

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
5 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.

10 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.

15 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
20 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
25 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
30 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
5 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.

10 [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
15 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.

20 [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
25 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
30 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 hKringe contain the cysteine rich domain and the Kringe domain of human ROR2. Each recombinant protein was transferred onto nylon membrane, probed with the 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 kringe 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 Kringe 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 kringe domain was replaced with the corresponding amino acid of mouse ROR2. Each recombinant protein was transferred onto nylon membrane, probed with the 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 kringe 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 10⁵ 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 +/- 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 K_d 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-methylphosphoramidite 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,
10 deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, 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 5 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 10 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 15 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 20 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, 25 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 30 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 & 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
30 antibody of interest can be cloned from a cell, *e.g.*, the genes encoding a monoclonal antibody

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, Trautnecker 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 Verhoeyen 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., Arnon 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
 5 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
 10 sarcoma, or telangiectaltic 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
 15 melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal 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
 20 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, cerebriiform carcinoma, cholangiocellular
 25 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
 30 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, scirrhus 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, tuberos 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.
- 15 **[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.
- 20 **[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.
- 25 **[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 30 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 5
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 10
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- 15
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 20
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, 25
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, 30
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), gossypol, genasense, polyphenol E, Chlorofusin, all
 trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand
 5 (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide,
 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;
 benzoylstauropine; beta lactam derivatives; beta-alethine; 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; diaziqune; 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; emitfur; 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; ilmofosine; 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; masoprocol; 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; pentrozole; 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; tricinibine; 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; meturedpa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; 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; spirolatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone
- 20 hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricirbine 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 (Armada/Kyowa Hakko),

10 AM-132 (Armada), AM-138 (Armada/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, Inanocene (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, (-)-Phenylhistin (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.
- [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.
- [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
- 30 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

[illegible]

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
5 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, 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
5 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
10 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
15 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-
20 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
25 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
30 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 5 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 In 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 In 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 In 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
5 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
10 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
15 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
20 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-
25 like domain includes 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
30 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 10 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, 15 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 20 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 25 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 30 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 expressin gdetectable 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 10 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 15 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 20 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 25 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 30 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 25 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 30 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 35 embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 100 nM. In 40 embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 90 nM. In 45 embodiments, the scFv binds the ROR2 protein with a K_D from 10 nM to 80 nM. In 50

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 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.

5 **[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.

10 **[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
15 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;
20 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.

25 **[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
30 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.

5 [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
10 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.

15 [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
20 386 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 the ROR2 protein is a human ROR2 protein. In embodiments, the antibody binds a ROR2
25 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-
30 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 nM. In embodiments, the antibody binds the ROR2 protein with a K_D from 1 nM to 150 nM. In
5 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.
- [0215] In embodiments, the antibody binds the ROR2 protein with a K_D from 0.01 nM to 140
20 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 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.

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
5 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
10 100% 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
15 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
20 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
25 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
30 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.

5 [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
10 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
15 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.

20 [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
25 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
30 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

5 [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) 10 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 15 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.

20 [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 25 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 30 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.
- 10 [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 15 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 20 immunoglobulin gamma Fc region receptor III-A, or variants or homologs thereof that maintain 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 25 occurring CD16 protein. In embodiments, the CD16 protein is substantially identical to the 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 30 immunoglobulin gamma Fc region receptor II-A, or variants or homologs thereof that maintain 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
5 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
10 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
20 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
30 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 a light chain variable domain includes the sequence of SEQ ID NO:16. In embodiments, the
25 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 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
30 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 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 a cervical cancer cell. In embodiments, the cancer cell is a gastric cancer cell. In embodiments, the cancer cell is a renal cancer cell. In embodiments, the cancer cell 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.

5 [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).

15 [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.

20 [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,
25 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
30 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
10 embodiments, the therapeutic agent is an anti-cancer agent. Exemplary anti-cancer agent include without limitation any anti-cancer agent conventionally used and known in the art, for example, calicheamicin, duocarmycin, pyrrolobenzodiazepine, (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 6 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 4 nM. 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.

10 [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 0.01 nM to about 1 nM. In embodiments, the antibody is administered at an amount from about 0.05 nM to about 1 nM. In embodiments, the antibody is administered at an amount from about 0.1 nM to about 1 nM. In embodiments, the antibody is administered at an amount from about 0.5 nM to about 1 nM.

[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.

- 10 [0295] It is understood that the 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., 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.

30

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
 5 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
 10 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.
 15 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.

20 [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
 25 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.
- [0335] Embodiment 11. The antibody of embodiment 10, wherein said ROR2 protein
10 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.
- [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,
25 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.
- [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
10 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.
- [0348] Embodiment 24. The antibody of embodiment 23, wherein said heavy chain variable
15 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).
- [0353] Embodiment 29. The antibody of any one of embodiments 23 to 25, wherein said
25 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
5 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
10 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.

15 [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.

20 [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
25 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
5 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.

10 [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
15 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
20 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
25 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
30 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.
- [0395] Embodiment 71. The antibody of any one of embodiments 64 to 67, wherein said
10 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.
- [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
15 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.
- [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
10 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.
- [0409] Embodiment 85. The method of embodiments 83 or 84, wherein said cancer is breast
15 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.
- [0413] Embodiment 89. The method of embodiment 88, wherein said subject is a subject
25 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.

10 [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.

20 [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
30 (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
GGGTTCCGAGACTCCAGACAAGAGGCTGGAGTGGGTCCGAACCATTAGTAG
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
ATCAACAGAAACCAGGTCAATCTCCTAACTACTGATTTACTGGGCATCCACC
CGGCACACTGGAGTCCCTGATCGCTTCACAGGTAGTGGATCTGGGACAGATT

CACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTGTC
AGCAATATAACATCTATCCGTGGACGTTCCGGTGGAGGCTCCAAGCTGGCAATC
AAA

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

DIVMTQSHKFMSTSIGDRVSITCKASQDVGHYVAWYQQKPGQSPKLLIYWASTR
HTGVPDRFTGSGSGTDFLTISNVQSEDLADYFCQYNIYPWTFGGGSKLAIK

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
ATCGGATGTCCAACCTTGCCTCAGGAGTCCCAGACAGGTTCAGTGGCAGTGGG
30 TCAGGAACTGCTTTACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGTGG
GTGTTTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGCTGGG
ACCAAGCTGGAGCTGAAA

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

35 DIVMTQAAPSPVPVTPGESVSISCRSSKSLLSHNGNTYLYWFLQRPQGSPQLLIYRM
SNLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTVGAGTKLEL
K

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

40 GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGCCTGGAGGGTCCC
TGAAACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACTATGGCATGTCTT
GGGTTCCGACAGACTCCAGACAAGAGGCTGGAGTGGGTGCGCAACCATTAGTAG

5 TGGTGGTGGTTCCACCTACTATCCAGACAGTGTGAAGGGGCGATTACCATCT
CCAGAGACAATGCCAAGAAGCTCCCTGTACCTGCAAATGAGCAGTCTGAAGTCT
GAGGACACAGCCATGTATTACTGTGCAAGACATCCCTATGATTACGGGTACTA
CTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

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

10 EVQLVESGGDLVKPGGSLKLSCAASGFTFSNYGMSWVRQTPDKRLEWVATISSG
GGSTYYPDSVKGRFTISRDNKNSLYLQMSSLKSEDAMYYCARHPYDYGYYFD
YWGQGTTLTVSS

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

15 GACATCTTGCTGACTCAGTCTCCAGACATCCTGTCTGTGAGTCCAGGAGAAAG
AGTCAGTTTCTCCTGCAGGGCCAGTCAGAGCATTGGCACAAGCATACACTGGT
ATCAGCAGAGAAACAAATGGTTCTCCAAGGCTTCTCATAAAATATGCTTCTGAG
TCTATCTCTGGGATCCCTTCCAGGTTTGTGGCAGTGGATCAGGGACAGATT
TACTCTTAGCATCAACAGTGTGGAGTCTGAAGATATTGCAGATTATTACTGTC
AACAAAGTGATAGCTGGCCATTCCCGTTCGGCTCGGGGACAAAATTGAAAA
AAAA

20 [0465] SEQ ID NO:12; 5C11 VL SEQ

DILLTQSPDILSVSPGERVSFSCRASQSIGTSIHWYQRTNGSPRLLIKYASESISGIP
SRFSGSGSGTDFTLSINSVESEDIADYYCQQSDSWPFPGSGTKLEKK

25 [0466] SEQ ID NO:13; 5G3 VH SEQ

30 GAGGTGCAGCTTGTTGAGTCTGGTGGAGGATTGGTGCAGCCTAAAGGGTCATT
GAAGCTCTCATGTGCAGCCTCTGGATTACCTTCAATACCTACGCCATGAACT
GGGTCCGCCAGGCTCCAGGAAAGGGTTTGAATGGGTTGCTCGCATAAGAAG
TAAAAGTAATAATTATGCAACATATTATGCCGATTTCAGTGAAAGACAGGTTCA
CCATCTCCAGAGATGATTACAAAAGCATGCTCCATCTGCAAATGAACAACTTG
AAAAGTGAAGACACAGCCATGTATTACTGTGTGAGACACGGTAGTAGCCTCTA
CTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

35 [0467] SEQ ID NO:14; 5G3 VH SEQ

40 EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRS
KSNYYATYYADSVKDRFTISRDDSQSMHLQMNNLKTEDTAMYYCVRHGSSLY
YAMDYWGQGTSTVTV
SS

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

GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTGCCTCTCTGGGAGAAAG
AGTCAGTCTCACTTGTCTGGGCAAGTCAGGAAATTAGTGGTTACTTAGGCTGGC
TTCAGCAGAAACCAGATGGAACATTAAACGCCTGATCTACGCCGCATCCACT
TTAGATTCTGGTGTCCCAAAAAGGTTTCAGTGGCAGTAGGTCTGGGTCAGCTTA
5 TTCTCTCACCATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATTACTGTCT
ACAATATGCTAGTTATCCGTACACGTTTCGGAGGGGGGACCAAGCTGGAAATA
AAA

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

10 DIQMTQSPSSLSASLGERVSLTCRASQEISGYLGWLQKPKDGTIKRLIYAASLTDSG
VPRFSGSRSGSAYSLTISSLESEDFADYYCLQYASYPYTFGGGKLEIK

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

ATGGCCCCGGGGCTCGGCGCTCCCGCGGCGGCGGCTGCTGTGCATCCCGGCCGT
15 CTGGGCGGCCGCCGCGCTTCTGCTCTCAGTGTCCCGGACTTCAGGTGAAGTGG
AGGTTCTGGATCCGAACGACCCCTTAGGACCCCTTGATGGGCAGGACGGCCCG
ATTCCAACCTCTGAAAGGTTACTTTCTGAATTTTCTGGAGCCAGTAAACAATAT
CACCATTGTCCAAGGCCAGACGGCAATTCTGCACTGCAAGGTGGCAGGAAAC
CCACCCCTAACGTGCGGTGGCTAAAGAATGATGCCCCGGTGGTGCAGGAGC
20 CGCGGCGGATCATCATCCGGAAGACAGAATATGGTTCACGACTGCGAATCCA
GGACCTGGACACGACAGACACTGGCTACTACCAGTGCCTGGCCACCAACGGG
ATGAAGACCATTACCGCCACTGGCGTCTCTGTTTGTGCGGCTGGGTCCAACGCA
CAGCCCAAATCATAACTTTCAGGATGATTACCACGAGGATGGGTTCGCCAGC
CTTACCGGGGAATTGCCTGTGCAAGCTTCATTGGCAACCGGACCATTTATGTG
25 GACTCGCTTCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCGGCCTTCA
CCATGATCGGCACGTCTACGCACCTGTGCGACCAAGTGCTCACAGTTCGCCATC
CCATCCTTCTGCCACTTCTGTGTTTCTCTGTGCGACGCGCGCTCCCGGGCACCC
AAGCCGCGTGAGCTGTGCCGCGACGAGTGCGAGGTGCTGGAGAGCGACCTGT
GCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCTT
30 CAGCTGCCCCAAGTGTGAGGCGCTGCCATGCCTGAGAGCCCCGACGCTGCCA
ACTGCATGCGCATTGGCATCCAGCCGAGAGGCTGGGCGCTACCATCAGTGC
TATAACGGCTCAGGCATGGATTACAGAGGAACGGCAAGCACCACCAAGTCAG
GCCACCAGTGCCAGCCGTGGGCCCTGCAGCACCCCCACAGCCACCACCTGTCC
AGCACAGACTTCCCTGAGCTTGAGGGGGGACGCCTACTGCCGGAACCCCG
35 GAGGCCAGATGGAGGGCCCCCTGGTGCTTTACGCAGAATAAAAACGTACGCAT
GGAAGTGTGTGACGTACCCTCGTGTAGTCCCCGAGACAGCAGCAAGATGGGG
ATTCTGTACATCTTGGTCCCCAGCATCGCAATTCCACTGGTCATCGCTTGCCCTT
TTCTTCTTGGTTTGCATGTGCCGAATAAGCAGAAGGCATCTGCGTCCACACC
GCAGCGGCGACAGCTGATGGCCTCGCCCAGCCAAGACATGGAAATGCCCTC
40 ATTAACCAGCACAAACAGGCCAACTCAAAGAGATCAGCCTGTCTGCGGTGA
GGTTCATGGAGGAGCTGGGAGAGGACCGGTTTGGGAAAGTCTACAAAGGTCA
CCTGTTTCGGCCCTGCCCCGGGGGAGCAGACCCAGGCTGTGGCCATCAAAACG
CTGAAGGACAAAGCGGAGGGGGCCCTGCGGGAGGAGTTCCGGCATGAGGCTA
TGCTGCGAGCACGGCTGCAACACCCCAACGTCGTCTGCCTGCTGGGCGTGGTG
45 ACCAAGGACCAGCCCCTGAGCATGATCTTCAGCTACTGTTTCGCACGGCGACCT
CCACGAATTCTGGTTCATGCGCTCGCCGCACTCGGACGTGGGCAGCACCGATG
ATGACCGCACGGTGAAGTCCGCCCTGGAGCCCCCGACTTCGTGCACCTTGTG
GCACAGATCGCGGCGGGGATGGAGTACCTATCCAGCCACCACGTGGTTCACA

AGGACCTGGCCACCCGCAATGTGCTAGTGTACGACAAGCTGAACGTGAAGAT
CTCAGACTTGGGCCTCTTCCGAGAGGTGTATGCCGCCGATTACTACAAGCTGC
TGGGGAACCTCGCTGCTGCCTATCCGCTGGATGGCCCCAGAGGCCATCATGTAC
GGCAAGTTCTCCATCGACTCAGACATCTGGTCCTACGGTGTGGTCTGTGGGA
5 GGTCTTCAGCTACGGCCTGCAGCCCTACTGCGGGTACTCCAACCAGGATGTGG
TGGAGATGATCCGGAACCGGCAGGTGCTGCCTTGCCCCGATGACTGTCCCGCC
TGGGTGTATGCCCTCATGATCGAGTGCTGGAACGAGTTCCCCAGCCGGCGGCC
CCGCTTCAAGGACATCCACAGCCGGCTCCGAGCCTGGGGCAACCTTTCCAACT
ACAACAGCTCGGCGCAGACCTCGGGGGCCAGCAACACCACGCAGACCAGCTC
10 CCTGAGCACCAGCCAGTGAGCAATGTGAGCAACGCCCGCTACGTGGGGCCCC
AAGCAGAAGGCCCCGCCCTTCCCACAGCCCCAGTTCATCCCCATGAAGGGCCA
GATCAGACCCATGGTGCCCCCGCCGCAGCTCTACGTCCCCGTCAACGGCTACC
AGCCGGTGCCGGCCTATGGGGCCTACCTGCCCAACTTCTACCCGGTGCAGATC
CCAATGCAGATGGCCCCGCAGCAGGTGCCTCCTCAGATGGTCCCCAAGCCCAG
15 CTCACACCACAGTGGCAGTGGCTCCACCAGCACAGGCTACGTCACCACGGCCC
CCTCCAACACATCCATGGCAGACAGGGCAGCCCTGCTCTCAGAGGGCGCTGAT
GACACACAGAACGCCCCAGAAGATGGGGCCCAGAGCACCGTGCAGGAAGCA
GAGGAGGAGGAGGAAGGCTCTGTCCCAGAGACTGAGCTGCTGGGGGACTGTG
ACACTCTGCAGGTGGACGAGGCCCAAGTCCAGCTGGAAGCTTGA

20

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

MARGSALPRRPLLCIPAVWAAAALLSVSRTSGEVEVLDPNDPLGPLDGDGPIPT
LKGYFLNLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIR
KTEYGSRLRIQDLDTDTGYQQCVATNGMKTITATGVLFVRLGPTHSPNHNFDQD
25 YHEDGFCQPYRGIACARFIGNRTIYVDSLQMGEIENRITAAFTMIGTSTHLSQCS
QFAIPSFCHFVFPLCDARSRTPKPRELCRDECEVLES DLCRQEYTIARSNPLILMRL
QLPKCEALPMPESDAANCMRIGIPAERLGRYHQCYNNGSGMDYRGTA STTKSGH
QCQPWALQHPHSHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQNK NVRMEL
CDVPSCSPRDSSKM GILYILVPSIAIPLVIACLFFLVCMCRNKQKASASTPQRRQLM
30 ASPSQDMEMPLINQHKQAKLKEISLSAVRFMEELGEDRFGKVYKGHLFGPAPGEQ
TQAVAIKTLKDKAEGPLREEFRHEAMLRARLQHPNVVCLLG VVTKDQPLSMIFS
CSHGDLHEFLVMRSPHSDVGSTDDDRTVKSALEPPDFVHLVAQIAAGMEYLSSH
HVVHKDLATRNVLVYDKLNVKISDLGLFREYV AADYYKLLGNSLLPIRWMAPEA
IMYGKFSIDSDIWSYGVVLWEVFSYGLQPYCGYSNQDVVEMIRNRQVLP PDDCP
35 AWVYALMIECWNEFPSRRPRFKDIHSRLRAWGNLSNYNSSAQTS GASNTTQTSSL
STSPVSNVSNARYVGPKQKAPFPQPQFIPMKGQIRPMVPPPQLYVPVNGYQPVPA
YGAYLPNFYVPVQIPMQMAPQQVPPQMV PKPSSHSGSGSTSTGYVTTAPSNTSMA
DRAALLSEGADDTQNA PEDGAQSTVQEAE EEEEGSVPETELLGDCDTLQVDEAQ
VQLEA

40

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

ATGGCTCGGGGCTGGGTGCGGCCGAGCCGTGTGCCTCTGTGCGCCGGGCCGT
CTGGACGGCTGCGGCGCTCCTGCTCTGGACACCCTGGACGGCAGGTGAAGTG
GAAGATTCGGAGGCAATCGACACCTTGGGACAACCTGATGGACCGGACAGCC
45 CACTTCCCACTCTGAAAGGCTACTTTCTGAATTTTCTGGAGCCAGTCAACAAT
ATCACCATTGTT CAGGGCCAGACGGCAATCCTGCACTGCAAGGTGGCGGGAA
ACCCACCTCCCAATGTGCGGTGGCTGAAGAATGATGCCCCGGTTGTGCAAGAG
CCACGAAGGGTCGTCATCCGGAAGACAGAATACGGCTCCCGGCTGCGGATCC

AAGACCTGGACACAACAGACACAGGCTACTACCAGTGTGTGGCTACCAACGG
GCTGAAGACCATCACTGCCACTGGGGTTCTATATGTGCGGCTCGGTCCGACGC
ACAGCCCGAACCACAATTTTCAGGATGACGATCAGGAAGATGGCTTCTGCCA
GCCGTACCGAGGGATCGCTTGTGCGCGCTTCATTGGGAACCGGACTATTTATG
5 TGGACTCCCTCCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCTGCCTTC
ACCATGATCGGCACCTCCACGCAACTGTCAGACCAGTGTTACAGTTTGCCAT
CCCATCCTTCTGCCACTTCGTCTTCCCTCTGTGCGACGCATGCTCCCGGGCGCC
CAAGCCTCGCGAACTGTGCCGGGATGAATGTGAGGTGCTGGAGAACGACCTG
TGCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCT
10 CCAGCTGCCCAAGTGCGAAGCGCTGCCCATGCCCGAGAGCCCGGATGCTGCG
AACTGCATGCGCATCGGGATCCCCGCGGAGAGGCTGGGTGCTACCACCAGT
GCTACAACGGCTCCGGCGCCGATTACAGGGGGATGGCCAGTACCACCAAGTC
AGGCCACCAGTGTCAGCCTTGGGCTCTGCAGCACCCCCACAGCCATCGCCTAT
CCAGCACGGAATTCCCTGAGCTGGGAGGAGGCCATGCCTACTGCCGGAACCC
15 CGGGGGCCAGATGGAAGGCCCCGTGGTGCTTTACGCAGAATAAAAAACGTACGC
GTGGAACGTGTGTGACGTACCCCCGTGTAGTCCCCGATATGGCAGCAAGATGGG
GATTCTGTACATCCTGGTCCCCAGCATTGCTATCCCCCTGGTCATCGCTTGCT
GTTCTTCCTCGTCTGCATGTGCCGCAACAAACAGAAGGCTTCGGCCTCCACCC
CACAGCGCCGGCAGCTGATGGCCTCTCCAGCCAGGACATGGAGATGCCACT
20 CATCAGCCAGCACAAACAGGCCAAACTCAAAGAGATCAGCTTGTCCACAGTG
AGGTTTCATGGAGGAGCTCGGGGAGGACCGGTTTGGAAGGTCTACAAAGGCC
ACCTGTTCCGGCCTGCCCCAGGAGAACCAACCCAGGCCGTGGCCATCAAGAG
GCTGAAAGACAAGGCTGAGGGGCCCTGCGGGAGGAGTTCCGGCAAGAGGCG
ATGCTCCGGGCCCGACTGCAGCACCCCAACATCGTCTGTCTCCTAGGCGTCGT
25 GACCAAGGACCAACCCTTGAGCATGATCTTCAGCTACTGTTCCCATGGCGACC
TTCATGAATTCCCTGGTCATGCGCTCGCCGCACTCCGATGTGGGCAGCACCGAT
GACGACCGCACAGTGAAGTCAGCCCTGGAGCCCCCGGACTTCGTGCACGTGG
TGGCGCAGATCGCTGCGGGGATGGAGTTCCTGTCCAGCCACCACGTGTGCCAT
AAGGACCTGGCCACACGCAATGTGCTGGTGTACGACAAGCTGAACGTGAGGA
30 TCTCAGACTTGGGCCTCTTCCGTGAGGTATACTCCGCAGATTACTACAACTC
ATGGGCAATTCACTGCTGCCCATCCGCTGGATGTCCCCCGAGGCCGTATGTA
TGGAAGTTCTCCATCGACTCTGACATCTGGTCCTACGGTGTGGTCTCTGGG
AGGTCTTTAGCTACGGCCTGCAGCCCTACTGTGGGTACTCCAACCAGGACGTG
GTGGAGATGATCCGGAGCCGGCAGGTGCTGCCCTGCCCGGATGACTGCCCCG
35 CCTGGGTCTATGCCCTCATGATTGAATGCTGGAATGAGTTCCCAAGCCGGAGG
CCCCGCTTTAAGGACATCCACAGCCGGCTCCGGTCTGGGGCAACCTATCCAA
CTATAATAGTTCCGCGCAGACCTCAGGAGCCAGCAACACCACACAGACCAGC
TCCCTGAGCACCAGCCCCGTAAGCAATGTGAGCAATGCCCGCTATATGGCCCC
CAAGCAGAAGGCCAGCCCTTCCCACAGCCTCAGTTCATCCCCATGAAGGGTC
40 AGATCAGACCCTTGGTGCCCCCGCACAGCTGTACATCCCGGTGAACGGCTAT
CAGCCGGTACCGGCATACGGGGCCTACCTGCCCAACTTCTACCCAGTCCAGAT
CCCCATGCAGATGGCCCCACAGCAGGTGCCCCCTCAGATGGTCCCCAAGCCGA
GCTCACACCACAGTGGCAGCGGCTCCACCAGCACTGGCTACGTACCACCGC
GCCCTCCAATACATCTGTGGCGGACAGGGCGGCCCTACTCTCTGAGGGCACCG
45 AGGATGTACAGAACATCGCGGAAGACGTGGCCCAGAGCCCTGTGCAGGAAGC
AGAGGAGGAGGAGGAGGGGTCTGTCCCTGAGACTGAACTCCTGGGAGACAAT
GACACGCTCCAGGTGACCGAGGCGGCTCATGTCCAGCTTGAAGCCTGA

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

MARGWVRPSRVPLCARAVWTAALLLWTPWTAGEVEDSEIDTLGQPDGPDSP
 LPTLKGYFLNFLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRR
 VVIRKTEYGSRLRIQDLDTTDTGYQQCVATNGLKTITATGVLYVRLGPTHSPNHN
 FQDDDDQEDGFCQPYRGIACARFIGNRITIVVDSLQMQGEIENRITAAFTMIGTSTQL
 5 SDQCSQFAIPSFCHFVFPLCDACSRAPKPRELCRDECEVLENDLCRQEYTIARSNPL
 ILMRLQLPKCEALPMPESPDAAANCMRIGIPAERLGRYHQCYNGSGADYRGMASST
 KSGHQCQPWALQHPHSHRLSSTEFPELGGGHAYCRNPGGQMEGPWCFTQNKNV
 RVELCDVPPCSPRYGSKMGILYILVPSIAIPLVIACLFFLVCMCRNKQKASASTPQR
 RQLMASPSQDMEMPLISQHKQAKLKEISLSTVRFMEELEGEDRFGKVYKGHLFGPA
 10 PGEPTQAVAIKTLKDKAEGPLREEFRQEAMLRARLQHPNIVCLLGVVTKDQPLSM
 IFSYCSHGDLHEFLVMRSPHSDVGSTDDDRTVKSALEPPDFVHVVAQIAAGMEFL
 SSHHVCHKDLATRNVLVYDKLNVRLSDLGFLREVYSADYYKLMGNSLLPIRWMS
 PEAVMYGKFSIDSDIWSYGVVLWEVFSYGLQPYCGYSNQDQVEMIRSRQVLPCP
 DDCPAWVYALMIECWNEFPSRRPRFKDIHSRLRSWGNLSNYNSSAQTSGASNTTQ
 15 TSSLSTSPVSNVSNARYMAPKQKAQFPQPQFIPMKGQIRPLVPPAQLYIPVNGYQ
 PVPAYGAYLPNFYPVQIPMQMAPQQVPPQMVPKPSHHSGSGSTSTGYVTTAPSN
 TSVADRAALLSEGTEDEVQNAEDVAQSPVQEAEEEEEGSVPETELLGDNDTLQVT
 EAAHVQLEA

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

ATGGCCCCGGGGCTCGGCGCTCCCGCGGCGGCGCTGCTGTGCATCCCGGCCGT
 CTGGGGCGGCCGCCGCTTCTGCTCTCAGTGTCCCGGACTTCAGGTGAAGTGG
 AGGTTCTGGATCCGAACGACCCCTTAGGACCCCTTGATGGGCAGGACGGCCCCG
 ATTCCAACCTCTGAAAGGTTACTTTCTGAATTTTCTGGAGCCAGTAAACAATAT
 25 CACCATTGTCCAAGGCCAGACGGCAATTCTGCACTGCAAGGTGGCAGGAAAC
 CCACCCCCCTAACGTGCGGTGGCTAAAGAATGATGCCCCGGTGGTGCAGGAGC
 CGCGGCGGATCATCATCCGGAAGACAGAATATGGTTCACGACTGCGAATCCA
 GGACCTGGACACGACAGACACTGGCTACTACCAGTGCCTGGCCACCAACGGG
 ATGAAGACCATTACCGCCACTGGCGTCTCTGTTTGTGCGGCTGGGTCCAACGCA
 30 CAGCCCAAATCATAACTTTAGGATGATTACCACGAGGATGGGTCTGCCAGC
 CTTACCGGGGAATTGCCTGTGCACGCTTCATTGGCAACCGGACCATTATGTG
 GACTCGCTTCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCGGCCTTCA
 CCATGATCGGCACGTCTACGCACCTGTGCGGACCAGTGCTCACAGTTCGCCATC
 CCATCCTTCTGCCACTTCGTGTTTCTCTGTGCGACGCGCGCTCCCGGGCACCC
 35 AAGCCGCGTGAGCTGTGCCGCGACGAGTGCGAGGTGCTGGAGAGCGACCTGT
 GCCGCCAGGAGTACACCATCGCCCCGCTCCAACCCGCTCATCCTCATGCGGCTT
 CAGCTGCCCCAAGTGTGAGGCGCTGCCCATGCCTGAGAGCCCCGACGCTGCCA
 ACTGCATGCGCATTGGCATCCAGCCGAGAGGCTGGGCGGCTACCATCAGTGC
 TATAACGGCTCAGGCATGGATTACAGAGGAACGGCAAGCACCACCAAGTCAG
 40 GCCACCAGTGCCAGCCGTGGGCCCCTGCAGCACCCCCACAGCCACCACCTGTCC
 AGCACAGACTTCCCTGAGCTTGGAGGGGGGCACGCCTACTGCCGGAACCCCG
 GAGGCCAGATGGAGGGCCCCTGGTGCTTTACGCAGAATAAAAACGTACGCAT
 GGAAGTGTGTGACGTACCCTCGTGTAGTCCCCGAGACAGCAGCAAGATGGGG

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

MARGSALPRRPLLCIPAVWAAAALLSVSRTSGEVEVLDPNDPLGPLDGDGPIPT
 LKGYFLNFLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIR
 KTEYGSRLRIQDLDTTDTGYQQCVATNGMKTITATGVLFVRLGPTHSPNHNQDD

YHEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTHLSDQCS
 QFAIPSFCHFVFPLCDARSRTPKPRELCRDECEVLESDLCRQEYTIARSNPLILMRL
 QLPKCEALPMPESPDAANCMRIGIPAERLGRYHQCYNNGSGMDYRGTAATTKSGH
 QCQPWALQHPHSHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQNKNVRMEL
 5 CDVPSCSPRDSSKMG

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

ATGGCTCGGGGCTGGGTGCGGCCGAGCCGTGTGCCTCTGTGCGCCCGGGCCGT
 CTGGACGGCTGCGGCGCTCCTGCTCTGGACACCCTGGACGGCAGGTGAAGTG
 10 GAAGATTCGGAGGCAATCGACACCTTGGGACAACCTGATGGACCGGACAGCC
 CACTTCCCACTCTGAAAGGCTACTTTCTGAATTTTCTGGAGCCAGTCAACAAT
 ATCACCATTGTTCAGGGCCAGACGGCAATCCTGCACTGCAAGGTGGCGGGAA
 ACCCACCTCCCAATGTGCGGTGGCTGAAGAATGATGCCCCGGTTGTGCAAGAG
 CCACGAAGGGTTCGTCATCCGGAAGACAGAATACGGCTCCCGGCTGCGGATCC
 15 AAGACCTGGACACAACAGACACAGGCTACTACCAGTGTGTGGCTACCAACGG
 GCTGAAGACCATCACTGCCACTGGGGTTCTATATGTGCGGCTCGGTCCGACGC
 ACAGCCCGAACCACAATTTTCAGGATGACGATCAGGAAGATGGCTTCTGCCA
 GCCGTACCGAGGGATCGCTTGTGCGCGCTTCATTGGGAACCGGACTATTTATG
 TGGACTCCCTCCAGATGCAGGGGGAGATTGAAAACCGAATCACAGCTGCCTTC
 20 ACCATGATCGGCACCTCCACGCAACTGTCAGACCAGTGTTACAGTTTGCCAT
 CCCATCCTTCTGCCACTTCGTCTTCCCTCTGTGCGACGCATGCTCCCGGGCGCC
 CAAGCCTCGCGAACTGTGCCGGGATGAATGTGAGGTGCTGGAGAACGACCTG
 TGCCGCCAGGAGTACACCATCGCCCGCTCCAACCCGCTCATCCTCATGCGGCT
 CCAGCTGCCCAAGTGCGAAGCGCTGCCCATGCCCGAGAGCCCGGATGCTGCG
 25 AACTGCATGCGCATCGGGATCCCCGCGGAGAGGCTGGGTGCTACCACCAGT
 GCTACAACGGCTCCGGCGCCGATTACAGGGGGATGGCCAGTACCACCAAGTC
 AGGCCACCAGTGTCAGCCTTGGGCTCTGCAGCACCCCCACAGCCATCGCCTAT
 CCAGCACGGAATTCCCTGAGCTGGGAGGAGGCCATGCCTACTGCCGGAACCC
 CGGGGGCCAGATGGAAGGCCCCGTGGTGCTTTACGCAGAATAAAAACGTACGC
 30 GTGGAACGTGTGTGACGTACCCCCGTGTAGTCCCCGATATGGCAGCAAGATGGG
 G

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

MARGWVRPSRVPLCARAVWTAALLLWTPWTAGEVEDSEAIDTLGQPDGPDSP
 35 LPTLKGYFLNFLEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEP
 VVIRKTEYGSRLRIQDLDTDTGYQCVATNGLKTITATGVLYVRLGPTHSPNHN
 FQDDDQEDGFCQPYRGIACARFIGNRTIYVDSLQMQGEIENRITAAFTMIGTSTQL
 SDQCSQFAIPSFCHFVFPLCDACSRAPKPRELCRDECEVLENDLCRQEYTIARSNPL
 40 ILMRLQLPKCEALPMPESPDAANCMRIGIPAERLGRYHQCYNNGSGADYRGMAS
 TTKSGHQCQPWALQHPHSHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQNKNV
 RVELCDVPSPRYGSKMG

[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

GYTFTDYE

[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
HGSSLIYYAMDY
- 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
EVQLVESGGDLVKPGGSLKLSCAAS
- [0503] SEQ ID NO:50; 6E6 VH FR2
MSWVRQTPDKRLEWVAT

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

HYVDSVKGRFTISRDNANHILYLQMSSLNSED TAMYYCAR

[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

MHWVKQTPVHG LEWIGA

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

AYNQKFKGKATLTADKSSSTAYMELSRITSEDSAVYYCTR

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

20 WGQGTSVTVSS

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

DIVMTQAAPSVFVTPGESVSISCRSS

[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

EVQLVESGGDLVKPGGSLKLSCAAS

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

MSWVRQTPDKRLEWVAT

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

10 YYPDSVKGRFTISRDNKNSLYLQMSSLKSEDTAMYYCAR

[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

ESISGIPSRFSGSGSGTDFTLINSVESEDIADYYC

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

20 FGSGTKLEKK

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

EVQLVESGGGLVQPKGSLKLSCAAS

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

MNWVRQAPKGLEWVAR

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

YYADSVKDRFTISRDDSQSMLHLQMNNLKTEDTAMYVCVR

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

WGQGTSTVTVSS

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

DIQMTQSPSSLSASLGGERVSLTCRAS

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

LGWLQQKPDGTIKRLIY

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

10 TLDSGVPKRFSGSRSGSAYSLTISSLESEDFADYYC

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

FGGGTKLEIK

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

ATMGWSCIIILFLVATATGVHS

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 LFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDSESRWQQGNVVFSCSVMEALH
NHYTQKSLSLSPGK

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

25 ATMGWSCIIILFLVATATGVHSDIVMTQSHKFMSTSIGDRVSITCKASQDVGHYVAWYQQKPGQS
PKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNIYPWTFGGGSKLAIK
GSTSGSGKPGSGEGSTKGEVQLVESGGDLVKPGGSLKLSCAASGFTFSNYGMSWVRQTPDKRLE
WVATISSGGGYTHYVDSVKGRFTISRDNANHILYLMSSSLNSEDAMYYCARHPRDFSYAMDYW

GQGTSVTVSSEFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDESRWQQGN
VFSCSVMEALHNHYTQKSLSLSPGK

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

ATMGWSCIIILFLVATATGVHSDIVMTQAAPSVPVTPGESVSISCRSSKSLHNSNGNTYLYWFLQ
RPGQSPQLLIYRMSNLASGVDPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTVGAGT
KLELKGSTSGSGKPGSGEGSTKGQVQLQQSGAELVRPGASVKLSCKALGYTFTDYEMHWVKQTP
VHGLEWIGAIHPGSGGTAYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTRRRPRFYG
10 MDYWGGTSTSVTVSSEFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDESRW
QQGNVFSCSVMEALHNHYTQKSLSLSPGK

[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

CTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTG
TGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTC
CTCACCGTCTCGACACGAGTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
25 CCTCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCTATAGCAAGCTCACCGT
GGACGAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
30 AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

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

GCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCG
ACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAATAGGAGACAGGGTCAGCATCAC
CTGCAAGGCCAGTCAGGATGTGGGTCAATTATGTGGCCTGGTATCAACAGAAACCAGGTCAATCT
35 CCTAAACTACTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCTTCACAGGTA
GTGGATCTGGGACAGATTTCACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTA
TTTCTGTGAGCAATATAACATCTATCCGTGGACGTTCCGTGGAGGCTCCAAGCTGGCAATCAAA
GGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCTACCAAGGGCGAGGTGCAGC
TGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC

TGGATTCACTTTT CAGTAATTATGGCATGTCTTGGGTTTCGCCAGACTCCAGACAAGAGGCTGGAG
TGGGTTCGCAACCATTAGTAGTGGTGGTGGTTACACTCACTATGTAGACAGTGTGAAGGGGCGAT
TCACCATTTCCAGAGACAATGCCAACCATATCCTGTACCTGCAAATGAGCAGTCTGAACCTCTGA
GGACACAGCCATGTATTATTGTGCAAGACACCCGAGGGATTTTTCCTATGCTATGGACTACTGG
5 GGTCAAGGGAACCTCAGTCACCGTCTCCTCAGAATTCTCTTCCCCCAAAAACCAAGGACACCC
TCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTGA
GGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGGAG
GAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCTGCACCAGGACTGGCTGA
ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCAT
10 CTCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAG
ATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCG
TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCTCTATAGCAAGCTCACCCTGGACGAGAGCAGGTGGCAGCAGGGGAAC
GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCC
15 TGTCTCCGGGTAAATGA

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

GCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCG
ATATTGTGATGACTCAGGCTGCACCCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATCTC
CTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCTGCAG
20 AGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCCTCAGGAGTCCCAG
ACAGGTTCACTGGCAGTGGGTGAGGAAGTCTTTTCACTGAGAATCAGTAGAGTGGAGGCTGA
GGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGCTGGGACC
AAGCTGGAGCTGAAAGGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCTACCA
AGGGCCAGGTTCAACTGCAACAGTCTGGGGCTGAGCTGGTGGGCTGGGGCTTCAGTGAAGCT
25 GTCTGCAAGGCTTTGGGCTACACATTTACTGACTATGAAATGCACTGGGTGAAGCAGACACCT
GTGCATGGCCTGGAATGGATTGGAGCTATTCATCCAGGAAGTGGTGGTACTGCCTATAATCAGA
AGTTCAAGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAG
CAGGCTGACATCTGAGGACTCTGCTGTCTATTACTGTACAAGAAGGAGGCTAGGTTCTATGGT
ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCAGAATTCTCTTCCCCCAAAAAC
30 CCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA
AAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCAT
CGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCA
35 TCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCC
CGTGCTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTCACCCTGGACGAGAGCAGGTGG
CAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA
AGAGCCTCTCCCTGTCTCCGGGTAAATGA

40 [0546] SEQ ID NO:93; CAR Leader peptide

MGWSCIIIFLVATATGVHS

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

VDESKYGPPCPPCP

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

VDESKYGPPCPPCPGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH
EALHNHYTQKSLSLGLGKM

[0549] SEQ ID NO:96; CAR hlgG4 + CH2/CH3

- 5 VDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKM

[0550] SEQ ID NO:97; CAR hCD28

- 10 FWVLVVGGLVACYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFA
AYRS

[0551] SEQ ID NO:98; CAR hCD137

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL

[0552] SEQ ID NO:99; CAR hCD3z

- 15 RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEGGKPRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

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

- MGWSCIIILFLVATATGVHSDIVMTQSHKFMSTSIGDRVSITCKASQDVGHYVAWYQQKPGQSPK
LLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNIYPWTFGGGSKLAIGKS
20 TSGSGKPGSGEGSTKGEVQLVESGGDLVKPGGSLKLSCAASGFTFSNYGMSWVRQTPDKRLEWV
ATISSGGGYTHYVDSVKGRFTISRDNANHILYLMSSLNSEDAMYYCARHPRDFSYAMDYWGQ
GTSVTVSSVDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
25 DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKMFVWLTVVVGGLVACYS
LTVTVAFIIFWVRSKRSRGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLLYIFK
QPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYD
LDKRRGRDPGEGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK
DTYDALHMQALPPR

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

- MGWSCIIILFLVATATGVHSDIVMTQAAPSVPVTPGESVVISCRSSKSLHNSNGNTYLYWFLQRP
GQSPQLLIYRMSNLASGVPDRFSGSGGTAFITLRISRVEAEDVGVYYCMQHLEYPLTVGAGTKL
ELKGSTSGSGKPGSGEGSTKGQVQLQQSGAELVRPGASVKLSCKALGYTFTDYEMHWVKQTPVH
GLEWIGAIHPGSGGTAYNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYCTRPRPRFYGMD
35 YWGQGTSTVTVSSVDESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI
EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGKMFVWLTVVVGGLV
40 CYSLLVTVAFIIFWVRSKRSRGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLL
YIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRRE

EYDVLDKRRGRDPGEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKGHDLGLYQGLS
TATKDTYDALHMQALPPR

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

5 MARGSALPRRPLLCPAVWAAAAALLLSVSRTSGEVEVLDPNDPLGPLDGQDGP IPTLKGYFLNF
LEPVNNITIVQGQTAILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIIRKTEYGSRLRIQDLDTT
DTGYYQCVATNGMKTITATGVLFVRLGPTHSPNHNFDQDDYHEDGFCQPYRGIACARFIGNRTIY
VDSLQMQGEIENRITAAFTMIGTSTHLSLSDQCSQFAIPSFCHFVFPLCDARSRTPKPRELCRDEC
EVLESDLCRQEYTIARSNPLILMRLQLPKCEALPMPESPDAANCMRIGIPAERLGRYHQCYNGS
10 GMDYRGTAATTKSGHQCPWALQHPHSHHLSSTDFPELGGGHAYCRNPGGQMEGPWCFTQNKNV
RMELCDVPSCSPRDSSKMGPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK

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

15 MHRPRRRGTRPPLLALLAALLLAARGAAQETELSVSAELVPTSSWNISSELNPKDSYLTLDPEM
NNITTSLGQTAEHLCKVSGNPPPTIRWFKNDAAPVVQEPRRLSFRSTIYGSRLRIRNLDTTDTGY
FQCVATNGKEVVSTGVLFVKFGPPPTASPGYSDEYEEDGFCQPYRGIACARFIGNRTVYMESL
HMQGEIENQITAAFTMIGTSSHLSDKCSQFAIPSLCHYAFPYCDETSSVPKPRDLRDECEILE
NVLCQTEYIFARSNPILMRLKLPNCEDLPQEPESPEAANCIRIGIPMADPINKNHCYNSTGVD
20 YRGTVSVTKSGRQCQPWNSQYPHTHTFTALRFPELNGGHSYCRNPGNQKEAPWCFTLDENFKSD
LCDIPACDSKDSKEKNKMEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK

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
TCTCCAACAAAGGCCTCCCGTCTTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG
AGAGCCACAGGTGTACACCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC
CGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAG
35 CAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCCCTAGGTAAAATG

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

GTCGACGAGTCCAAATATGGTCCCCCATGCCCACCATGCCCAGCACCTGAGTTCTTGGGGGGAC
CATCAGTCTTCTGTTCCTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGT
40 CACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGAT

GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTG
 TGGTCAGCGTCCTCACCCTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT
 CTCCAACAAAGGCCCTCCCGTCCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
 GAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGA
 5 CCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC
 GGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC
 AGGCTAACCGTGACAAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATG
 AGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCCCTAGGTAAATG

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

10 TTTTGGGTGCTGGTGGTGGTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGTGGCCT
 TTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGAC
 TCCCCGCCGCCCCGGGCCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCA
 GCCTATCGCTCC

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

15 AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAAACTA
 CTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTG

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

AGAGTGAAAGTTTCAGCAGGAGCGCAGACGCCCCCGCTACCAGCAGGGCCAGAACCAGCTCTATA
 ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCC
 20 TGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAA
 GATAAGATGGCGGAGGCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGGCAAGGGGC
 ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCA
 GGCCCTGCCCCCTCGCTGA

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

25 ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCGACATTG
 TGATGACCCAGTCTCACAAATTTCATGTCCACATCAATAGGAGACAGGGTCAGCATCACCTGCAA
 GGCCAGTCAGGATGTGGGTTCATTATGTGGCCTGGTATCAACAGAAAACAGGTCAATCTCCTAAA
 CTACTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCTTCACAGGTAGTGGAT
 CTGGGACAGATTTCACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGATTATTTCTG
 30 TCAGCAATATAACATCTATCCGTGGACGTTTCGGTGGAGGCTCCAAGCTGGCAATCAAAGGCTCC
 ACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCCACCAAGGGCGAGGTGCAGCTGGTGG
 AGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATT
 CACTTTTCAGTAATTATGGCATGTCTTGGGTTCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTG
 GCAACCATTAGTAGTGGTGGTGGTTACACTCACTATGTAGACAGTGTGAAGGGGCGATTACCA
 35 TTTCCAGAGACAATGCCAACCATATCCTGTACCTGCAAATGAGCAGTCTGAACTCTGAGGACAC
 AGCCATGTATTATTGTGCAAGACACCCGAGGGATTTTCTATGCTATGGACTACTGGGGTCAG
 GGAACCTCAGTCACCGTCTCCTCAGTCGACGAGTCCAAATATGGTCCCCCATGCCACCATGCC
 CAGCACCTGAGTTCTTGGGGGGACCATCAGTCTTCTGTTCCTTCCCCCAAAACCAAGGACACTCT
 CATGATCTCCCGGACCCCTGAGGTACAGTGCAGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT
 40 GTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
 AGCAGTTCAACAGCACGTACCGTGTGGTTCAGCGTCCCTCACCCTCCTGCACCAGGACTGGCTGAA
 CGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCTCCCGTCCCTCCATCGAGAAAAACCATC
 TCCAAGGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGA
 TGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGT

GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCC
GACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCT
GTCCCTAGGTAAAAATGTTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTG
5 CTAGTAACAGTGGCCTTTATTATTTTTCTGGGTGAGGAGTAAGAGGAGCAGGGGCGGACACAGTG
ACTACATGAACATGACTCCCCGCCGCCCTGGGCCCCACCCGCAAGCATTACCAGCCCTATGCCCC
ACCACGCGACTTCGCAGCCTATCGCTCCAAACGGGGCAGAAAAGAACTCCTGTATATATTCAAA
CAACCATTTATGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAG
AAGAAGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTTCCAGCAGGAGCGCAGACGCCCCCGCGTA
10 CCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTT
TTGGACAAGAGACGTGGCCGGGACCCCTGAGATGGGGGAAAGCCGAGAAGGAAGAACCCCTCAGG
AAGGCCTGTACAATGAACTGCAGAAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAA
AGGCGAGCGCCGGAGGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAG
GACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA

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

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCCGATATTG
TGATGACTCAGGCTGCACCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATCTCCTGCAG
GTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCTGCAGAGGCCA
GGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGAGTCCCAGACAGGT
20 TCAGTGGCAGTGGGTGAGGAAGTCTTTACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGT
GGGTGTTTATTACTGTATGCAACATCTAGAATATCCTCTCACGGTCGGTGCTGGGACCAAGCTG
GAGCTGAAAGGCTCCACCTCTGGATCCGGCAAGCCCGGATCTGGCGAGGGATCCACCAAGGGCC
AGGTTCAACTGCAACAGTCTGGGGCTGAGCTGGTGGGCTTCCAGTGAAGCTGTCTCTG
CAAGGCTTTGGGCTACACATTTACTGACTATGAAATGCACTGGGTGAAGCAGACACCTGTGCAT
25 GGCCTGGAATGGATTGGAGCTATTTCATCCAGGAAGTGGTGGTACTGCCTATAATCAGAAGTTCA
AGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGGCT
GACATCTGAGGACTCTGCTGTCTATTACTGTACAAGAAGGAGGCCTAGGTTCTATGGTATGGAC
TACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCAGTCGACGAGTCCAAATATGGTCCCCCAT
GCCCCACCATGCCCAGCACCTGAGTTTCTGGGGGGACCATCAGTCTTCTGTTCCTCCCCCAAAACC
30 CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAG
GAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAA
AGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCTGCACCA
GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCCTCCCGTCTCCATC
GAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCAT
35 CCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAG
CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCC
GTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGC
AGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAA
GAGCCTCTCCCTGTCCCTAGGTAAAAATGTTTTGGGTGCTGGTGGTGGTGGTGGAGTCTGGCT
40 TGCTATAGCTTGCTAGTAACAGTGGCCTTTATTATTTTTCTGGGTGAGGAGTAAGAGGAGCAGGG
GCGGACACAGTGACTACATGAACATGACTCCCCGCCGCCCTGGGCCCCACCCGCAAGCATTACCA
GCCCTATGCCCCACCAAGCAGTTCGCAGCCTATCGCTCCAAACGGGGCAGAAAAGAACTCCTG
TATATATTCAAACAACCATTTATGAGACCAGTACAACTACTCAAGAGGAAGATGGCTGTAGCT
GCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGAGAGTGAAGTTTCCAGCAGGAGCGCAGA
45 CGCCCCCGGTACACAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAG
GAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCCTGAGATGGGGGGAAAGCCGAGAAGGA
AGAACCCTCAGGAAGGCTGTACAATGAACTGCAGAAAAGATAAGATGGCGGAGGCCTACAGTGA
GATTGGGATGAAAGGCGAGCGCCGGAGGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGT
ACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA

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

HQCYNGSGMDYRGTA STTKSGHQCQPWALQHPHSHHLSSTDFPELGGGHAYCRNPGG
QMEGPWCFTQNKNVRMELCDVPSCS

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

5 AILHCKVAGNPPPNVRWLKNDAPVVQEPRRIIRKTEYGSRLRIQDLDTTDTGYYQCVAT
NGMKTITAT