gly Ser Gly Ser Thr Ser Thr Gly Tyr Val Thr Thr Ala Pro Ser Asn
865 870 875 880

Thr Ser Met Ala Asp Arg Ala Ala Leu Leu Ser Glu Gly Ala Asp Asp
885 890 895

Thr Gln Asn Ala Pro Glu Asp Gly Ala Gln Ser Thr Val Gln Glu Ala
900 905 910

Glu Glu Glu Glu Glu Gly Ser Val Pro Glu Thr Glu Leu Leu Gly Asp
915 920 925

Cys Asp Thr Leu Gln Val Asp Glu Ala Gln Val Gln Leu Glu Ala
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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

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<212> PRT
<213> Mus musculus

<400> 20

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Gly Glu Val Glu Asp Ser Glu Ala Ile Asp Thr Leu Gly Gln Pro Asp
35 40 45

Gly Pro Asp Ser Pro Leu Pro Thr Leu Lys Gly Tyr Phe Leu Asn Phe
50 55 60

Leu Glu Pro Val Asn Asn Ile Thr Ile Val Gln Gly Gln Thr Ala Ile
65 70 75 80

Leu His Cys Lys Val Ala Gly Asn Pro Pro Pro Asn Val Arg Trp Leu
85 90 95

Lys Asn Asp Ala Pro Val Val Gln Glu Pro Arg Arg Val Val Ile Arg
100 105 110

Lys Thr Glu Tyr Gly Ser Arg Leu Arg Ile Gln Asp Leu Asp Thr Thr
115 120 125

Asp Thr Gly Tyr Tyr Gln Cys Val Ala Thr Asn Gly Leu Lys Thr Ile
130 135 140

Thr Ala Thr Gly Val Leu Tyr Val Arg Leu Gly Pro Thr His Ser Pro
145 150 155 160

Asn His Asn Phe Gln Asp Asp Asp Gln Glu Asp Gly Phe Cys Gln Pro
165 170 175

Tyr Arg Gly Ile Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Ile Tyr
180 185 190

Val Asp Ser Leu Gln Met Gln Gly Glu Ile Glu Asn Arg Ile Thr Ala
195 200 205

Ala Phe Thr Met Ile Gly Thr Ser Thr Gln Leu Ser Asp Gln Cys Ser
210 215 220

Gln Phe Ala Ile Pro Ser Phe Cys His Phe Val Phe Pro Leu Cys Asp
225 230 235 240

Ala Cys Ser Arg Ala Pro Lys Pro Arg Glu Leu Cys Arg Asp Glu Cys
245 250 255

Glu Val Leu Glu Asn Asp Leu Cys Arg Gln Glu Tyr Thr Ile Ala Arg
260 265 270

Ser Asn Pro Leu Ile Leu Met Arg Leu Gln Leu Pro Lys Cys Glu Ala
275 280 285

Leu Pro Met Pro Glu Ser Pro Asp Ala Ala Asn Cys Met Arg Ile Gly
290 295 300

Ile Pro Ala Glu Arg Leu Gly Arg Tyr His Gln Cys Tyr Asn Gly Ser
305 310 315 320

Gly Ala Asp Tyr Arg Gly Met Ala Ser Thr Thr Lys Ser Gly His Gln
325 330 335

Cys Gln Pro Trp Ala Leu Gln His Pro His Ser His Arg Leu Ser Ser
340 345 350

Thr Glu Phe Pro Glu Leu Gly Gly Gly His Ala Tyr Cys Arg Asn Pro
355 360 365

Gly Gly Gln Met Glu Gly Pro Trp Cys Phe Thr Gln Asn Lys Asn Val
370 375 380

Arg Val Glu Leu Cys Asp Val Pro Pro Cys Ser Pro Arg Tyr Gly Ser
385 390 395 400

Lys Met Gly Ile Leu Tyr Ile Leu Val Pro Ser Ile Ala Ile Pro Leu
405 410 415

Val Ile Ala Cys Leu Phe Phe Leu Val Cys Met Cys Arg Asn Lys Gln
420 425 430

Lys Ala Ser Ala Ser Thr Pro Gln Arg Arg Gln Leu Met Ala Ser Pro
435 440 445

Ser Gln Asp Met Glu Met Pro Leu Ile Ser Gln His Lys Gln Ala Lys
450 455 460

Leu Lys Glu Ile Ser Leu Ser Thr Val Arg Phe Met Glu Glu Leu Gly
465 470 475 480

Glu Asp Arg Phe Gly Lys Val Tyr Lys Gly His Leu Phe Gly Pro Ala
485 490 495

Pro Gly Glu Pro Thr Gln Ala Val Ala Ile Lys Thr Leu Lys Asp Lys
500 505 510

Ala Glu Gly Pro Leu Arg Glu Glu Phe Arg Gln Glu Ala Met Leu Arg
515 520 525

Ala Arg Leu Gln His Pro Asn Ile Val Cys Leu Leu Gly Val Val Thr
530 535 540

Lys Asp Gln Pro Leu Ser Met Ile Phe Ser Tyr Cys Ser His Gly Asp
545 550 555 560

Leu His Glu Phe Leu Val Met Arg Ser Pro His Ser Asp Val Gly Ser
565 570 575

Thr Asp Asp Asp Arg Thr Val Lys Ser Ala Leu Glu Pro Pro Asp Phe
580 585 590

Val His Val Val Ala Gln Ile Ala Ala Gly Met Glu Phe Leu Ser Ser
595 600 605

His His Val Cys His Lys Asp Leu Ala Thr Arg Asn Val Leu Val Tyr
610 615 620

Asp Lys Leu Asn Val Arg Ile Ser Asp Leu Gly Leu Phe Arg Glu Val
625 630 635 640

Tyr Ser Ala Asp Tyr Tyr Lys Leu Met Gly Asn Ser Leu Leu Pro Ile
645 650 655

Arg Trp Met Ser Pro Glu Ala Val Met Tyr Gly Lys Phe Ser Ile Asp
660 665 670

Ser Asp Ile Trp Ser Tyr Gly Val Val Leu Trp Glu Val Phe Ser Tyr
675 680 685

Gly Leu Gln Pro Tyr Cys Gly Tyr Ser Asn Gln Asp Val Val Glu Met
690 695 700

Ile Arg Ser Arg Gln Val Leu Pro Cys Pro Asp Asp Cys Pro Ala Trp
705 710 715 720

Val Tyr Ala Leu Met Ile Glu Cys Trp Asn Glu Phe Pro Ser Arg Arg
725 730 735

Pro Arg Phe Lys Asp Ile His Ser Arg Leu Arg Ser Trp Gly Asn Leu
740 745 750

Ser Asn Tyr Asn Ser Ser Ala Gln Thr Ser Gly Ala Ser Asn Thr Thr
755 760 765

Gln Thr Ser Ser Leu Ser Thr Ser Pro Val Ser Asn Val Ser Asn Ala
770 775 780

Arg Tyr Met Ala Pro Lys Gln Lys Ala Gln Pro Phe Pro Gln Pro Gln

785	790	795	800
Phe Ile Pro Met Lys Gly Gln Ile Arg Pro Leu Val Pro Pro Ala Gln			
805	810	815	
Leu Tyr Ile Pro Val Asn Gly Tyr Gln Pro Val Pro Ala Tyr Gly Ala			
820	825	830	
Tyr Leu Pro Asn Phe Tyr Pro Val Gln Ile Pro Met Gln Met Ala Pro			
835	840	845	
Gln Gln Val Pro Pro Gln Met Val Pro Lys Pro Ser Ser His His Ser			
850	855	860	
Gly Ser Gly Ser Thr Ser Thr Gly Tyr Val Thr Thr Ala Pro Ser Asn			
865	870	875	880
Thr Ser Val Ala Asp Arg Ala Ala Leu Leu Ser Glu Gly Thr Glu Asp			
885	890	895	
Val Gln Asn Ile Ala Glu Asp Val Ala Gln Ser Pro Val Gln Glu Ala			
900	905	910	
Glu Glu Glu Glu Glu Gly Ser Val Pro Glu Thr Glu Leu Leu Gly Asp			
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Asn Asp Thr Leu Gln Val Thr Glu Ala Ala His Val Gln Leu Glu Ala			
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 <212> DNA
 <213> Artificial Sequence

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aacgaccctt taggaccctt tgatgggcag gacggcccga ttccaactct gaaaggttac	180
tttctgaatt ttctggagcc agtaaacaat atcaccattg tccaaggcca gacggcaatt	240
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cgaatccagg acctggacac gacagacact ggctactacc agtgcgtggc caccaacggg	420
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gagattgaaa accgaatcac agcggccttc accatgatcg gcacgtctac gcacctgtcg	660

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gcgcgctccc	gggcacccaa	gccgcgtgag	ctgtgccgcg	acgagtgcga	ggtgctggag	780
agcgacctgt	gccgccagga	gtacaccatc	gcccgctcca	accgctcat	cctcatgcgg	840
cttcagctgc	ccaagtgtga	ggcgctgccc	atgcctgaga	gccccgacgc	tgccaactgc	900
atgcgcattg	gcatcccagc	cgagaggctg	ggccgctacc	atcagtgcta	taacggctca	960
ggcatggatt	acagaggaac	ggcaagcacc	accaagtcag	gccaccagtg	ccagccgtgg	1020
gccctgcagc	acccccacag	ccaccacctg	tccagcacag	acttcctga	gcttgaggagg	1080
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aagatgggg						1209

<210> 22
 <211> 403
 <212> PRT
 <213> Homo sapiens

<400> 22

Met	Ala	Arg	Gly	Ser	Ala	Leu	Pro	Arg	Arg	Pro	Leu	Leu	Cys	Ile	Pro
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Ala	Val	Trp	Ala	Ala	Ala	Ala	Leu	Leu	Leu	Ser	Val	Ser	Arg	Thr	Ser
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Gly	Glu	Val	Glu	Val	Leu	Asp	Pro	Asn	Asp	Pro	Leu	Gly	Pro	Leu	Asp
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Gly	Gln	Asp	Gly	Pro	Ile	Pro	Thr	Leu	Lys	Gly	Tyr	Phe	Leu	Asn	Phe
	50					55					60				

Leu	Glu	Pro	Val	Asn	Asn	Ile	Thr	Ile	Val	Gln	Gly	Gln	Thr	Ala	Ile
65					70					75					80

Leu	His	Cys	Lys	Val	Ala	Gly	Asn	Pro	Pro	Pro	Asn	Val	Arg	Trp	Leu
				85					90					95	

Lys	Asn	Asp	Ala	Pro	Val	Val	Gln	Glu	Pro	Arg	Arg	Ile	Ile	Ile	Arg
			100					105					110		

Lys	Thr	Glu	Tyr	Gly	Ser	Arg	Leu	Arg	Ile	Gln	Asp	Leu	Asp	Thr	Thr
		115					120					125			

Asp	Thr	Gly	Tyr	Tyr	Gln	Cys	Val	Ala	Thr	Asn	Gly	Met	Lys	Thr	Ile
	130					135					140				

Thr	Ala	Thr	Gly	Val	Leu	Phe	Val	Arg	Leu	Gly	Pro	Thr	His	Ser	Pro
145					150					155					160

Asn His Asn Phe Gln Asp Asp Tyr His Glu Asp Gly Phe Cys Gln Pro
165 170 175

Tyr Arg Gly Ile Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Ile Tyr
180 185 190

Val Asp Ser Leu Gln Met Gln Gly Glu Ile Glu Asn Arg Ile Thr Ala
195 200 205

Ala Phe Thr Met Ile Gly Thr Ser Thr His Leu Ser Asp Gln Cys Ser
210 215 220

Gln Phe Ala Ile Pro Ser Phe Cys His Phe Val Phe Pro Leu Cys Asp
225 230 235 240

Ala Arg Ser Arg Thr Pro Lys Pro Arg Glu Leu Cys Arg Asp Glu Cys
245 250 255

Glu Val Leu Glu Ser Asp Leu Cys Arg Gln Glu Tyr Thr Ile Ala Arg
260 265 270

Ser Asn Pro Leu Ile Leu Met Arg Leu Gln Leu Pro Lys Cys Glu Ala
275 280 285

Leu Pro Met Pro Glu Ser Pro Asp Ala Ala Asn Cys Met Arg Ile Gly
290 295 300

Ile Pro Ala Glu Arg Leu Gly Arg Tyr His Gln Cys Tyr Asn Gly Ser
305 310 315 320

Gly Met Asp Tyr Arg Gly Thr Ala Ser Thr Thr Lys Ser Gly His Gln
325 330 335

Cys Gln Pro Trp Ala Leu Gln His Pro His Ser His His Leu Ser Ser
340 345 350

Thr Asp Phe Pro Glu Leu Gly Gly Gly His Ala Tyr Cys Arg Asn Pro
355 360 365

Gly Gly Gln Met Glu Gly Pro Trp Cys Phe Thr Gln Asn Lys Asn Val
370 375 380

Arg Met Glu Leu Cys Asp Val Pro Ser Cys Ser Pro Arg Asp Ser Ser
385 390 395 400

Lys Met Gly

<210> 23
<211> 1209
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 23

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atcgacacct tgggacaacc tgatggaccg gacagcccac ttcccactct gaaaggctac      180
tttctgaatt ttctggagcc agtcaacaat atcaccattg ttcagggccca gacggcaatc      240
ctgcactgca aggtggcggg aaaccacact cccaatgtgc ggtggctgaa gaatgatgcc      300
ccggttgtgc aagagccacg aagggtcgtc atccggaaga cagaatacgg ctcccggctg      360
cggatccaag acctggacac aacagacaca ggctactacc agtgtgtggc taccaacggg      420
ctgaagacca tctactccac tggggttcta tatgtcggc tcggtccgac gcacagcccg      480
aaccacaatt ttcaggatga cgatcaggaa gatggcttct gccagccgta ccgagggatc      540
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gaccagtgtt cacagtttgc catcccatcc ttctgccact tcgtcttccc tctgtgcgac      720
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ctccagctgc ccaagtgcga agcgtgccc atgcccgaga gcccggatgc tgcgaactgc      900
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ggcgcggatt acagggggat ggccagtacc accaagtcag gccaccagtg tcagccttgg     1020
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ggccatgcct actgccgaa ccccgggggc cagatggaag gcccgtggtg ctttacgcag     1140
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<210> 24

<211> 403

<212> PRT

<213> Mus musculus

<400> 24

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1           5           10          15
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Ala Val Trp Thr Ala Ala Ala Leu Leu Leu Trp Thr Pro Trp Thr Ala
          20           25           30
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Gly Glu Val Glu Asp Ser Glu Ala Ile Asp Thr Leu Gly Gln Pro Asp
          35           40           45
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Gly Pro Asp Ser Pro Leu Pro Thr Leu Lys Gly Tyr Phe Leu Asn Phe
          50           55           60
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Leu Glu Pro Val Asn Asn Ile Thr Ile Val Gln Gly Gln Thr Ala Ile
65 70 75 80

Leu His Cys Lys Val Ala Gly Asn Pro Pro Pro Asn Val Arg Trp Leu
85 90 95

Lys Asn Asp Ala Pro Val Val Gln Glu Pro Arg Arg Val Val Ile Arg
100 105 110

Lys Thr Glu Tyr Gly Ser Arg Leu Arg Ile Gln Asp Leu Asp Thr Thr
115 120 125

Asp Thr Gly Tyr Tyr Gln Cys Val Ala Thr Asn Gly Leu Lys Thr Ile
130 135 140

Thr Ala Thr Gly Val Leu Tyr Val Arg Leu Gly Pro Thr His Ser Pro
145 150 155 160

Asn His Asn Phe Gln Asp Asp Asp Gln Glu Asp Gly Phe Cys Gln Pro
165 170 175

Tyr Arg Gly Ile Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Ile Tyr
180 185 190

Val Asp Ser Leu Gln Met Gln Gly Glu Ile Glu Asn Arg Ile Thr Ala
195 200 205

Ala Phe Thr Met Ile Gly Thr Ser Thr Gln Leu Ser Asp Gln Cys Ser
210 215 220

Gln Phe Ala Ile Pro Ser Phe Cys His Phe Val Phe Pro Leu Cys Asp
225 230 235 240

Ala Cys Ser Arg Ala Pro Lys Pro Arg Glu Leu Cys Arg Asp Glu Cys
245 250 255

Glu Val Leu Glu Asn Asp Leu Cys Arg Gln Glu Tyr Thr Ile Ala Arg
260 265 270

Ser Asn Pro Leu Ile Leu Met Arg Leu Gln Leu Pro Lys Cys Glu Ala
275 280 285

Leu Pro Met Pro Glu Ser Pro Asp Ala Ala Asn Cys Met Arg Ile Gly
290 295 300

Ile Pro Ala Glu Arg Leu Gly Arg Tyr His Gln Cys Tyr Asn Gly Ser
305 310 315 320

Gly Ala Asp Tyr Arg Gly Met Ala Ser Thr Thr Lys Ser Gly His Gln
325 330 335

Cys Gln Pro Trp Ala Leu Gln His Pro His Ser His Arg Leu Ser Ser
340 345 350

Thr Glu Phe Pro Glu Leu Gly Gly Gly His Ala Tyr Cys Arg Asn Pro
355 360 365

Gly Gly Gln Met Glu Gly Pro Trp Cys Phe Thr Gln Asn Lys Asn Val
370 375 380

Arg Val Glu Leu Cys Asp Val Pro Pro Cys Ser Pro Arg Tyr Gly Ser
385 390 395 400

Lys Met Gly

<210> 25
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 25

Gly Phe Thr Phe Ser Asn Tyr Gly
1 5

<210> 26
<211> 8
<212> PRT
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<220>
<223> Synthetic polypeptide

<400> 26

Ile Ser Ser Gly Gly Gly Tyr Thr
1 5

<210> 27
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 27

His Pro Arg Asp Phe Ser Tyr Ala Met Asp Tyr
1 5 10

<210> 28
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 28

Gln Asp Val Gly His Tyr
1 5

<210> 29

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 29

Trp Ala Ser
1

<210> 30

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 30

Gln Gln Tyr Asn Ile Tyr Pro Trp Thr
1 5

<210> 31

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 31

Gly Tyr Thr Phe Thr Asp Tyr Glu
1 5

<210> 32

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 32

Ile His Pro Gly Ser Gly Gly Thr
1 5

<210> 33

<211> 10

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<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 33

Arg Arg Pro Arg Phe Tyr Gly Met Asp Tyr
1 5 10

<210> 34

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 34

Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 35

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 35

Arg Met Ser
1

<210> 36

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 36

Met Gln His Leu Glu Tyr Pro Leu Thr
1 5

<210> 37

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 37

Gly Phe Thr Phe Ser Asn Tyr Gly
1 5

<210> 38

<211> 8

<212> PRT

<213> Artificial Sequence

<220>
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<400> 38

Ile Ser Ser Gly Gly Gly Ser Thr
1 5

<210> 39
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 39

His Pro Tyr Asp Tyr Gly Tyr Tyr Phe Asp Tyr
1 5 10

<210> 40
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 40

Gln Ser Ile Gly Thr Ser
1 5

<210> 41
<211> 3
<212> PRT
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<220>
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<400> 41

Tyr Ala Ser
1

<210> 42
<211> 9
<212> PRT
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<400> 42

Gln Gln Ser Asp Ser Trp Pro Phe Pro
1 5

<210> 43
<211> 8
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<220>
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<400> 43

Gly Phe Thr Phe Asn Thr Tyr Ala
1 5

<210> 44
<211> 10
<212> PRT
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<220>
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<400> 44

Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr
1 5 10

<210> 45
<211> 11
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<400> 45

His Gly Ser Ser Leu Tyr Tyr Ala Met Asp Tyr
1 5 10

<210> 46
<211> 6
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<400> 46

Gln Glu Ile Ser Gly Tyr
1 5

<210> 47
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<400> 47

Ala Ala Ser
1

<210> 48
<211> 9
<212> PRT

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<223> Synthetic polypeptide

<400> 48

Leu Gln Tyr Ala Ser Tyr Pro Tyr Thr
1 5

<210> 49

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 49

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser
20 25

<210> 50

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 50

Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val Ala
1 5 10 15

Thr

<210> 51

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 51

His Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Asn His Ile Leu Tyr Leu Gln Met Ser Ser Leu Asn Ser Glu Asp
20 25 30

Thr Ala Met Tyr Tyr Cys Ala Arg
35 40

<210> 52
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 52

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> 53
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 53

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Ile Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser
20 25

<210> 54
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 54

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
1 5 10 15

Tyr

<210> 55
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 55

Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
1 5 10 15

Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala
20 25 30

Asp Tyr Phe Cys

<210> 56
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 56

Phe Gly Gly Gly Ser Lys Leu Ala Ile Lys
 1 5 10

<210> 57
 <211> 25
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 57

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Leu
 20 25

<210> 58
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 58

Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile Gly
 1 5 10 15

Ala

<210> 59
 <211> 40
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 59

Ala Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
 1 5 10 15

Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp
 20 25 30

Ser Ala Val Tyr Tyr Cys Thr Arg
35 40

<210> 60
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 60

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> 61
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 61

Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser
20 25

<210> 62
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 62

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile
1 5 10 15

Tyr

<210> 63
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 63

Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
1 5 10 15

Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly
20 25 30

Val Tyr Tyr Cys
35

<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 64

Val Gly Ala Gly Thr Lys Leu Glu Leu Lys
1 5 10

<210> 65
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 65

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser
20 25

<210> 66
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 66

Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val Ala
1 5 10 15

Thr

<210> 67
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 67

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp
20 25 30

Thr Ala Met Tyr Tyr Cys Ala Arg
35 40

<210> 68
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 68

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
1 5 10

<210> 69
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 69

Asp Ile Leu Leu Thr Gln Ser Pro Asp Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser
20 25

<210> 70
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 70

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
1 5 10 15

Lys

<210> 71
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 71

Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
1 5 10 15

Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala
20 25 30

Asp Tyr Tyr Cys
35

<210> 72

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 72

Phe Gly Ser Gly Thr Lys Leu Glu Lys Lys
1 5 10

<210> 73

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 73

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser
20 25

<210> 74

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 74

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1 5 10 15

Arg

<210> 75

<211> 40

<212> PRT

<213> Artificial Sequence

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<223> Synthetic polypeptide

<400> 75

Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp
1 5 10 15

Ser Gln Ser Met Leu His Leu Gln Met Asn Asn Leu Lys Thr Glu Asp
20 25 30

Thr Ala Met Tyr Tyr Cys Val Arg
35 40

<210> 76

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> SEQ ID NO:77

<400> 76

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> 77

<211> 26

<212> PRT

<213> Artificial Sequence

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<223> Synthetic polypeptide

<400> 77

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Thr Cys Arg Ala Ser
20 25

<210> 78

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 78

Leu Gly Trp Leu Gln Gln Lys Pro Asp Gly Thr Ile Lys Arg Leu Ile
1 5 10 15

Tyr

<210> 79

<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 79

Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly Ser Arg Ser Gly
1 5 10 15

Ser Ala Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala
20 25 30

Asp Tyr Tyr Cys
35

<210> 80
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 80

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 81
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 81

Ala Thr Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala
1 5 10 15

Thr Gly Val His Ser
20

<210> 82
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 82

Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

<210> 83
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 83

Glu Phe
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<210> 84
<211> 206
<212> PRT
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<220>
<223> Synthetic polypeptide

<400> 84

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
1 5 10 15

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
20 25 30

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
35 40 45

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
50 55 60

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
65 70 75 80

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
85 90 95

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
100 105 110

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
115 120 125

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
130 135 140

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
145 150 155 160

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Glu Ser Arg Trp
165 170 175

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
180 185 190

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
195 200 205

<210> 85

<211> 474

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 85

Ala Thr Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala
1 5 10 15

Thr Gly Val His Ser Asp Ile Val Met Thr Gln Ser His Lys Phe Met
20 25 30

Ser Thr Ser Ile Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln
35 40 45

Asp Val Gly His Tyr Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser
50 55 60

Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro
65 70 75 80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr
100 105 110

Asn Ile Tyr Pro Trp Thr Phe Gly Gly Gly Ser Lys Leu Ala Ile Lys
115 120 125

Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
130 135 140

Lys Gly Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro
145 150 155 160

Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
165 170 175

Asn Tyr Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu
180 185 190

Trp Val Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr His Tyr Val Asp
195 200 205

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn His Ile
 210 215 220

Leu Tyr Leu Gln Met Ser Ser Leu Asn Ser Glu Asp Thr Ala Met Tyr
 225 230 235 240

Tyr Cys Ala Arg His Pro Arg Asp Phe Ser Tyr Ala Met Asp Tyr Trp
 245 250 255

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Phe Leu Phe Pro Pro
 260 265 270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 275 280 285

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 290 295 300

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 305 310 315 320

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 325 330 335

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 340 345 350

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 355 360 365

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 370 375 380

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 385 390 395 400

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 405 410 415

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 420 425 430

Leu Tyr Ser Lys Leu Thr Val Asp Glu Ser Arg Trp Gln Gln Gly Asn
 435 440 445

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 450 455 460

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 465 470

<210> 86
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 86

Ala Thr Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala
1 5 10 15

Thr Gly Val His Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val
20 25 30

Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys
35 40 45

Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln
50 55 60

Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu
65 70 75 80

Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala
85 90 95

Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
100 105 110

Tyr Cys Met Gln His Leu Glu Tyr Pro Leu Thr Val Gly Ala Gly Thr
115 120 125

Lys Leu Glu Leu Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser
130 135 140

Gly Glu Gly Ser Thr Lys Gly Gln Val Gln Leu Gln Gln Ser Gly Ala
145 150 155 160

Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Leu
165 170 175

Gly Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro
180 185 190

Val His Gly Leu Glu Trp Ile Gly Ala Ile His Pro Gly Ser Gly Gly
195 200 205

Thr Ala Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
210 215 220

Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu
225 230 235 240

Asp Ser Ala Val Tyr Tyr Cys Thr Arg Arg Arg Pro Arg Phe Tyr Gly
 245 250 255
 Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Phe
 260 265 270
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 275 280 285
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 290 295 300
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 305 310 315 320
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 325 330 335
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 340 345 350
 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 355 360 365
 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 370 375 380
 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 385 390 395 400
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 405 410 415
 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 420 425 430
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Glu Ser Arg Trp
 435 440 445
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 450 455 460
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 465 470 475

<210> 87

<211> 63

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 87
gccaccatgg gatggtcacg tatcatcctt tttctagtag caactgcaac cgggtgtacat 60
tcc 63

<210> 88
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 88
ggctccacct ctggatccgg caagcccgga tctggcgagg gatccaccaa gggc 54

<210> 89
<211> 6
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 89
gaattc 6

<210> 90
<211> 621
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 90
ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc 60
gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 120
gtggagggtgc ataatgcca gacaaagccg cgggaggagc agtacaacag cacgtaccgt 180
gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 240
aaggtctcca acaaagccct ccagcccc atcgagaaaa ccatctcaa agccaaaggg 300
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 360
caggctcagc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 420
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 480
ggctccttct tcctctatag caagctcacc gtggacgaga gcaggtggca gcaggggaac 540
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 600
tccctgtctc cgggtaaatg a 621

<210> 91
<211> 1425
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 91

gccaccatgg gatggtcattg tatcatcctt tttctagtag caactgcaac cgggtgtacat	60
tccgacattg tgatgaccca gtctcacaaa ttcattgtcca catcaatagg agacagggtc	120
agcatcacct gcaaggccag tcaggatgtg ggctcattatg tggcctggta tcaacagaaa	180
ccagggtcaat ctctaaact actgatttac tgggcatcca cccggcacac tggagtccct	240
gatcgcttca caggtagtgg atctgggaca gatttcactc tcaccattag caatgtgcag	300
tctgaagact tggcagatta tttctgtcag caatataaca tctatccgtg gacgttcggt	360
ggaggctcca agctggcaat caaaggctcc acctctggat ccggcaagcc cggatctggc	420
gagggatcta ccaagggcga ggtgcagctg gtggagtctg ggggagactt agtgaagcct	480
ggagggtccc tgaactctc ctgtgcagcc tctggattca ctttcagtaa ttatggcatg	540
tcttgggttc gccagactcc agacaagagg ctggagtggg tcgcaaccat tagtagtggt	600
ggtggttaca ctactatgt agacagtgtg aaggggcgat tcaccatttc cagagacaat	660
gccaaccata tcctgtacct gcaaatgagc agtctgaact ctgaggacac agccatgtat	720
tattgtgcaa gacacccgag ggatttttcc tatgctatgg actactgggg tcagggaacc	780
tcagtcaccg tctcctcaga attcctcttc cccccaaac ccaaggacac cctcatgac	840
tcccggaccc ctgaggctcac atgcgtgggtg gtggacgtga gccacgaaga ccctgaggtc	900
aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag	960
gagcagtaca acagcacgta ccgtgtgggtc agcgtcctca ccgtcctgca ccaggactgg	1020
ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc ccccatcgag	1080
aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca	1140
tcccgggagg agatgaccaa gaaccagggtc agcctgacct gcctgggtcaa aggcttctat	1200
cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc	1260
acgcctcccg tgctggactc cgacggctcc ttcttctct atagcaagct caccgtggac	1320
gagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac	1380
aaccactaca cgagaagag cctctccctg tctccgggta aatga	1425

<210> 92

<211> 1437

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 92

gccaccatgg gatggtcattg tatcatcctt tttctagtag caactgcaac cgggtgtacat	60
tccgatattg tgatgactca ggctgcaccc tctgtacctg tctctcctgg agagtcagta	120
tccatctcct gcaggcttag taagagtctc ctgcatagta atggcaacac ttacttgtat	180
tggttcctgc agaggccagg ccagtctcct cagctcctga tatatcggt gtccaacctt	240

gcctcaggag tcccagacag gttcagtggc agtgggtcag gaactgcttt cacactgaga	300
atcagtagag tggaggctga ggatgtgggt gtttattact gtatgcaaca tctagaatat	360
cctctcacgg tcggtgctgg gaccaagctg gagctgaaag gctccacctc tggatccggc	420
aagcccggat ctggcgaggg atctaccaag ggccaggttc aactgcaaca gtctggggct	480
gagctggatga ggcttggggc ttcagtgaag ctgtcctgca aggctttggg ctacacattt	540
actgactatg aaatgcactg ggtgaagcag acacctgtgc atggcctgga atggattgga	600
gctattcatc caggaagtgg tggtagtgc tataatcaga agttcaaggg caaggccaca	660
ctgactgcag acaaatcctc cagcacagcc tacatggagc tcagcaggct gacatctgag	720
gactctgctg tctattactg tacaagaagg aggcctaggt tctatggtat ggactactgg	780
ggtcaaggaa cctcagtcac cgtctcctca gaattcctct tcccccaaa acccaaggac	840
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtaggacgt gagccacgaa	900
gacctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca	960
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg	1020
caccaggact ggctgaatgg caaggagtac aagtgcagg tctccaacaa agccctcca	1080
gcccccatcg agaaaacat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac	1140
accctgcccc catcccggga ggagatgacc aagaaccagg tcagcctgac ctgcctggtc	1200
aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac	1260
aactacaaga ccacgcctcc cgtgtggac tccgacggct cttcttcct ctatagcaag	1320
ctcaccgtgg acgagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat	1380
gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga	1437

<210> 93
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 93

Met	Gly	Trp	Ser	Cys	Ile	Ile	Leu	Phe	Leu	Val	Ala	Thr	Ala	Thr	Gly
1				5					10					15	

Val His Ser

<210> 94
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 94

Val Asp Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 95
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> SEQ ID NO:96

<400> 95

Val Asp Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Lys
1 5 10 15

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
20 25 30

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
35 40 45

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
50 55 60

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
65 70 75 80

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
85 90 95

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
100 105 110

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
115 120 125

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
130 135 140

Gly Lys Met
145

<210> 96
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 96

Val Asp Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

20

25

30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 35 40 45

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
 195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 210 215 220

Leu Ser Leu Ser Leu Gly Lys Met
 225 230

<210> 97

<211> 68

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 97

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
 1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
20 25 30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
35 40 45

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
50 55 60

Ala Tyr Arg Ser
65

<210> 98

<211> 42

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 98

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 99

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 99

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala

85

90

95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 100 105 110

<210> 100

<211> 718

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 100

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1 5 10 15

Val His Ser Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr
 20 25 30

Ser Ile Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val
 35 40 45

Gly His Tyr Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
 50 55 60

Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg
 65 70 75 80

Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn
 85 90 95

Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Ile
 100 105 110

Tyr Pro Trp Thr Phe Gly Gly Gly Ser Lys Leu Ala Ile Lys Gly Ser
 115 120 125

Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly
 130 135 140

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
 145 150 155 160

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 165 170 175

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
 180 185 190

Ala Thr Ile Ser Ser Gly Gly Gly Tyr Thr His Tyr Val Asp Ser Val
 195 200 205

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn His Ile Leu Tyr
210 215 220

Leu Gln Met Ser Ser Leu Asn Ser Glu Asp Thr Ala Met Tyr Tyr Cys
225 230 235 240

Ala Arg His Pro Arg Asp Phe Ser Tyr Ala Met Asp Tyr Trp Gly Gln
245 250 255

Gly Thr Ser Val Thr Val Ser Ser Val Asp Glu Ser Lys Tyr Gly Pro
260 265 270

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
275 280 285

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
290 295 300

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
305 310 315 320

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
325 330 335

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
340 345 350

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
355 360 365

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
370 375 380

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
385 390 395 400

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
405 410 415

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
420 425 430

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
435 440 445

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
450 455 460

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
465 470 475 480

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met

485

490

495

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
500 505 510

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
515 520 525

Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
530 535 540

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
545 550 555 560

Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
565 570 575

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
580 585 590

Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
595 600 605

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
610 615 620

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
625 630 635 640

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
645 650 655

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
660 665 670

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
675 680 685

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
690 695 700

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
705 710 715

<210> 101

<211> 722

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 101

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1 5 10 15
 Val His Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val
 20 25 30
 Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu
 35 40 45
 Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro
 50 55 60
 Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser
 65 70 75 80
 Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr
 85 90 95
 Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
 100 105 110
 Met Gln His Leu Glu Tyr Pro Leu Thr Val Gly Ala Gly Thr Lys Leu
 115 120 125
 Glu Leu Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu
 130 135 140
 Gly Ser Thr Lys Gly Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
 145 150 155 160
 Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Leu Gly Tyr
 165 170 175
 Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His
 180 185 190
 Gly Leu Glu Trp Ile Gly Ala Ile His Pro Gly Ser Gly Gly Thr Ala
 195 200 205
 Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser
 210 215 220
 Ser Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser
 225 230 235 240
 Ala Val Tyr Tyr Cys Thr Arg Arg Arg Pro Arg Phe Tyr Gly Met Asp
 245 250 255
 Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Val Asp Glu Ser
 260 265 270
 Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly

275

280

285

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 290 295 300

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 305 310 315 320

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 325 330 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 340 345 350

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 355 360 365

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 370 375 380

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 385 390 395 400

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 405 410 415

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 420 425 430

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 435 440 445

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 450 455 460

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 465 470 475 480

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 485 490 495

Leu Gly Lys Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
 500 505 510

Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg
 515 520 525

Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro
 530 535 540

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
 545 550 555 560

Arg Asp Phe Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu
565 570 575

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
580 585 590

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
595 600 605

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
610 615 620

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
625 630 635 640

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
645 650 655

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
660 665 670

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
675 680 685

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
690 695 700

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
705 710 715 720

Pro Arg

<210> 102

<211> 634

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 102

Met Ala Arg Gly Ser Ala Leu Pro Arg Arg Pro Leu Leu Cys Ile Pro
1 5 10 15

Ala Val Trp Ala Ala Ala Ala Leu Leu Leu Ser Val Ser Arg Thr Ser
20 25 30

Gly Glu Val Glu Val Leu Asp Pro Asn Asp Pro Leu Gly Pro Leu Asp
35 40 45

Gly Gln Asp Gly Pro Ile Pro Thr Leu Lys Gly Tyr Phe Leu Asn Phe

50

55

60

Leu Glu Pro Val Asn Asn Ile Thr Ile Val Gln Gly Gln Thr Ala Ile
 65 70 75 80

Leu His Cys Lys Val Ala Gly Asn Pro Pro Pro Asn Val Arg Trp Leu
 85 90 95

Lys Asn Asp Ala Pro Val Val Gln Glu Pro Arg Arg Ile Ile Ile Arg
 100 105 110

Lys Thr Glu Tyr Gly Ser Arg Leu Arg Ile Gln Asp Leu Asp Thr Thr
 115 120 125

Asp Thr Gly Tyr Tyr Gln Cys Val Ala Thr Asn Gly Met Lys Thr Ile
 130 135 140

Thr Ala Thr Gly Val Leu Phe Val Arg Leu Gly Pro Thr His Ser Pro
 145 150 155 160

Asn His Asn Phe Gln Asp Asp Tyr His Glu Asp Gly Phe Cys Gln Pro
 165 170 175

Tyr Arg Gly Ile Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Ile Tyr
 180 185 190

Val Asp Ser Leu Gln Met Gln Gly Glu Ile Glu Asn Arg Ile Thr Ala
 195 200 205

Ala Phe Thr Met Ile Gly Thr Ser Thr His Leu Ser Asp Gln Cys Ser
 210 215 220

Gln Phe Ala Ile Pro Ser Phe Cys His Phe Val Phe Pro Leu Cys Asp
 225 230 235 240

Ala Arg Ser Arg Thr Pro Lys Pro Arg Glu Leu Cys Arg Asp Glu Cys
 245 250 255

Glu Val Leu Glu Ser Asp Leu Cys Arg Gln Glu Tyr Thr Ile Ala Arg
 260 265 270

Ser Asn Pro Leu Ile Leu Met Arg Leu Gln Leu Pro Lys Cys Glu Ala
 275 280 285

Leu Pro Met Pro Glu Ser Pro Asp Ala Ala Asn Cys Met Arg Ile Gly
 290 295 300

Ile Pro Ala Glu Arg Leu Gly Arg Tyr His Gln Cys Tyr Asn Gly Ser
 305 310 315 320

Gly Met Asp Tyr Arg Gly Thr Ala Ser Thr Thr Lys Ser Gly His Gln
 325 330 335

Cys Gln Pro Trp Ala Leu Gln His Pro His Ser His His Leu Ser Ser
 340 345 350

Thr Asp Phe Pro Glu Leu Gly Gly Gly His Ala Tyr Cys Arg Asn Pro
 355 360 365

Gly Gly Gln Met Glu Gly Pro Trp Cys Phe Thr Gln Asn Lys Asn Val
 370 375 380

Arg Met Glu Leu Cys Asp Val Pro Ser Cys Ser Pro Arg Asp Ser Ser
 385 390 395 400

Lys Met Gly Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 405 410 415

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 420 425 430

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 435 440 445

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 450 455 460

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 465 470 475 480

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 485 490 495

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 500 505 510

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 515 520 525

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 530 535 540

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 545 550 555 560

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 565 570 575

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 580 585 590

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 595 600 605

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
610 615 620

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
625 630

<210> 103
<211> 634
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 103

Met His Arg Pro Arg Arg Arg Gly Thr Arg Pro Pro Leu Leu Ala Leu
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Leu Ala Ala Leu Leu Leu Ala Ala Arg Gly Ala Ala Ala Gln Glu Thr
20 25 30

Glu Leu Ser Val Ser Ala Glu Leu Val Pro Thr Ser Ser Trp Asn Ile
35 40 45

Ser Ser Glu Leu Asn Lys Asp Ser Tyr Leu Thr Leu Asp Glu Pro Met
50 55 60

Asn Asn Ile Thr Thr Ser Leu Gly Gln Thr Ala Glu Leu His Cys Lys
65 70 75 80

Val Ser Gly Asn Pro Pro Pro Thr Ile Arg Trp Phe Lys Asn Asp Ala
85 90 95

Pro Val Val Gln Glu Pro Arg Arg Leu Ser Phe Arg Ser Thr Ile Tyr
100 105 110

Gly Ser Arg Leu Arg Ile Arg Asn Leu Asp Thr Thr Asp Thr Gly Tyr
115 120 125

Phe Gln Cys Val Ala Thr Asn Gly Lys Glu Val Val Ser Ser Thr Gly
130 135 140

Val Leu Phe Val Lys Phe Gly Pro Pro Pro Thr Ala Ser Pro Gly Tyr
145 150 155 160

Ser Asp Glu Tyr Glu Glu Asp Gly Phe Cys Gln Pro Tyr Arg Gly Ile
165 170 175

Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Val Tyr Met Glu Ser Leu
180 185 190

His Met Gln Gly Glu Ile Glu Asn Gln Ile Thr Ala Ala Phe Thr Met
195 200 205

Ile Gly Thr Ser Ser His Leu Ser Asp Lys Cys Ser Gln Phe Ala Ile
 210 215 220

Pro Ser Leu Cys His Tyr Ala Phe Pro Tyr Cys Asp Glu Thr Ser Ser
 225 230 235 240

Val Pro Lys Pro Arg Asp Leu Cys Arg Asp Glu Cys Glu Ile Leu Glu
 245 250 255

Asn Val Leu Cys Gln Thr Glu Tyr Ile Phe Ala Arg Ser Asn Pro Met
 260 265 270

Ile Leu Met Arg Leu Lys Leu Pro Asn Cys Glu Asp Leu Pro Gln Pro
 275 280 285

Glu Ser Pro Glu Ala Ala Asn Cys Ile Arg Ile Gly Ile Pro Met Ala
 290 295 300

Asp Pro Ile Asn Lys Asn His Lys Cys Tyr Asn Ser Thr Gly Val Asp
 305 310 315 320

Tyr Arg Gly Thr Val Ser Val Thr Lys Ser Gly Arg Gln Cys Gln Pro
 325 330 335

Trp Asn Ser Gln Tyr Pro His Thr His Thr Phe Thr Ala Leu Arg Phe
 340 345 350

Pro Glu Leu Asn Gly Gly His Ser Tyr Cys Arg Asn Pro Gly Asn Gln
 355 360 365

Lys Glu Ala Pro Trp Cys Phe Thr Leu Asp Glu Asn Phe Lys Ser Asp
 370 375 380

Leu Cys Asp Ile Pro Ala Cys Asp Ser Lys Asp Ser Lys Glu Lys Asn
 385 390 395 400

Lys Met Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 405 410 415

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 420 425 430

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 435 440 445

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 450 455 460

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 465 470 475 480

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
485 490 495

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
500 505 510

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
515 520 525

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
530 535 540

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
545 550 555 560

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
565 570 575

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
580 585 590

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
595 600 605

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
610 615 620

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
625 630

<210> 104
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

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<210> 105
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 105
gtcgacgagt ccaaatatgg tccccatgc ccaccatgcc ca 42

<210> 106
<211> 441
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 106

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cagccccgag agccacaggt gtacaccctg ccccatccc aggaggagat gaccaagaac	180
caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg	240
gagagcaatg ggagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac	300
ggctccttct tcctctacag caggctaacc gtggacaaga gcaggtggca ggagggaat	360
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc	420
tccctgtccc taggtaaaat g	441

<210> 107

<211> 696

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 107

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ggaccatcag tcttctgtt cccccaaaa cccaaggaca ctctcatgat ctcccggacc	120
cctgagggtca cgtgcgtggt ggtggacgtg agccaggaag accccgaggt ccagttcaac	180
tggtacgtgg atggcgtgga ggtgcataat gccaaagaca agccgcggga ggagcagttc	240
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaacggc	300
aaggagtaca agtgaagggt ctccaacaaa ggcctcccgt cctccatcga gaaaaccatc	360
tccaaagcca aagggcagcc ccgagagcca cagggtgtaca ccctgcccc atcccaggag	420
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta cccagcgac	480
atgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cagcctccc	540
gtgctggact ccgacggctc tttcttctc tacagcaggc taaccgtgga caagagcagg	600
tggcaggagg ggaatgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac	660
acacagaaga gcctctccct gtccctaggt aaaatg	696

<210> 108

<211> 204

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 108

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gcctttatta ttttctgggt gaggagtaag aggagcaggc tcctgcacag tgactacatg	120

aacatgactc cccgccgccc cgggcccacc cgcaagcatt accagcccta tgccccacca	180
cgcgacttcg cagcctatcg ctcc	204
<210> 109	
<211> 126	
<212> DNA	
<213> Artificial Sequence	
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<223> Synthetic polynucleotide	
<400> 109	
aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa	60
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt	120
gaactg	126
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<211> 339	
<212> DNA	
<213> Artificial Sequence	
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<223> Synthetic polynucleotide	
<400> 110	
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tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc	120
cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat	180
gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc	240
cggaggggca agggggcacga tggcctttac cagggtctca gtacagccac caaggacacc	300
tacgacgccc ttcacatgca ggccctgccc cctcgctga	339
<210> 111	
<211> 2157	
<212> DNA	
<213> Artificial Sequence	
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<223> Synthetic polynucleotide	
<400> 111	
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acctgcaagg ccagtcagga tgtgggtcat tatgtggcct ggtatcaaca gaaaccaggt	180
caatctccta aactactgat ttactgggca tccaccggc aactggagt ccctgatcgc	240
ttcacaggta gtggatctgg gacagatttc actctacca ttagcaatgt gcagtctgaa	300
gacttggcag attatttctg tcagcaatat aacatctatc cgtggacgtt cggtaggagc	360
tccaagctgg caatcaaagg ctccacctct ggatccggca agcccggatc tggcgaggga	420
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gttcgccaga ctccagacaa gaggctggag tgggtcgcaa ccattagtag tgggtggtggt	600
tacactcact atgtagacag tgtgaagggg cgattcacca tttccagaga caatgccaac	660
catatcctgt acctgcaaat gagcagtctg aactctgagg acacagccat gtattattgt	720
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gaaggaggat gtgaactgag agtgaagttc agcaggagcg cagacgcccc cgcgtagcag	1860
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caggaaggcc tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt	2040
gggatgaaag gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggctctcag	2100
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<210> 112

<211> 2169

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 112

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attgtgatga ctcaggctgc accctctgta cctgtcactc ctggagagtc agtatccatc	120
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tcctgcaggt ctagtaagag tctcctgcat agtaatggca acacttactt gtattggttc	180
ctgcagaggc caggccagtc tcctcagctc ctgatatatc ggatgtccaa ccttgccctca	240
ggagtcccag acaggttcag tggcagtgagg tcaggaactg ctttcacact gagaatcagt	300
agagtggagg ctgaggatgt ggggtgtttat tactgtatgc aacatctaga atatcctctc	360
acggtcgggtg ctgggaccaa gctggagctg aaaggctcca cctctggatc cggcaagccc	420
ggatctggcg agggatccac caagggccag gttcaactgc aacagtctgg ggctgagctg	480
gtgaggcctg gggcttcagt gaagctgtcc tgcaaggctt tgggctacac atttactgac	540
tatgaaatgc actgggtgaa gcagacacct gtgcatggcc tggaatggat tggagctatt	600
catccaggaa gtggtggtac tgcctataat cagaagttca agggcaaggc cacactgact	660
gcagacaaat cctccagcac agcctacatg gagctcagca ggctgacatc tgaggactct	720
gctgtctatt actgtacaag aaggaggcct aggttctatg gtatggacta ctgggggtcaa	780
ggaacctcag tcaccgtctc ctacgtcgac gagtccaaat atgggtcccc atgcccacca	840
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gacactctca tgatctcccc gacccctgag gtcacgtgcg tgggtggtgga cgtgagccag	960
gaagaccccc aggtccagtt caactggtac gtggatggcg tggaggtgca taatgccaa	1020
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aacatgactc cccgccgccc tgggcccacc cgcaagcatt accagcccta tgccccacca	1680
cgcgacttcg cagcctatcg ctccaaacgg ggcagaaaga aactcctgta tatattcaaa	1740
caaccattta tgagaccagt acaaactact caagaggaag atggctgtag ctgccgattt	1800
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gagtacgatg ttttgacaa gagacgtggc cgggaccctg agatgggggg aaagccgaga	1980
aggaagaacc ctcaggaagg cctgtacaat gaactgcaga aagataagat ggcgagggcc	2040
tacagtgaga ttgggatgaa aggcgagcgc cggaggggca aggggcacga tggcctttac	2100
cagggtctca gtacagccac caaggacacc tacgacgcc ttcacatgca ggccctgccc	2160
cctcgctga	2169

<210> 113
<211> 82
<212> PRT
<213> Homo sapiens

<400> 113

His Gln Cys Tyr Asn Gly Ser Gly Met Asp Tyr Arg Gly Thr Ala Ser
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Thr Thr Lys Ser Gly His Gln Cys Gln Pro Trp Ala Leu Gln His Pro
20 25 30

His Ser His His Leu Ser Ser Thr Asp Phe Pro Glu Leu Gly Gly Gly
35 40 45

His Ala Tyr Cys Arg Asn Pro Gly Gly Gln Met Glu Gly Pro Trp Cys
50 55 60

Phe Thr Gln Asn Lys Asn Val Arg Met Glu Leu Cys Asp Val Pro Ser
65 70 75 80

Cys Ser

<210> 114
<211> 69
<212> PRT
<213> Homo sapiens

<400> 114

Ala Ile Leu His Cys Lys Val Ala Gly Asn Pro Pro Pro Asn Val Arg
1 5 10 15

Trp Leu Lys Asn Asp Ala Pro Val Val Gln Glu Pro Arg Arg Ile Ile
20 25 30

Ile Arg Lys Thr Glu Tyr Gly Ser Arg Leu Arg Ile Gln Asp Leu Asp
35 40 45

Thr Thr Asp Thr Gly Tyr Tyr Gln Cys Val Ala Thr Asn Gly Met Lys
50 55 60

Thr Ile Thr Ala Thr
65