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## (54) ANTI-ROR1 ANTIBODIES

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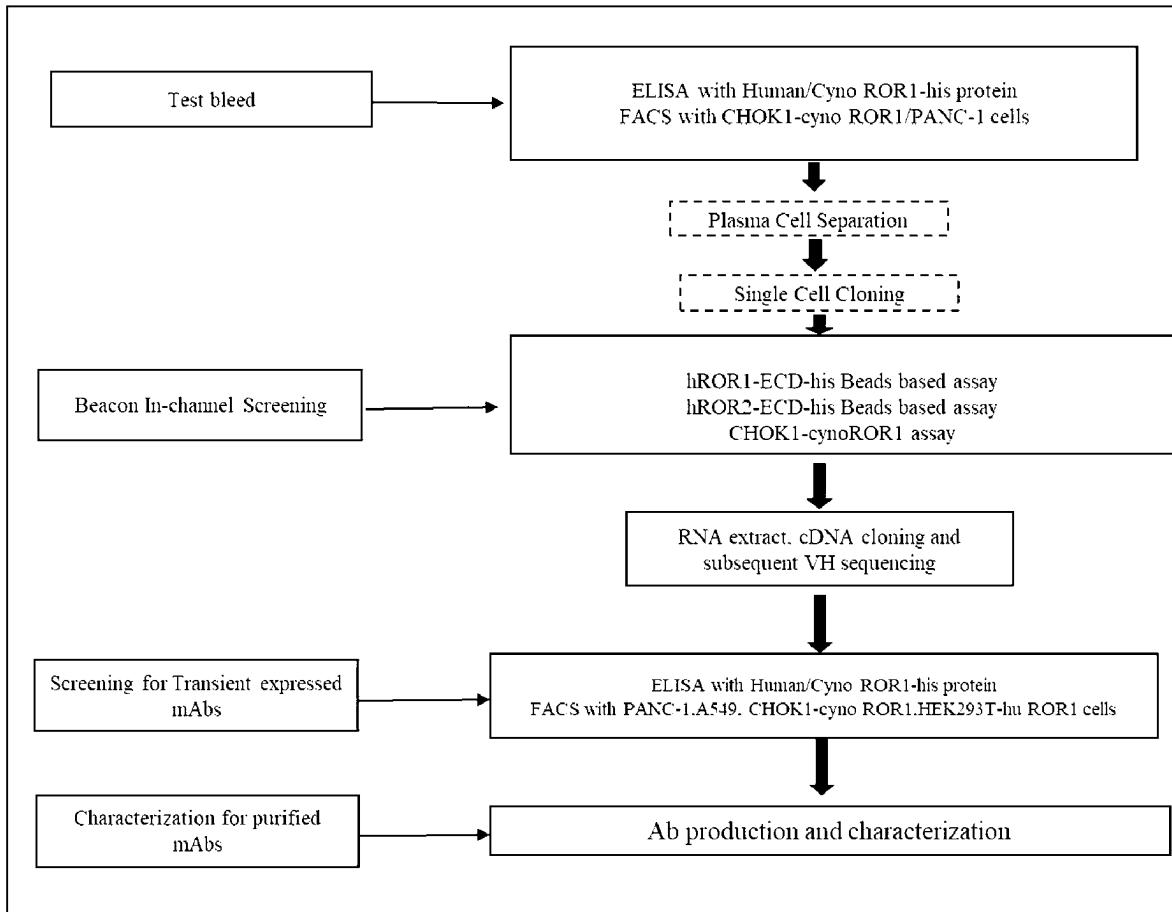
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## (57) ABSTRACT

Provided are antibodies and antigen-binding fragments thereof that recognize ROR1. In some embodiments, the antibodies provide a means of treating ROR1-positive cancer. In some embodiments, the antibodies are used to diagnose or image ROR1-positive cancer.

Specification includes a Sequence Listing.



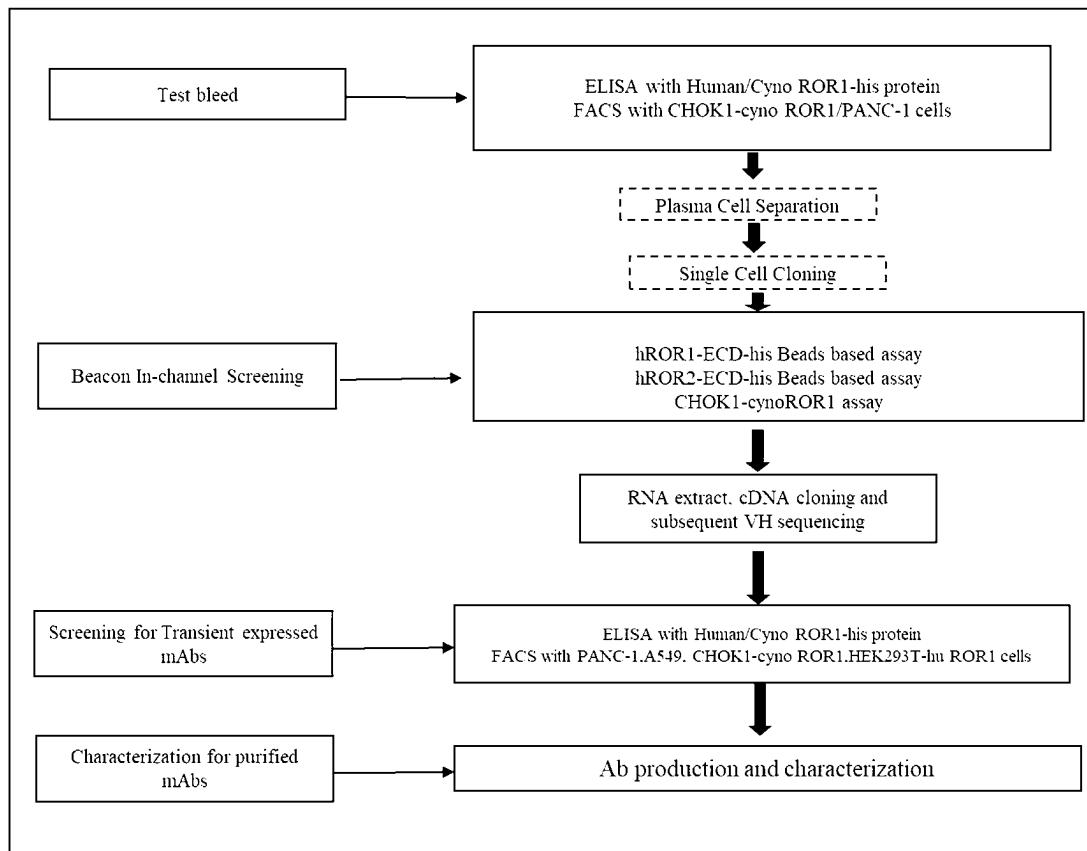
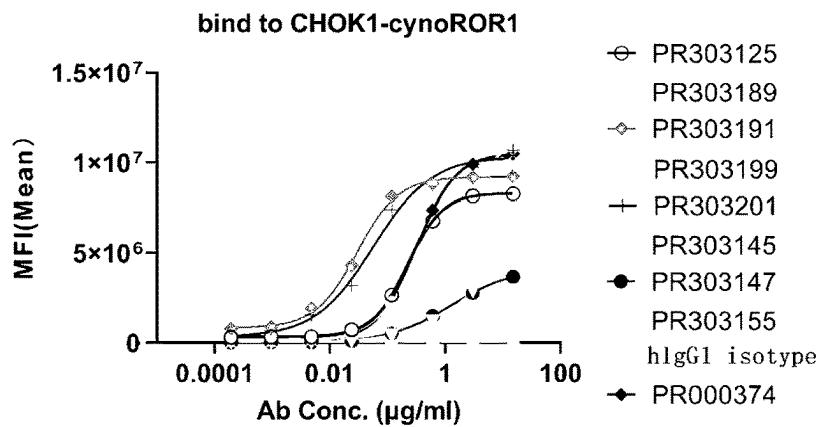
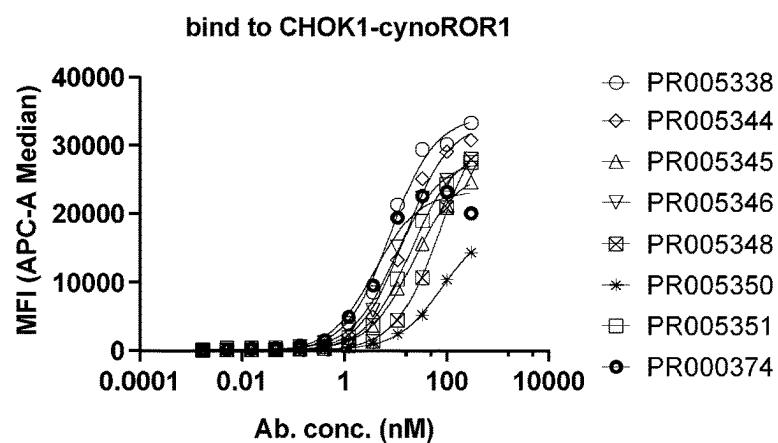
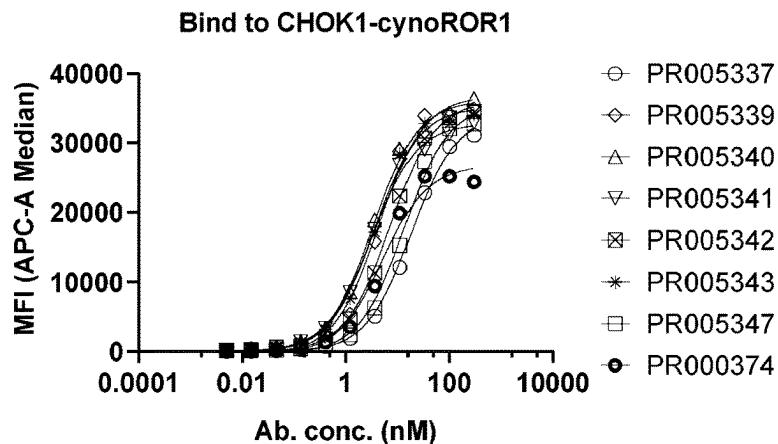
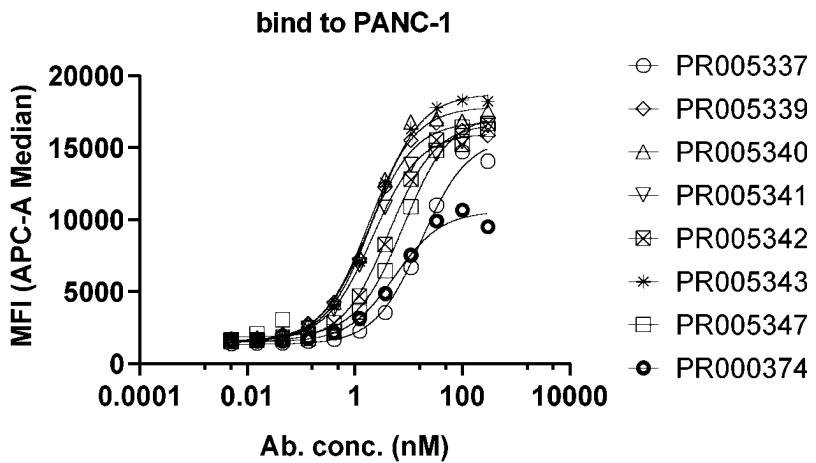


FIG. 1

**A****FIG. 2**

A



B

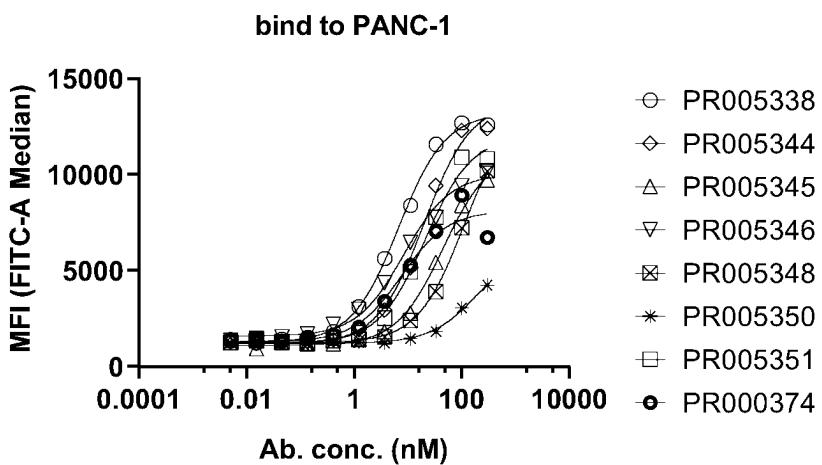
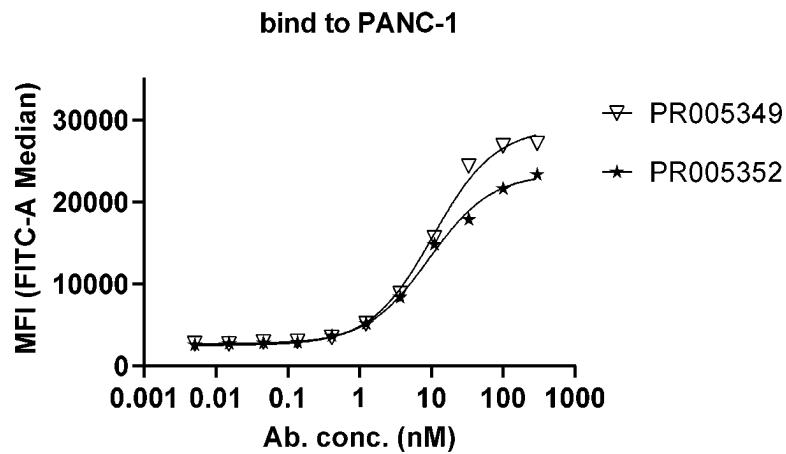


FIG. 3

C



D

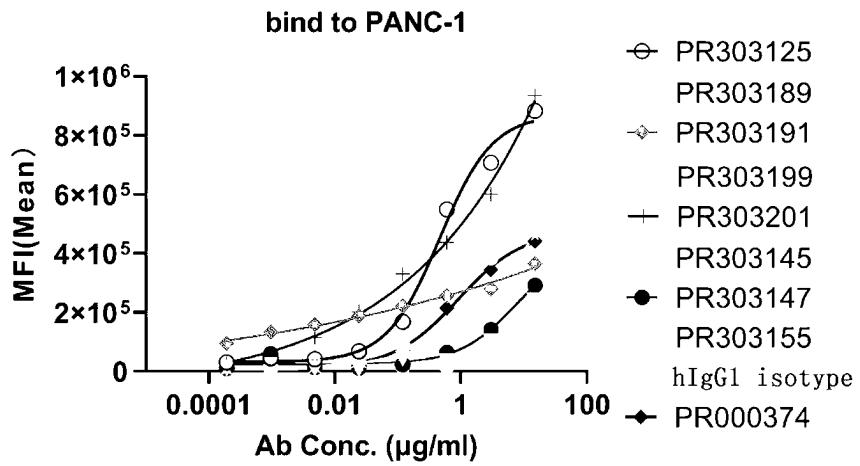


FIG. 3 (continued)

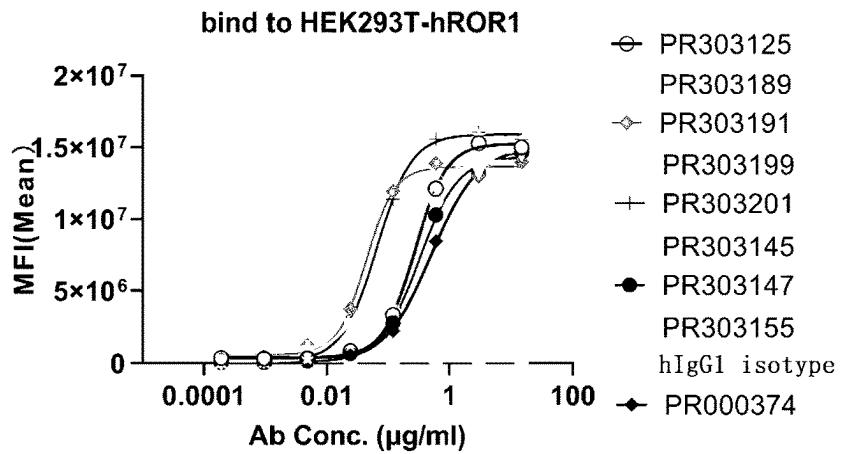


FIG. 4

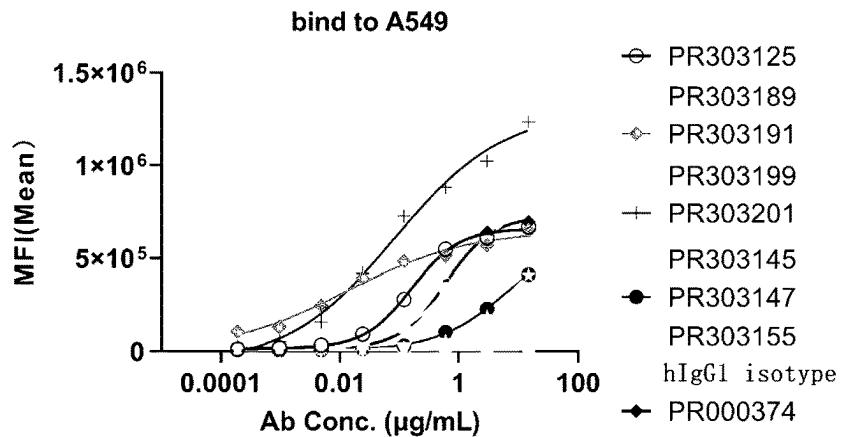


FIG. 5

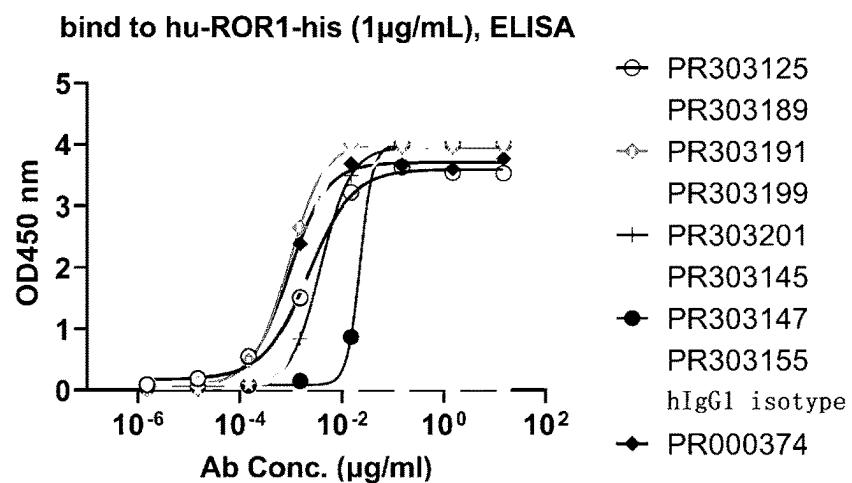
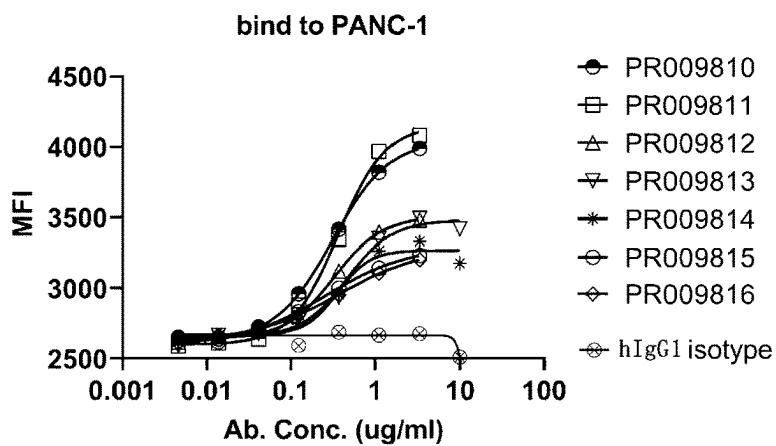
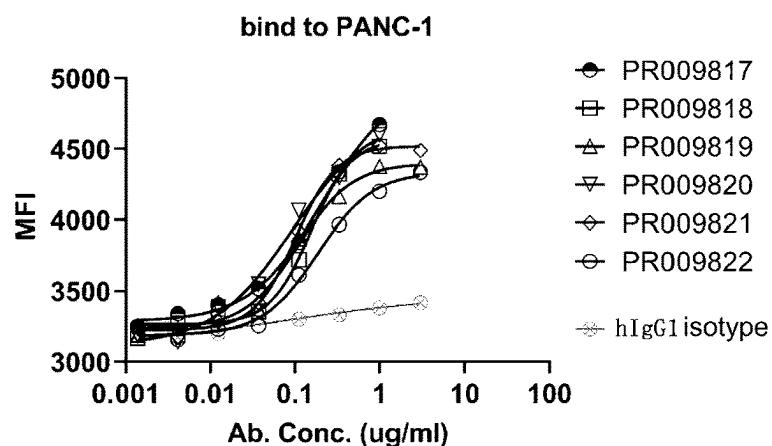


FIG. 6

A



B



C

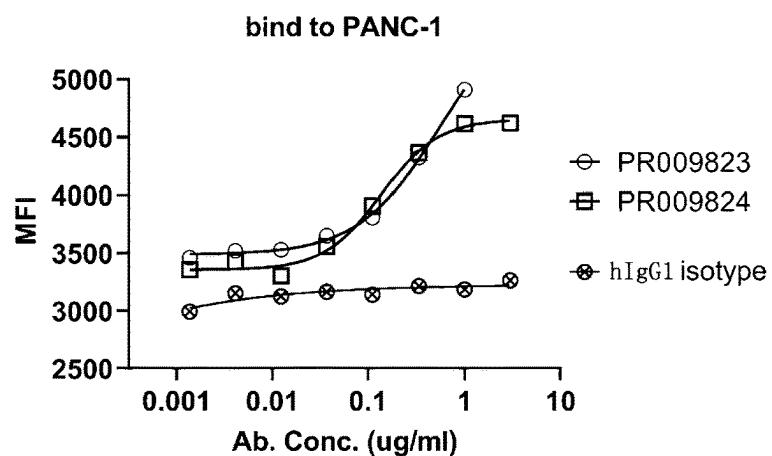
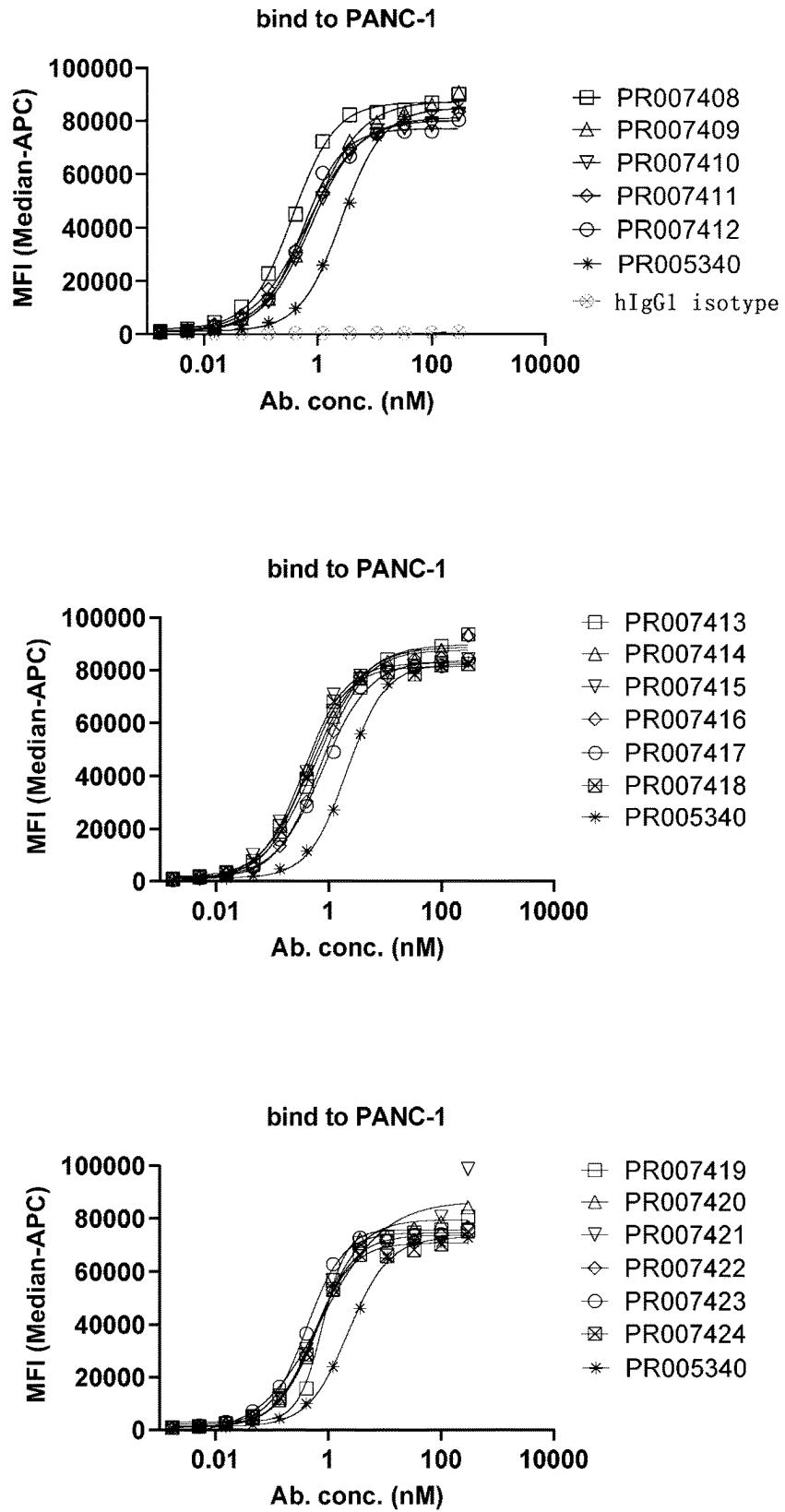


FIG. 7

**A****FIG. 8**

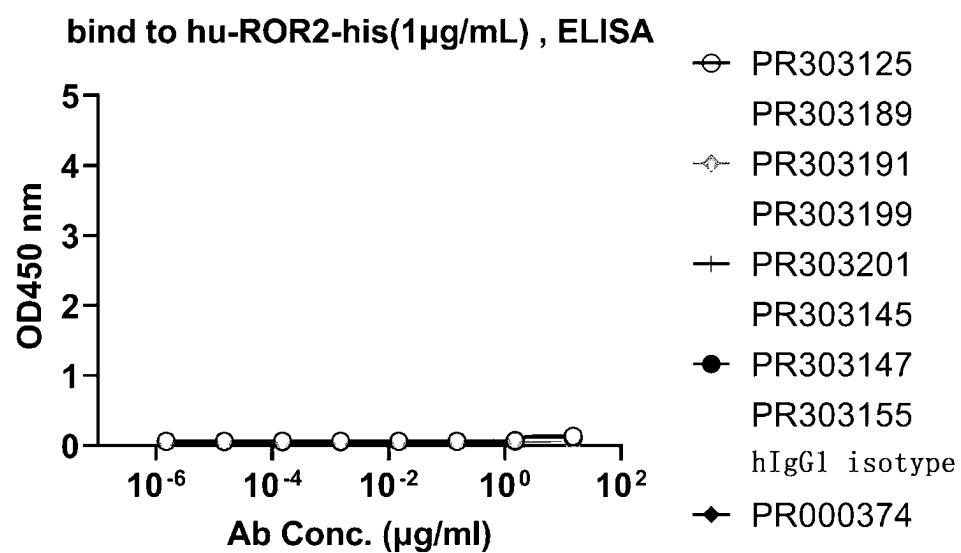
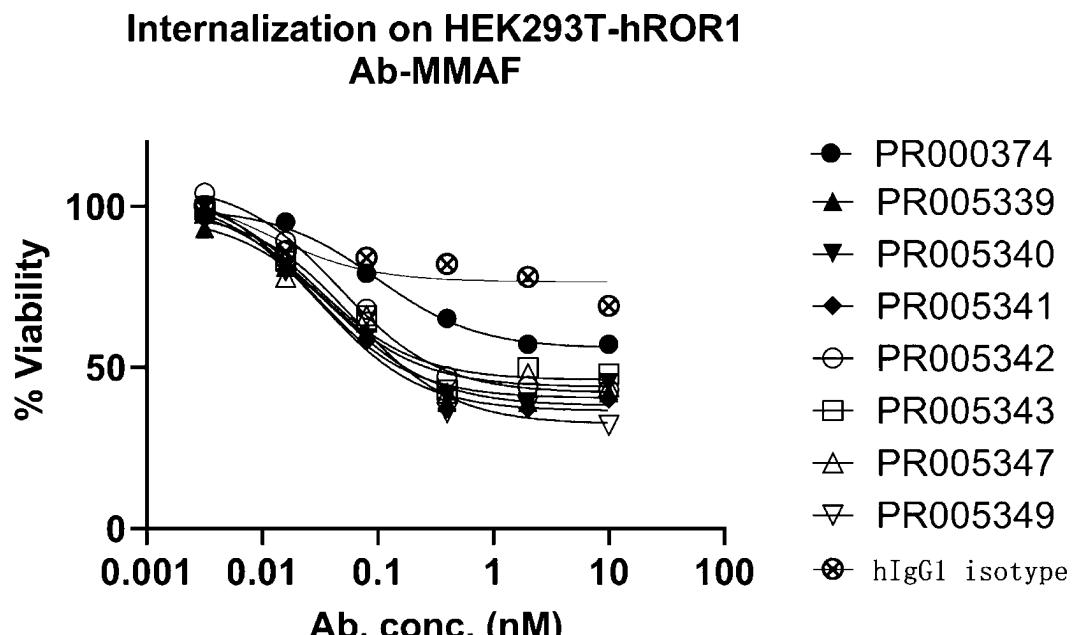


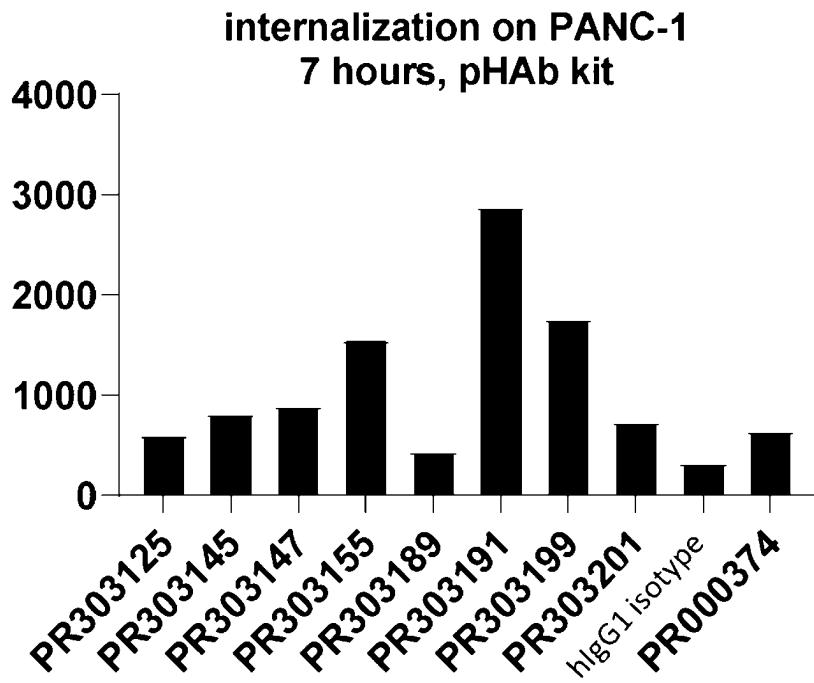
FIG. 9



	IC50	Span
PR000374	0.10	43.53
PR005339	0.04	58.99
PR005340	0.03	66.51
PR005341	0.03	67.33
PR005342	0.05	65.27
PR005343	0.03	58.8
PR005347	0.03	57.6
PR005349	0.06	66.33
hIgG1 isotype	0.01	29.27

FIG. 10

A



B

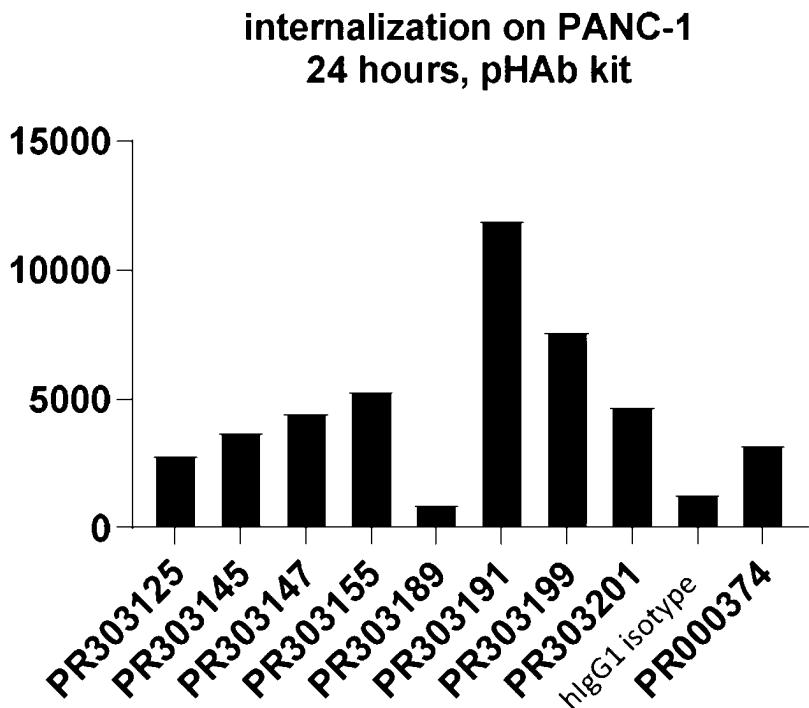


FIG. 11

## ANTI-ROR1 ANTIBODIES

### FIELD OF THE INVENTION

**[0001]** The invention relates to antibodies and antigen-binding fragments thereof that bind to ROR1 and use thereof.

### BACKGROUND OF THE INVENTION

**[0002]** Receptor tyrosine kinase like orphan receptor 1 (ROR1) is highly expressed during embryonic and infant development, and the expression level decreases significantly in children and adults. The expression of ROR1 was significantly increased in a variety of blood cancers and solid tumors. Blood cancers that highly express ROR1 include, e.g., B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and marginal zone lymphoma (MZL). In solid tumors, the types of cancers expressing ROR1 include, e.g., breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, adrenal cancer and many other cancers. Therefore, ROR1 has become a new tumor specific target. Many data show that ROR1 plays an important role in promoting tumor growth and metastasis, inducing drug resistance, and inhibiting apoptosis.

**[0003]** The current consensus about ROR1 signal transduction is that ROR1 can play an important role in a variety of physiological processes, including regulating cell division, proliferation, migration, and cell chemotaxis, especially wnt5a, by mediating the signal transmission of non-classical wnt pathways. Wnt5a is a typical non-classical activator of wnt signaling pathway and participates in phosphorylation of NF- $\kappa$ B subunit p65, activating NF- $\kappa$ B pathway in tumor cells, promoting cell migration and invasion, EMT, cancer metastasis, etc. Wnt5a/ROR1 is highly expressed in many cancers. As the receptor of Wnt5a, ROR1 participates in the activation of tumor cell NF- $\kappa$ B channel.

**[0004]** ROR1 is considered a potential target because it is a tyrosine kinase receptor with drug resistance; and it is expressed on the cell surface. More importantly, it is highly expressed in tumor cells, but very low in healthy adult tissues.

**[0005]** There is a lack of antibodies that have high affinity with ROR1, do not cross react with ROR2 and have good binding ability and internalization activity, especially fully human antibodies.

### SUMMARY OF THE INVENTION

**[0006]** The present invention provides novel antibodies binding to ROR1 or antigen binding fragments thereof, which can be in a form of a heavy chain-only antibody (HCAb).

**[0007]** In an aspect, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), and wherein the VH comprises

HCDRs 1-3 of a VH having the amino acid sequence set forth in any one of SEQ ID NOS: 147-202.

**[0008]** In some embodiments, the VH comprises HCDRs 1-3 having the amino acid sequences set forth in:

- [0009] SEQ ID NOS: 11, 40, 100 respectively,
- [0010] SEQ ID NOS: 12, 41, 101 respectively,
- [0011] SEQ ID NOS: 12, 42, 102 respectively,
- [0012] SEQ ID NOS: 12, 40, 103 respectively,
- [0013] SEQ ID NOS: 12, 43, 104 respectively,
- [0014] SEQ ID NOS: 13, 44, 105 respectively,
- [0015] SEQ ID NOS: 12, 40, 106 respectively,
- [0016] SEQ ID NOS: 12, 45, 107 respectively,
- [0017] SEQ ID NOS: 12, 40, 108 respectively,
- [0018] SEQ ID NOS: 14, 46, 109 respectively,
- [0019] SEQ ID NOS: 12, 47, 110 respectively,
- [0020] SEQ ID NOS: 12, 48, 111 respectively,
- [0021] SEQ ID NOS: 12, 45, 112 respectively,
- [0022] SEQ ID NOS: 15, 49, 113 respectively,
- [0023] SEQ ID NOS: 16, 50, 114 respectively,
- [0024] SEQ ID NOS: 12, 51, 115 respectively,
- [0025] SEQ ID NOS: 18, 56, 126 respectively,
- [0026] SEQ ID NOS: 21, 40, 130 respectively,
- [0027] SEQ ID NOS: 22, 60, 131 respectively,
- [0028] SEQ ID NOS: 12, 40, 132 respectively,
- [0029] SEQ ID NOS: 23, 61, 133 respectively,
- [0030] SEQ ID NOS: 19, 57, 127 respectively,
- [0031] SEQ ID NOS: 20, 58, 128 respectively,
- [0032] SEQ ID NOS: 14, 59, 129 respectively,
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- [0052] SEQ ID NOS: 17, 40, 118 respectively,
- [0053] SEQ ID NOS: 17, 55, 118 respectively,
- [0054] SEQ ID NOS: 17, 55, 103 respectively,
- [0055] SEQ ID NOS: 12, 55, 117 respectively, or
- [0056] SEQ ID NOS: 12, 55, 118 respectively.

**[0057]** In some embodiments, the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to any one of SEQ ID NOS: 147-202.

**[0058]** In some embodiments, the antibody comprises an Fc region.

**[0059]** In some embodiments, the antibody comprises a heavy chain (HC), and wherein the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to any one of SEQ ID NOS: 205-260.

- [0060] In some embodiments, the antibody does not comprise a light chain.
- [0061] In some embodiments, the antibody comprises two heavy chains.
- [0062] In some embodiments, the antibody is a chimeric antibody, a humanized antibody, or a human antibody.
- [0063] In some embodiments, the antibody is of an isotype selected from the group consisting of IgG, IgA, IgM, IgE and IgD.
- [0064] In some embodiments, the antibody is of a subtype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.
- [0065] In some embodiments, the antigen binding fragment is selected from the group consisting of HCAb, VH<sub>H</sub>, nanobody, Fab, Fab', F(ab')<sub>2</sub>, Fd, Fd', and dAb.
- [0066] In some embodiments, the antibody is a monoclonal antibody, a bi-specific or a multi-specific antibody.
- [0067] In some embodiments, the antibody is monovalent, bivalent or multivalent.
- [0068] In some embodiments, the antibody or antigen binding fragment is attached to a fluorescent label, radiolabel or cytotoxic agent.
- [0069] In another aspect, the invention provides a bi-specific antibody, comprising the antibody or antigen-binding fragment thereof of the invention and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen; preferably, the second antigen binding region specifically binds to CD3.
- [0070] In still another aspect, the invention provides a nucleic acid comprising a nucleotide sequence encoding the antibody or the antigen binding fragment thereof of the invention or the bi-specific antibody of the invention.
- [0071] In yet another aspect, the invention provides a vector comprising the nucleic acid of the invention.
- [0072] In another aspect, the invention provides a host cell comprising the nucleic acid of the invention or the vector of the invention.
- [0073] In another aspect, the invention provides an antibody-drug conjugate (ADC), comprising the antibody or the antigen binding fragment thereof of the invention or the bi-specific antibody of the invention.
- [0074] In still another aspect, the invention provides a pharmaceutical composition comprising (i) the antibody or the antigen binding fragment thereof of the invention, the bi-specific antibody of the invention, the nucleic acid of the invention, the vector of the invention, the host cell of the invention, or the antibody-drug conjugate of the invention; and (ii) a pharmaceutically acceptable carrier or excipient.
- [0075] In some embodiments, the composition further comprises a second therapeutic agent selected from the group consisting of an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.
- [0076] In another aspect, the invention provides a method of treating a cancer in a subject, comprising administering to the subject an effective amount of the antibody or the antigen binding fragment thereof of the invention, the bi-specific antibody of the invention, the nucleic acid of the invention, the vector of the invention, the host cell of the invention, the antibody-drug conjugate of the invention, or the pharmaceutical composition of the invention.
- [0077] In some embodiments, the cancer is a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.
- [0078] In some embodiments, the method further comprises administering to the subject a second therapeutic agent.
- [0079] In some embodiments, the second therapeutic agent is selected from an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.
- [0080] In another aspect, the invention provides use of the antibody or the antigen binding fragment thereof of the invention, the bi-specific antibody of the invention, the nucleic acid of the invention, the vector of the invention, the host cell of the invention, the antibody-drug conjugate of the invention, or the pharmaceutical composition of the invention in the manufacture of a medicament for treating a cancer in a subject.
- [0081] In some embodiments, the cancer is a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.
- [0082] In some embodiments, the medicament further comprises a second therapeutic agent, preferably the second therapeutic agent is selected from an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.
- [0083] In some embodiments, the medicament is administered in combination with a second therapeutic agent, preferably the second therapeutic agent is selected from an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.
- [0084] In another aspect, the invention provides the antibody or the antigen binding fragment thereof of the invention, the bi-specific antibody of the invention, the nucleic acid of the invention, the vector of the invention, the host cell of the invention, the antibody-drug conjugate of the invention, or the pharmaceutical composition of the invention for use in treating a cancer in a subject.
- [0085] In some embodiments, the cancer is a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL),

breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

[0086] In some embodiments, the antibody or the antigen binding fragment thereof of the invention, the bi-specific antibody of the invention, the nucleic acid of the invention, the vector of the invention, the host cell of the invention, the antibody-drug conjugate of the invention, or the pharmaceutical composition of the invention is administered in combination with a second therapeutic agent, preferably the second therapeutic agent is selected from an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.

[0087] In another aspect, the invention provides a method for diagnosing ROR1 positive cancer in a subject comprising:

[0088] (a) obtaining a biological sample from the subject,

[0089] (b) contacting the sample with the antibody or the antigen binding fragment thereof of the invention, and

[0090] (c) detecting binding of the antibody to the sample,

[0091] wherein an increase in binding of the antibody or antigen binding fragment thereof to the sample as compared to binding of the antibody or antigen binding fragment thereof to a control sample identifies the subject as having a ROR1 positive cancer.

[0092] In another aspect, the invention provides a method for imaging a ROR1 positive cancer in a subject comprising:

[0093] (a) administering the antibody or antigen binding fragment thereof of the invention to the subject, wherein the antibody is conjugated to a detectable marker, and

[0094] (b) detecting the presence of the marker.

[0095] In some embodiments, the detectable marker is <sup>111</sup>In, and preferably the detection of the marker is by single-photon emission computed tomography. In some embodiments, the detectable marker is <sup>89</sup>Zr, and preferably the detection of the marker is by positron emission tomography.

#### DESCRIPTION OF THE DRAWINGS

[0096] FIG. 1. The work flow of screening strategy and process for Single B-cell Cloning Screening.

[0097] FIG. 2. Binding of HCAb antibodies to CHO-K1-cynoROR1 cells.

[0098] FIG. 3. Binding of HCAb antibodies to PANC-1 cells.

[0099] FIG. 4. Binding of HCAb antibodies to HEK293T-hROR1 cells.

[0100] FIG. 5. Binding of HCAb antibodies to A549 cells.

[0101] FIG. 6. Binding of HCAb antibodies to hu-ROR1-ECD-his by ELISA.

[0102] FIG. 7. Binding of PR005340 variants of monovalent form (VH-Flag-His) to PANC-1 cells.

[0103] FIG. 8. Binding of PR005340 variants of bivalent form (HCAb) to PANC-1 cells.

[0104] FIG. 9. Binding of HCAb antibodies to hu-ROR2-his by ELISA.

[0105] FIG. 10. Internalization of HCAb antibodies on HEK293T-hROR1 cells by Ab-MMAF cytotoxicity method.

[0106] FIG. 11. Internalization of HCAb antibodies on PANC-1 cells by pHAb kit.

#### SEQUENCE LISTING

[0107] The sequences of the heavy chain, the variable region of heavy chain, the CDRs of the heavy chain of anti-ROR1 HCAb antibodies of the invention are indicated in Tables 1-3 below. The sequences of the light chain, heavy chain, the variable region of light chain, the variable region of heavy chain, the CDRs of the light chain and heavy chain of reference antibody PR000374 are indicated in Table 4 below.

TABLE 1

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
PR005337	EVQLVESGGGLVKGPGSRLRLSCAASGFTFSDDYYMSWIRQAPGKGLEWVS YISSLGGSTIHYADSVKGGRFTSRDNAKNSLYLQMNSLRTEDTAVYYCAR DPPTSNSDWVSLHFDHWGQGTLTVTSSEPKSSDKTHTCPPCPAPELLGGP SVELFPKKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHN AATKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I SKAKGQPREPOVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	205
PR005338	EVQLVESGGGLVKGPGSRLRLSCAASGFTFSDDYYMSWIRQAPGKGLEWISYIS SSGGTTIHYADSVKGGRFTISRDNAKNSLYLQMNSLRTEDTAVYYCARDAPSSN SDWVSLQFDYWGQGTLTVTSSEPKSSDKTHTCPPCPAPELLGGPVSFLFPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHN AKTTPKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I SKAKGQPREPOVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE GSFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	206
PR005339	EVQLVESGGGLVKGPGSRLKLSCAASGFTFSDDYYMSWIRQAPGKGVEWIS YISNNNGSTIHYADSVKGGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR DFNNGWYEDFDYWGQGTLTVTSSEPKSSDKTHTCPPCPAPELLGGPSVF LFPPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHN AKTTPKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I SKAKGQPREPOVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE	207

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
	NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	
PR005340	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYYMSWIRQAPGKGLEWISYIS SSGSTIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARDIPSSSS DWPSLQFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYN TYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	208
PR005341	EVQLVESGGGLVKPGGSLRLSCVASGFTFSDDYYMSWIRQAPGKGLEWIS YISSSGSIYIYAEHSVKGRTISRDNAKNSLYLQMNSLRAEDTALYYCART PPSSDNWYEDFDYWGQGALVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFL LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP PREEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAK KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	209
PR005342	EVQLVESGGGLVKPGGSLRLSCAASGFNFSDYYMSWIRQAPGKGLEWIS YISNSSSSTIYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYCARD TTNGWYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFLF PPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP REEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	210
PR005343	EVQLVESGGGLVKPGGSLRLSCVASGFTFSDDYYMSWIRQAPGKGMEWIS YISSSGSTKNYANSVKGRTISRDNAKNSLYLQMNSLRAEDTAAYYCAR VPPYNASWYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPS VFLFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY YTQKSLSLSPGK	211
PR005344	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYYMSWIRQAPGKGLEWIS YISNSSSSIYSANHSVKGRTISRDNAKNSLYLQMNSLRAEDTALYYCARS PRGAFYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFLF PPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP REEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY QKSLSLSPGK	212
PR005345	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYYMSWIRQAPGKGLEWIA YISSSGSTIIYSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARD TPSSSSDWVSLQFDYWGQGTPVTVSSEPKSSDKTHTCPCCPAPELLGGPS VFLFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY YTQKSLSLSPGK	213
PR005346	EVQLVESGGGLVKPGGSLRLSCVTSGFTFSDDYYMSWIRQAPGKGLEWS NISKNGPTIYAEHSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DSSSSDWVSLQFDYWGQGTPVTVSSEPKSSDKTHTCPCCPAPELLGGPS VFLFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY QKSLSLSPGK	214
PR005347	EVQLVESGGGLVKPGGSLRLSCVTSGFTFSDDYYMSWIRQAPGKGMEWIS YISTTGSTKNYANSVKGRTISRDNAKSSLYLQMNSLRAEDTAAYYCAR VPPSNASWYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSV FLFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY YTQKSLSLSPGK	215

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
PR005348	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYMSWIRQAPGKGLEWS YISRSGSTKYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAVYCAR DAPSSNSDWVSLHFDHWGQGTLVTSSEPKSSDKTHTCPCTPPCAPELLGGP SVFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	216
PR005349	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYMSWIRQAPGKGLEWS YISNSSSISYANSVKGRFTVSRDANKNSLYLQMNSLRAEDTALYYCARS PRSAFYEDFDYWGQGTLVTSSEPKSSDKTHTCPCTPPCAPELLGGPSVFLFP PKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	217
PR005350	EVQLVESGGGLVKPGGSLRLSCAASGFTLSDSQMSWIRQAPGKGVEWWS YISSSSNTIYYGDSVKGRTFTSRDANKNSLFQMNSLRAEDTALYYCARV PPSSSNWYEDFDIWGQGTLVTSSEPKSSDKTHTCPCTPPCAPELLGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	218
PR005351	EVQLVESGGGLVKPGGSLRLSCAASGFTLSDFQMSWIRQAPGKGLEWV AYIDTNGSTRYYAESVKGRTFTSRDANKNSLNQMNGLRAEDTALYYC ARIPSYTNTIYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTALYYCART PPVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	219
PR005352	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDDYMSWIRQAPGKGLEWIS YISSLGGSIYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTALYYCART PPSSSNWYEDFDYWGGALTVTSSEPKSSDKTHTCPCTPPCAPELLGGPSVFL LFPFPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	220
PR303125	EVQLVESGGGLVQPGGSLRLSCAASGFTFSHHMSWVRQAPGKGLEWV SAISGSGDSTHYAASVKGRTFTSRDN SKNTLYLQMNSLRAEDTAVYCCET LLRFLES LGNDGFKIWGQGTMTVTSSEPKSSDKTHTCPCTPPCAPELLGGPS VLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	253
PR303189	EVQLVESGGGLVKPGGSLRLSCAASGFTNLSDSYMSWIRQAPGKGLEWS CISSSGSTI YYADSVKGRFTVSRDANKNSLYLQMNSLRAEDTALYYCAR DCVIGIRDSDI WGQGTMTVTSSEPKSSDKTHTCPCTPPCAPELLGGPSVFL PPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	257
PR303191	EVQLVESGGGLVQPGGSLRLSCAASGFIFGSYAMS WVRQAPGKGLEWS GISGTGGNTYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAVYFCER GITIHGVIIPPDYRGQGTLVTSSEPKSSDKTHTCPCTPPCAPELLGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKG QPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	258

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
PR303199	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIA YISSLGGTIIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARE YYGSENYDHFDFWGGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFL FPPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK	259
PR303201	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGNAMSWVRQAPGKGLEWV SAISGSGDKTYAAASVKGRTFTISRDNSNNNTVYLQMNSLRAEDTAVYCE KGAFRTTMDYWGGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFLFP PKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK QPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYQ KSLSLSPGK	260
PR303145	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNFWMYWVRQAPGKGLEWS HISGSGRTIYYAESVKGRTFTISRDNAKNSLYLQMNSLRAEDTAMYYCAR DLSSGNYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFL FPPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK	254
PR303147	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFWMYWVRQAPGKGLEWV VSRINSDGSNTYADSVKGRFTISRDNAKNTLYLQMNSLRVEDTAVYSC AREGSGWYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSV FLFPPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY YTQKSLSLSPGK	255
PR303155	EVQLVESGGGLVKPGGSLRLSCAASGFTLSDDYMSWIRQAPGKGLEWIS YISSLGGTIIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD VSSGWYEDFDYWGQGTLVTVSSEPKSSDKTHTCPCCPAPELLGGPSVFLF PPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK	256
PR009810	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYAHHSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSEDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	238
PR009811	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYHSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	239
PR009812	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYSHSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSEDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	240
PR009813	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYSSSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSIDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	241
PR009814	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYSPSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSKDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	242
PR009815	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYSPSVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSIDWVDLQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	243
PR009816	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGGSIHYASAVKGRTFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSIDWVDELQFDYWGQGTLVTVSSQGGSDYKDDDKASHHHHHHH	244

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
PR009817	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYSTSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	245
PR009818	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYSSSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSEDWVDELQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	246
PR009819	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	247
PR009820	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYAGSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	248
PR009821	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSEDWVMLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	249
PR009822	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYATSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSIDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	250
PR009823	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHAYASSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	25
PR009824	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSWIHYSTSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSIDWVDLQFDYWGQGTIVTVSSQGGSDYKDDDKASHHHHHHH	252
PR007408	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSSEPKSSEPKSSDKTHTCPPCPAPEELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNH YTQKSLSLSPGK	221
PR007409	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD IPSSSDWVDLQFDYWGQGTIVTVSSSEPKSSEPKSSDKTHTCPPCPAPEELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNH YTQKSLSLSPGK	222
PR007410	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD PSSSSDWVDLQFDYWGQGTIVTVSSSEPKSSEPKSSDKTHTCPPCPAPEELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ ENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNH YTQKSLSLSPGK	223
PR007411	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVDLQFDYWGQGTIVTVSSSEPKSSEPKSSDKTHTCPPCPAPEELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNH YTQKSLSLSPGK	224
PR007412	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSLGIHYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSDWVSLQFDYWGQGTIVTVSSSEPKSSEPKSSDKTHTCPPCPAPEELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS	225

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
	KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	
PR007413	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YINTRGSPIGYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	226
PR007414	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSTRYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	227
PR007415	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	228
PR007416	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YINTRGSPIGYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD IPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	229
PR007417	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSTRYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD IPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	230
PR007418	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD IPSSSSDWVDLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	231
PR007419	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YINTRGSPIGYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVSLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	232
PR007420	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YISSSGSTRYYADSVKGRFTI SRDANKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVSLQFDYWGQGTIVTSSSEPCKSSDKTHCCPCPAPELLGGPS VFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHN TKPREEQYNSTYRVVSVLTVLHQDWLNLGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVTLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ	233

TABLE 1-continued

Sequences of the heavy chain of HCAb antibodies		
Clone	Heavy chain	SEQ ID NO
	PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNH YTQKSLSLSPGK	
PR007421	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVSLQFDYWGQGTLVTVSSEPKSSDKTHTCPPCPAPELLGGPS VFLFPKKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNH YTQKSLSLSPGK	234
PR007422	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD IPSSSSDWVSLQFDYWGQGTLVTVSSEPKSSDKTHTCPPCPAPELLGGPSV FLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGP ENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNH YTQKSLSLSPGK	235
PR007423	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD IPSSSSDWVSLQFDYWGQGTLVTVSSEPKSSDKTHTCPPCPAPELLGGPS VFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHNAKT TKPREEQYNSTYRVVSVLTVLIIQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNH YTQKSLSLSPGK	236
PR007424	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWIS YIDSSGRPLAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARD MPSSSSDWVSLQFDYWGQGTLVTVSSEPKSSDKTHTCPPCPAPELLGGPS VFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYDGVEVHNAKT TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNH YTQKSLSLSPGK	237

TABLE 2

Sequences of the heavy chain variable region of HCAb antibodies		
Clone	Heavy chain variable region	SEQ ID NO
PR005337	EVQLVESGGGLVKPGGSLRLSCAASGFI FSDYYMSWIRQAPGKGLEWV SYI SSSG STI HYAD SVK GRFT IS RDNA KNS LY LQM NSL R T ED T A V YY CA RDPPTSNSDWVSLHDHWGQGTLTVSS	147
PR005338	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYI SSSG STI HYAD SVK GRFT IS RDNA KNS LY LQM NSL R T ED T A V YY CA RDAPSSNSDWVSLQFDYWGQGTLTVSS	148
PR005339	EVQLVESGGGLVKPGGSLKLSCAASGFTFSDFYMSWIRQAPGKGVEWI SYI SNN G STI HYAD SVK GRFT IS RDNA KNS LY LQM NSL R A E D T A V YY C ARDFNNNGWYEDFDYWGQGTLTVSS	149
PR005340	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYI SSSG STI HYAD SVK GRFT IS RDNA KNS LY LQM NSL R A E D T A I YY C DIPSSSSDWVSLQFDYWGQGTLTVSS	150
PR005341	EVQLVESGGGLVKPGGSLRLSCVASGFTFSDFYMSWIRQAPGKGLEWI SYI SSSG SSI YYA E SVK GRFT IS RDNA KNS LY LQM NR L R A E D T A L YY C RTPPSSDNWYEDFDYWGQGALTVSS	151
PR005342	EVQLVESGGGLVKPGGSLRLSCAASGFNFSDYYMSWIRQAPGKGLEWI SYI SNS SSI YYA E SVK GRFT IS RDNA KNS LY LQM SR L R A E D T A M YY C RDTTNGWYEDFDYWGQGTLTVSS	152

TABLE 2-continued

Sequences of the heavy chain variable region of HCAb antibodies		
Clone	Heavy chain variable region	SEQ ID NO
PR005343	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGMWI SYISSLNGSTIYANSVKGRFTISRDNAKNSLYLQMNSLRAEDTAAYYC ARVPPYNASWYEDFDYWGQGTLVTVSS	153
PR005344	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI SYISSLNGSTIYANSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCA RSPRGAFYEDFDYWGQGTLVTVSS	154
PR005345	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI AYISSLNGSTIYHSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCA RDTPSSSDWVSLQFDYWGQGTLVTVSS	155
PR005346	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEW VSNISKNGTIYIAESVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYC ARDSSGWYSEFDYWGQGTLVTVSS	156
PR005347	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI SYISSLNGSTIYANSVKGRFTISRDNAKNSLYLQMNSLRAEDTAAYYC ARVPPSNASWYEDFDYWGQGTLVTVSS	157
PR005348	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEW SYISSLNGSTIYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDAPSNSDWVSLHFHDHWQGTLVTVSS	158
PR005349	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI SYISSLNGSTIYANSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCA RSPRSAFYEDFDYWGQGTLVTVSS	159
PR005350	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDQSMSWIRQAPGKGVEW VSISSLNGSTIYGDHSVKGRTISRDNAKNSLFLQMNSLRAEDTAVYYC ARVPPSSSNWYEDFDHWQGTLVTVSS	160
PR005351	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDQSMSWIRQAPGKGLEW VAYIDTNGSTRYYAESVKGRFTISRDNAKNSLFLQMNSLRAEDTALYYC YCARIPSYTSWWYEDFDHWQGTLVTVSS	161
PR005352	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI SYISSLNGSTIYADSVKGRFTISRDNAKNSLYLQMNRRAEDTALYYCA RTPPSSNNWYEDFDYWGQGALVTVSS	162
PR303125	EVQLLESGGGLVQPGGSLRSLSCAASGFTPSSSHMSWVRQAPGKGLEW VSAISGSGDSTHYAASVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC CETLLRFLESLGNDGFKIWQGTMVTVSS	195
PR303189	EVQLVESGGGLVKGPGGLRSLSCAASGFNLSDSYMSWIRQAPGKGLEW VSCISSLNGSTIYADSVKGRFTISRDNAKNSLYLQMNLRAEDTALYYC CARDCVIGIRDDSDIWQGQGTMVTVSS	199
PR303191	EVQLLESGGGLVQPGGSLRSLSCAASGFTPSGSYAMSWVRQAPGKGLEW VSGISGTGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYF CERGITIHGVVIIPPDYRGQGTLVTVSS	200
PR303199	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI AYISSLNGSTIYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCA REYYGSENYDFDHWQGQGTLVTVSS	201
PR303201	EVQLLESGGGLVQPGGSLRSLSCAASGFTPSGNAMSWSVRQAPGKGLEW VSAISGSGDCTYYAASVKGRFTISRDNSMNTVYLQMNSLRAEDTAVYYC CEKGAFRTMDYWGQGTLVTVSS	202
PR303145	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSNNSWMSWIRQAPGKGVEW SHISGSGRTIYIAESVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYC ARDLSSGWYEDFDYWGQGTLVTVSS	196
PR303147	EVQLVESGGGLVQPGGSLRSLSCAASGFTPSNFWMYWVRQAPGKGLV WVSRIINSDGSSSTNYADSVKGRFTISRDNAKNTLYLQMNSLRVEDTAVY SCAREGSGGWYEDFDYWGQGTLVTVSS	197
PR303155	EVQLVESGGGLVKGPGGLRSLSCAASGFTPSDYYMSWIRQAPGKGLEWI SYISSLNGSTIYADSVKGRFTISRDNAARNNSLYLQMNSLRAEDTALYYCA RDVSSGWYEDFDYWGQGTLVTVSS	198

TABLE 2-continued

Sequences of the heavy chain variable region of HCab antibodies		
Clone	Heavy chain variable region	SEQ ID NO
PR009810	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYAHHSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSEDWVDLQFDYWGQGTLVTVSS	180
PR009811	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYHSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVDLQFDYWGQGTLVTVSS	181
PR009812	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSHSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSEDWVDLQFDYWGQGTLVTVSS	182
PR009813	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSSSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSIDWVVELQFDYWGQGTLVTVSS	183
PR009814	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSPSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSKDWVDLQFDYWGQGTLVTVSS	184
PR009815	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSPSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSIDWVVELQFDYWGQGTLVTVSS	185
PR009816	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSPSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVDLQFDYWGQGTLVTVSS	186
PR009817	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSTSVDKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVVELQFDYWGQGTLVTVSS	187
PR009818	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSSSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSEDWVVELQFDYWGQGTLVTVSS	188
PR009819	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSSSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSSDWVVELQFDYWGQGTLVTVSS	189
PR009820	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYAGSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVVELQFDYWGQGTLVTVSS	190
PR009821	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSSSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSEDWVMLQFDYWGQGTLVTVSS	191
PR009822	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYATSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSIDWVDLQFDYWGQGTLVTVSS	192
PR009823	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYASSSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVDLQFDYWGQGTLVTVSS	193
PR009824	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYSTSVDKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSIDWVDLQFDYWGQGTLVTVSS	194
PR007408	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSYIHYADSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDMPSSSSDWVDLQFDYWGQGTLVTVSS	163
PR007409	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSWIHYADSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDIPSSSSDWVDLQFDYWGQGTLVTVSS	164
PR007410	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDFYMSWIRQAPGKGLEWI SYISSSGSYIHYADSVKGRTISRDNAKNSLYLQMNSLRAEDTAIYYCA RDIPSSSSDWVDLQFDYWGQGTLVTVSS	165

TABLE 2-continued

Sequences of the heavy chain variable region of HCAb antibodies		
Clone	Heavy chain variable region	SEQ ID NO
PR007411	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYISSLGGSTIHYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR DMPSSSDWVDLQFDYWGQGTLTVSS	166
PR007412	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYISSLGGSTIHYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVSLQFDYWGQGTLTVSS	167
PR007413	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYINTRGSPIGYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVDLQFDYWGQGTLTVSS	168
PR007414	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYISSLGGSTTRYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVDLQFDYWGQGTLTVSS	169
PR007415	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVDLQFDYWGQGTLTVSS	170
PR007416	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYINTRGSPIGYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDIPSSSDWVDLQFDYWGQGTLTVSS	171
PR007417	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYISSLGGSTTRYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDIPSSSDWVDLQFDYWGQGTLTVSS	172
PR007418	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDIPSSSDWVSLQFDYWGQGTLTVSS	173
PR007419	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYINTRGSPIGYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVSLQFDYWGQGTLTVSS	174
PR007420	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYISSLGGSTTRYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVSLQFDYWGQGTLTVSS	175
PR007421	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVSLQFDYWGQGTLTVSS	176
PR007422	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDIPSSSDWVSLQFDYWGQGTLTVSS	177
PR007423	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDIPSSSDWVDLQFDYWGQGTLTVSS	178
PR007424	EVQLVESGGGLVKGGSRLSCAASGFTPSDFYMSWIRQAPGKGLEWI SYIDSSGRPLAYADSVVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR RDMPSSSDWVSLQFDYWGQGTLTVSS	179

TABLE 3

Sequences of the heavy chain CDRs 1-3 of HCAb antibodies (Chothia numbering system)						
Clone	Heavy chain CDR1	SEQ ID NO	Heavy chain CDR2	SEQ ID NO	Heavy chain CDR3	SEQ ID NO
PR005337	GFI FSDY	11	SSSGST	40	DPPTSN SDWVSLHF DH	100
PR005338	GFT FSDY	12	SSSGTT	41	DAPSSNSD WVSLQFDY	101
PR005339	GFT FSDY	12	SNNGST	42	DFNNGWYEDF DY	102

TABLE 3 -continued

Sequences of the heavy chain CDRs 1-3 of HCAb antibodies (Chothia numbering system)						
Clone	Heavy chain CDR1	SEQ NO	Heavy chain CDR2	SEQ NO	Heavy chain CDR3	SEQ ID NO
PR005340	GFTFSDY	12	SSSGST	40	DIPSSSDWVSLQFDY	103
PR005341	GFTFSDY	12	SSSGSS	43	TPPSSDNWYEDFDY	104
PR005342	GFNFSDY	13	SNSSST	44	DTTNGWYEDFDY	105
PR005343	GFTFSDY	12	SSSGST	40	VPPYNASWYEDFDY	106
PR005344	GFTFSDY	12	SNSSSS	45	SPRGAFYEDFDY	107
PR005345	GFTFSDY	12	SSSGST	40	DTPSSSDWVSLQFDY	108
PR005346	GFTLSDY	14	SKNGFT	46	DSSGWYSEFDY	109
PR005347	GFTFSDY	12	STTGST	47	VPPSNASWYEDFDY	110
PR005348	GFTFSDY	12	SRSGST	48	DAPSSNSDWVSLHFDH	111
PR005349	GFTFSDY	12	SNSSSS	45	SPRSAFYEDFDY	112
PR005350	GFTLSDS	15	SSSGNT	49	VPPSSSNWYEDFDI	113
PR005351	GFKLSDF	16	DTNGST	50	IPSYTSSWYEDFDH	114
PR005352	GFTFSDY	12	SSSGGS	51	TPPSSNNWYEDFDY	115
PR303125	GFTFSSH	18	SGSGDS	56	LLRFLESLGNDGFKI	126
PR303189	GFNLSDS	21	SSSGST	40	DCVIGIRDDSDI	130
PR303191	GFIFGSY	22	SGTGGN	60	GITIHGVVIIPPDY	131
PR303199	GFTFSDY	12	SSSGST	40	EYYGSENYDHFDY	132
PR303201	GFTFSGN	23	SGSGDK	61	GAFRTTMDY	133
PR303145	GFTFSNY	19	SGSGRT	57	DLSSGWYEDFDY	127
PR303147	GFTFSNF	20	NSDGSS	58	EGSGWYEDFDY	128
PR303155	GFTLSDY	14	SSNGST	59	DVSSGWYEDFDY	129
PR009810	GFTFSDF	17	SSSGSW	53	DMPSSSEDWVDLQFDY	119
PR009811	GFTFSDF	17	SSSGSW	53	DMPSSSSDWVVDLQFDY	116
PR009812	GFTFSDF	17	SSSGSW	53	DMPSSSEDWVDLQFDY	119
PR009813	GFTFSDF	17	SSSGSW	53	DMPSSSIDWVELQFDY	120
PR009814	GFTFSDF	17	SSSGSW	53	DMPSSSKDWVVDLQFDY	121
PR009815	GFTFSDF	17	SSSGSW	53	DMPSSSIDWVDLQFDY	122
PR009816	GFTFSDF	17	SSSGSW	53	DMPSSSIDWVELQFDY	120
PR009817	GFTFSDF	17	SSSGSW	53	DMPSSSDWVVDLQFDY	116
PR009818	GFTFSDF	17	SSSGSW	53	DMPSSSEDWVELQFDY	123
PR009819	GFTFSDF	17	SSSGSW	53	DMPSSSSDWVVDLQFDY	116
PR009820	GFTFSDF	17	SSSGSW	53	DMPSSSDWVELQFDY	124
PR009821	GFTFSDF	17	SSSGSW	53	DMPSSSEDWVMLQFDY	125
PR009822	GFTFSDF	17	SSSGSW	53	DMPSSSIDWVDLQFDY	122
PR009823	GFTFSDF	17	SSSGSW	53	DMPSSSSDWVVDLQFDY	116

TABLE 3 -continued

Sequences of the heavy chain CDRs 1-3 of HCAb antibodies (Chothia numbering system)						
Clone	Heavy chain CDR1	SEQ ID NO	Heavy chain CDR2	SEQ ID NO	Heavy chain CDR3	SEQ ID NO
PR009824	GFTFSDF	17	SSSGSW	53	DMPSSSIDWVDLQFDY	122
PR007408	GFTFSDF	17	SSSGSY	52	DMPSSSDWVDLQFDY	116
PR007409	GFTFSDF	17	SSSGSW	53	DIPSSSDWVDLQFDY	117
PR007410	GFTFSDF	17	SSSGSY	52	DIPSSSDWVDLQFDY	117
PR007411	GFTFSDF	17	SSSGST	40	DMPSSSDWVDLQFDY	116
PR007412	GFTFSDF	17	SSSGSW	53	DMPSSSDWVSLQFDY	118
PR007413	GFTFSDF	17	NTRGSP	54	DMPSSSDWVDLQFDY	116
PR007414	GFTFSDF	17	SSSGST	40	DMPSSSDWVDLQFDY	116
PR007415	GFTFSDF	17	DSSGRP	55	DMPSSSDWVDLQFDY	116
PR007416	GFTFSDF	17	NTRGSP	54	DIPSSSDWVDLQFDY	117
PR007417	GFTFSDF	17	SSSGST	40	DIPSSSDWVDLQFDY	117
PR007418	GFTFSDF	17	DSSGRP	55	DIPSSSDWVDLQFDY	117
PR007419	GFTFSDF	17	NTRGSP	54	DMPSSSDWVSLQFDY	118
PR007420	GFTFSDF	17	SSSGST	40	DMPSSSDWVSLQFDY	118
PR007421	GFTFSDF	17	DSSGRP	55	DMPSSSDWVSLQFDY	118
PR007422	GFTFSDF	17	DSSGRP	55	DIPSSSDWVSLQFDY	103
PR007423	GFTFSDY	12	DSSGRP	55	DIPSSSDWVDLQFDY	117
PR007424	GFTFSDY	12	DSSGRP	55	DMPSSSDWVSLQFDY	118

TABLE 4

Sequences of reference antibody PR000374		
	Sequence	SEQ ID NO
Heavy Chain	EVQLVESGGGLVQPGRSLRLSCTASGSDINDYPITWVRQAPGQGLEWIG FINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTEDTAVYYCAR GYSTYYRDFNWIWGQQTLTVTSSASTKGPSPVPLAPSSKSTSAGTAALGC LVKDYFPEPVTVWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVFVSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPCPAPELLGGPSVFL PPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVSVLTQLHQDWLNGKEYCKVSNKALPAPIEKTIS KAKGQPREFPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPNENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPKG	204
Heavy chain variable region	EVQLVESGGGLVQPGRSLRLSCTASGSDINDYPITWVRQAPGQGLEWIG FINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTEDTAVYYCAR GYSTYYRDFNWIWGQQTLTVSS	146
HCDR1	GSDINDY	10
HCDR2	NSGGS	39
HCDR3	GYSTYYRDFNI	99
Light Chain	DIQMTQSPSSLSASVGDRVТИNCQASQSIDSNLAWFQQKPGQQPKLLIYR ASNLASGVPDFRGSGSGSTDFTLTISLEAEDVATYYCLGGVGAVSYRT SFGGGKVEIKRTVAAPSVDIFPPSDEQLKSGTASVVCCLNNFYREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC	261

TABLE 4 -continued

Sequences of reference antibody PR000374		
	Sequence	SEQ ID NO
Light chain variable region	DIQMTQSPSSLSASVGDRVTINQASQSIDSNLAWFQQKPGQPPKLLIYR ASNLASGVPDFRSGSGTDFTLTISSLEAEDVATYYCLGGVGAVSYRT SFGGGTKEIK	203
LCDR1	QASQSIDSNLA	140
LCDR2	RASNLAS	142
LCDR3	LGGVGAVSYRTS	144

## DETAILED DESCRIPTION OF THE INVENTION

[0108] The aforementioned features and advantages of the invention as well as additional features and advantages thereof will be more clearly understood hereafter as a result of a detailed description of the following embodiments when taken in conjunction with the drawings.

[0109] The embodiments described herein with reference to drawings are explanatory, illustrative, and used to generally understand the present invention. The embodiments shall not be construed to limit the scope of the present invention. The same or similar elements and the elements having same or similar functions are denoted by like reference numerals throughout the descriptions.

[0110] Unless indicated or defined otherwise, all terms used have their usual meaning in the art, which will be clear to the skilled person. Reference is for example made to the standard handbooks, such as Leuenberger, H. G. W, Nagel, B. and Klbl, H. eds., "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Helvetica Chimica Acta (1995), CH-4010 Basel, Switzerland; Sambrook et al., "Molecular Cloning: A Laboratory Manual" (2nd Ed.), Vols. 1-3, Cold Spring Harbor Laboratory Press (1989); F. Ausubel et al. eds., "Current protocols in molecular biology", Green Publishing and Wiley InterScience, New York (1987); Roitt et al., "Immunology" (6th Ed.), Mosby/ Elsevier, Edinburgh (2001); and Janeway et al., "Immunobiology" (6th Ed.), Garland Science Publishing/Churchill Livingstone, New York (2005), as well as the general background art cited above.

[0111] As used herein, singular forms "a", "and," and "the" include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to "an antibody" includes a plurality of antibodies and reference to "an antibody" in some embodiments includes multiple antibodies, and so forth.

[0112] Unless indicated or defined otherwise, the term "comprise", and variations such as "comprises" and "comprising", should be understood to imply the inclusion of a stated elements or step or group of elements or steps but not the exclusion of any other element or step or group of elements or steps. The term "comprising" encompasses "including" as well as "consisting" e.g., a composition "comprising" X may consist exclusively of X or may include something additional e.g., X+Y.

[0113] The term "about" in relation to a numerical value x is optional and means, for example, x±10% or x±5%.

[0114] As used herein, the term "antibody" refers to an immunoglobulin molecule which has the ability to specifically bind to a specific antigen. An antibody often comprises a variable region and a constant region. The constant regions of antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (such as effector cells) and components of the complement system such as C1q, the first component in the classical pathway of complement activation.

[0115] A "heavy chain variable region" (VH) consists of a "framework" region interrupted by three "complementarity determining regions" or "CDRs". The framework regions serve to align the CDRs for specific binding to an epitope of an antigen. The CDRs include the amino acid residues of an antibody that are primarily responsible for antigen binding. From amino-terminus to carboxyl-terminus, VH domain comprises the following framework (FR) and CDR regions: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[0116] The assignment of amino acids to VH domain is in accordance with any conventional definition of CDRs. Conventional definitions include, the Kabat definition (Kabat, Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, MD, 1987 and 1991), the Chothia definition (Chothia & Lesk, J. Mol. Biol. 196:901-917, 1987; Chothia et al., Nature 342:878-883, 1989); a composite of Chothia Kabat CDR in which CDR-H1 is a composite of Chothia and Kabat CDRs; the AbM definition used by Oxford Molecular's antibody modelling software; and, the contact definition of Martin et al. (world wide web bioinfo.org.uk/abs). Kabat provides a widely used numbering convention (Kabat numbering system) in which corresponding residues between different heavy chains or between different light chains are assigned the same number. The present disclosure can use CDRs defined according to any of these numbering systems, although preferred embodiments use Chothia defined CDRs.

[0117] The term "antibody" as used herein should be understood in its broadest meaning, and includes monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, antibody fragments, and multi-specific antibodies containing at least two different antigen binding regions (e.g., bi-specific antibodies). The antibody may contain additional modifications, such as non-naturally occurring amino acids, mutations in Fc regions, and mutations in glycosylation sites. Antibodies also include post-translation modified antibodies, fusion proteins containing the antigenic determinants of the antibody, and immuno-

globulin molecules containing any other modifications to antigen recognition sites, as long as these antibodies exhibit desired biological activity.

[0118] The terms “heavy chain-only antibody”, “heavy chain antibody” and “HCAb” are used interchangeably herein and refer, in the broadest sense, to antibodies, or more or more portions of an antibody, e.g., one or more arms of an antibody, lacking the light chain of a conventional antibody. The terms specifically include, without limitation, homodimeric antibodies comprising the VH antigen-binding domain and the CH1, CH2 and CH3 constant domains; functional (antigen-binding) variants of such antibodies, soluble VH variants, Ig-NAR comprising a homodimer of one variable domain (V-NAR) and five C-like constant domains (C-NAR) and functional fragments thereof; and soluble single domain antibodies (sUniDabs™).

[0119] In one embodiment, a heavy chain-only antibody is composed of a variable region antigen-binding domain composed of FRI, CDR1, FR2, CDR2, FR3, CDR3, and FR4. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and CH1, CH2 and CH3 domains. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and CH2 and CH3 domains. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH1 domain. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH2 domain. In a further embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH3 domain. Heavy chain-only antibodies in which the CH1 and/or CH2 and/or CH3 domain is truncated are also included herein. In a further embodiment, a heavy chain is composed of an antigen binding domain, and at least one CH (CH1, CH2, CH3, or CH4) domain but no hinge region.

[0120] The heavy chain-only antibody can be in the form of a dimer, in which two heavy chains are disulfide bonded or otherwise, covalently or non-covalently, attached with each other. The heavy chain-only antibody may belong to the IgG subclass, but antibodies belonging to other subclasses, such as IgM, IgA, IgD and IgE subclass, are also included herein. In a particular embodiment, a heavy chain antibody is of the IgG1, IgG2, IgG3, or IgG4 subtype, in particular the IgG1 or IgG4 subtype.

[0121] In one embodiment, the heavy-chain antibody is of the IgG1 or IgG4 subtype, wherein one or more of the CH domains is modified to alter an effector function of the antibody. Modifications of CH domains that alter effector function are further described herein.

[0122] As used herein, the term “antigen binding fragment” of an antibody refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., ROR1). It has been shown that the antigen binding function of an antibody can be performed by fragments of a full-length antibody.

[0123] Examples of antigen binding fragments encompassed within the term “antigen binding portion” of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fab' fragment, which is essentially an Fab with part of

the hinge region (see, FUNDAMENTAL IMMUNOLOGY (Paul ed., 3.sup.rd ed. 1993); (iv) a Fd fragment consisting of the VH and CH1 domains; (v) a Fd' fragment having VH and CH1 domains and one or more cysteine residues at the C-terminus of the CH1 domain; (vi) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (vii) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; (viii) an isolated complementarity determining region (CDR); and (ix) a nanobody, a heavy chain variable region containing a single variable domain and two constant domains. Furthermore, although the two domains of the Fv fragment, VL and VH are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term “antigen binding fragment” of an antibody. Furthermore, the term also includes a “linear antibody” comprising a pair of tandem Fd segments (VH-CH1-VH-CH1), which forms an antigen binding region together with a complementary light chain polypeptide, and a modified version of any of the foregoing fragments, which retains antigen binding activity.

[0124] These antigen binding fragments can be obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0125] As used herein, the term “binding” or “specifically binding” refers to a non-random binding reaction between two molecules, such as between an antibody and its target antigen. The binding specificity of an antibody can be determined based on affinity and/or avidity. The affinity, represented by the equilibrium constant for the dissociation of an antigen with an antibody (KD), is a measure for the binding strength between an antigenic determinant (epitope) and an antigen-binding site on the antibody: the lesser the value of the KD, the stronger the binding strength between an antigenic determinant (epitope) and the antibody. Alternatively, the affinity can also be expressed as the affinity constant (KA), which is 1/KD.

[0126] Avidity is the measure of the strength of binding between an antibody and the pertinent antigen. Avidity is related to both the affinity between an antigenic determinant (epitope) and its antigen binding site on the antibody and the number of pertinent binding sites present on the antibody. Typically, an antibody will bind with a dissociation constant (KD) of  $10^{-5}$  to  $10^{-12}$  M or less, and preferably  $10^{-7}$  to  $10^{-12}$  M or less and more preferably  $10^{-8}$  to  $10^{-12}$  M, and/or with a binding affinity of at least  $10^7$  M<sup>-1</sup>, preferably at least  $10^8$  M<sup>-1</sup>, more preferably at least  $10^9$  M<sup>-1</sup>, such as at least  $10^{12}$  M<sup>-1</sup>. Any K<sub>D</sub> value greater than  $10^{-4}$  M is generally considered to indicate non-specific binding. Specifically binding of an antibody to an antigen or antigenic determinant can be determined in any suitable manner known per se, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA), bio-layer interferometry (BLI) assay and sandwich competition assays, and the different variants thereof known per se in the art.

[0127] The term “epitope” refers to a site on an antigen to which an antibody binds. An epitope can be formed from

contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of one or more proteins. Epitopes formed from contiguous amino acids (also known as linear epitopes) are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding (also known as conformational epitopes) are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. The epitope defines the smallest binding site of an antibody and therefore is the specific target of the antibody or antigen binding fragment thereof.

[0128] As used herein, the term "sequence identity" refers to the extent to which two sequences (amino acid) have the same residue at the same positions in an alignment. For example, "an amino acid sequence is X % identical to SEQ ID NO: Y" refers to % identity of the amino acid sequence to SEQ ID NO: Y and is elaborated as X % of residues in the amino acid sequence are identical to the residues of sequence disclosed in SEQ ID NO: Y. Generally, computer programs are employed for such calculations. Exemplary programs that compare and align pairs of sequences, include ALIGN (Myers and Miller, 1988), FASTA (Pearson and Lipman, 1988; Pearson, 1990) and gapped BLAST (Altschul et al., 1997), BLASTP, BLASTN, or GCG (Devereux et al., 1984).

[0129] Also, in determining the degree of sequence identity between two amino acid sequences, the skilled person may take into account so-called conservative amino acid substitutions, which can generally be described as amino acid substitutions in which an amino acid residue is replaced with another amino acid residue of similar chemical structure and which has little or essentially no influence on the function, activity or other biological properties of the polypeptide. Such conservative amino acid substitutions are well known in the art, for example from WO 04/037999, GB-A-2 357 768, WO 98/49185, WO 00/46383 and WO 01/09300; and (preferred) types and/or combinations of such substitutions may be selected on the basis of the pertinent teachings from WO 04/037999 as well as WO 98/49185 and from the further references cited therein.

[0130] Such conservative substitutions preferably are substitutions in which one amino acid within the following groups (a)-(e) is substituted by another amino acid residue within the same group: (a) small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro and Gly; (b) polar, negatively charged residues and their (uncharged) amides: Asp, Asn, Glu and Gln; (c) polar, positively charged residues: His, Arg and Lys; (d) large aliphatic, nonpolar residues: Met, Leu, Ile, Val and Cys; and (e) aromatic residues: Phe, Tyr and Trp.

[0131] Particularly preferred conservative substitutions are as follows: Ala into Gly or into Ser; Arg into Lys; Asn into Gln or into His; Asp into Glu; Cys into Ser; Gln into Asn; Glu into Asp; Gly into Ala or into Pro; His into Asn or into Gln; Ile into Leu or into Val; Leu into Ile or into Val; Lys into Arg, into Gln or into Glu; Met into Leu, into Tyr or into Ile; Phe into Met, into Leu or into Tyr; Ser into Thr; Thr into Ser; Trp into Tyr; Tyr into Trp; and/or Phe into Val, into Ile or into Leu.

[0132] Any amino acid substitutions applied to the polypeptides described herein may also be based on the analysis of the frequencies of amino acid variations between homologous proteins of different species developed by Schulz et al.,

Principles of Protein Structure, Springer-Verlag, 1978, on the analyses of structure forming potentials developed by Chou and Fasman, Biochemistry 13: 211, 1974 and Adv. Enzymol., 47: 45-149, 1978, and on the analysis of hydrophobicity patterns in proteins developed by Eisenberg et al., Proc. Nat. Acad. Sci. USA 81: 140-144, 1984; Kyte & Doolittle, J Mol. Biol. 157: 105-132, 1981, and Goldman et al., Ann. Rev. Biophys. Chem. 15: 321-353, 1986, all incorporated herein in their entirety by reference.

[0133] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a substantially homogeneous antibody population. That is, each antibodies constituting the population are the same, except for possible naturally occurring mutations in small amount. Monoclonal antibodies are highly specific and are directed against a single antigen. The term "monoclonal antibody" herein is not limited to antibodies produced by hybridoma technology, and should not be interpreted as requiring production of antibodies by any specific method.

[0134] The term "bi-specific antibody" is in the context of the present invention to be understood as an antibody having two different antigen-binding regions defined by different antibody sequences. This can be understood as different target binding but includes as well binding to different epitopes in one target.

[0135] As used herein, the term "tumor associated antigen" refers to an antigen that is differentially expressed in cancer cells compared to normal cells, and therefore can be used to target cancer cells.

[0136] As used herein, the term "bi-specific T-cell engager" or "BiTE" refers to single polypeptide chain molecules that having two antigen-binding domains, one of which binds to a T-cell antigen and the second of which binds to an antigen present on the surface of a target (See, PCT Publication WO 05/061547; Baeruerle et al., 2008, Drugs of the Future 33: 137-147; Bargou, et al., 2008, Science 321:974-977, which are incorporated herein by reference in their entireties). Thus, the BiTE of the disclosure has an antigen binding region that binds to ROR1 and a second antigen binding region that is directed towards a T-cell antigen.

[0137] As used herein, the term "vector" is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked.

[0138] As used herein, the term "host cell" refers to a cell into which an expression vector has been introduced.

[0139] The term "pharmaceutically acceptable" means that the carrier or adjuvant is compatible with the other ingredients of the composition and not substantially deleterious to the recipient thereof and/or that such carrier or adjuvant is approved or approvable for inclusion in a pharmaceutical composition for parenteral administration to humans.

[0140] As used herein, the terms "treatment," "treating," and the like, refer to administering an agent, or carrying out a procedure, for the purposes of obtaining an effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of effecting a partial or complete cure for a disease and/or symptoms of the disease. "Treatment," as used herein, may include treatment of a disease or disorder (e.g. cancer) in a mammal, particularly in a human, and includes: (a) preventing the disease or a symptom of a disease from occurring in a subject which may be predis-

posed to the disease but has not yet been diagnosed as having it (e.g., including diseases that may be associated with or caused by a primary disease; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. Treating may refer to any indicia of success in the treatment or amelioration or prevention of a cancer, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disease condition more tolerable to the patient; slowing in the rate of degeneration or decline; or making the final point of degeneration less debilitating. The treatment or amelioration of symptoms is based on one or more objective or subjective parameters; including the results of an examination by a physician. Accordingly, the term “treating” includes the administration of the antibodies or compositions or conjugates disclosed herein to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with diseases (e.g., cancers). The term “therapeutic effect” refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or side effects of the disease in the subject.

[0141] The term “effective amount” as used herein means the amount that, when administered to a subject for treating a disease, is sufficient to effect treatment for that disease.

[0142] The term “subject”, as used herein, refers to any mammalian subject for whom diagnosis, treatment, or therapy is desired. “Mammal” for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and laboratory, zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, mice, rats, rabbits, guinea pigs, monkeys etc.

[0143] The term “Receptor tyrosine kinase like orphan receptor 1” or “ROR1” includes any ROR1 variants, isoforms and species homologs which are naturally expressed by cells of any origin, or are expressed on cells transfected with genes or cDNA encoding the ROR1 which are naturally expressed on cells of any origin.

[0144] The terms “cyno ROR1”, “cynomolgus ROR1”, and “Cynomolgus macaques ROR1” are used interchangeably herein, and are refer to cynomolgus monkey ROR1. The terms include any ROR1 variants, isoforms and species homologs which are naturally expressed by cynomolgus monkey cells, or are expressed on cells of any origin transfected with genes or cDNA encoding the cynomolgus monkey ROR1 which are naturally expressed on cynomolgus monkey cells.

[0145] The terms “human ROR1”, “huROR1” and “hROR1” are used interchangeably herein, and are refer to any ROR1 variants, isoforms and species homologs which are naturally expressed by human cells, or are expressed on cells of any origin transfected with genes or cDNA encoding the human ROR1 which are naturally expressed on human cells.

#### Anti-ROR1 Antibodies

[0146] The invention provides antibodies against receptor tyrosine kinase like orphan receptor 1 (ROR1).

[0147] In a first aspect, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), and wherein the VH comprises HCDRs 1-3 of a VH having the amino acid sequence set

forth in any one of SEQ ID NOS: 147-202. In some preferred embodiments, the CDRs are determined by Chothia numbering system.

[0148] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 11, 40, and 100 respectively.

[0149] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 41, and 101 respectively.

[0150] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 42, and 102 respectively.

[0151] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 40, and 103 respectively.

[0152] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 43, and 104 respectively.

[0153] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 13, 44, and 105 respectively.

[0154] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 40, and 106 respectively.

[0155] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 45, and 107 respectively.

[0156] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 12, 40, and 108 respectively.

[0157] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in SEQ ID NOS: 14, 46, and 109 respectively.







- [0235] (39) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 185;
- [0236] (40) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 186;
- [0237] (41) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 187;
- [0238] (42) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 188;
- [0239] (43) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 189;
- [0240] (44) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 190;
- [0241] (45) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 191;
- [0242] (46) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 192;
- [0243] (47) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 193;
- [0244] (48) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 194;
- [0245] (49) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 195;
- [0246] (50) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 196;
- [0247] (51) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 197;
- [0248] (52) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 198;
- [0249] (53) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 199;
- [0250] (54) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 200;

- [0251] (55) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 201; or
- [0252] (56) the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 202.
- [0253] In some embodiments, the antibody comprises an Fe region. In some embodiments, the Fe region may be of any isotype, including, but not limited to, IgG1, IgG2, IgG3 and IgG4, and may comprise one or more mutations or modifications. In one embodiment, the Fc region is of IgG1 isotype or derived therefrom, optionally with one or more mutations or modifications. In one embodiment, the Fe region is human IgG1 Fc.
- [0254] In one embodiment, the Fc region is effector-function-deficient. For example, the Fe region may be of an IgG1 isotype, or a non-IgG1 type, e.g., IgG2, IgG3 or IgG4, which has been mutated such that the ability to mediate effector functions, such as ADCC, has been reduced or even eliminated. Such mutations have e.g., been described in Dall'Acqua W F et al., J Immunol. 177(2):1129-1138 (2006) and Hezareh M, J Virol.; 75(24):12161-12168 (2001). In some embodiments, the Fe region of the antibody comprises a wild type IgG1 Fe with L234A, L235A and G237A mutations.
- [0255] In some embodiments, the antibody is mutated at one or more post-translational modifications sites. In one embodiment, the Fe region comprises a mutation removing the acceptor site for Asn-linked glycosylation or is manipulated to eliminate the effector function of the antibody.
- [0256] In some embodiments, the invention provides an antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain (HC), and wherein
- [0257] (1) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 205;
- [0258] (2) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 206;
- [0259] (3) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 207;
- [0260] (4) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 208;
- [0261] (5) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 209;
- [0262] (6) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 210;
- [0263] (7) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 211;



- [0296] (40) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 244;
- [0297] (41) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 245;
- [0298] (42) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 246;
- [0299] (43) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 247;
- [0300] (44) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 248;
- [0301] (45) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 249;
- [0302] (46) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 250;
- [0303] (47) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 251;
- [0304] (48) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 252;
- [0305] (49) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 253;
- [0306] (50) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 254;
- [0307] (51) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 255;
- [0308] (52) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 256;
- [0309] (53) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 257;
- [0310] (54) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 258;
- [0311] (55) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 259; or

[0312] (56) the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 260.

[0313] In some embodiments, the antibody of the invention comprises a heavy chain and a light chain. In some embodiments, the antibody of the invention comprises two heavy chains and two light chains.

[0314] Based on the amino acid sequence of heavy chain constant regions of the antibody, an immunoglobulin molecule can be divided into five classes (isotypes): IgA, IgD, IgE, IgG, and IgM, and can be further divided into different subtypes, such as IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, etc. The light chain of the antibody can be classified as a lambda ( $\lambda$ ) chain or a kappa ( $\kappa$ ) chain, based on the amino acid sequence of the light chain. The antibodies disclosed herein can be of any classes or subtypes above.

[0315] In some embodiments, the antibody can be of an isotype selected from the group consisting of IgG, IgA, IgM, IgE and IgD. In some embodiments, the antibody can be of a subtype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4. In a preferred embodiment, the antibody is an IgG1 antibody.

[0316] In some embodiments, the antibody of the invention does not comprise a light chain. In some specific embodiments, the antibody only comprises one or two heavy chains. In some preferred embodiments, the antibody of the invention is composed of one heavy chain. In some preferred embodiments, the antibody of the invention is composed of two heavy chains.

[0317] In some embodiments, the antibody of the invention is a homodimeric antibody comprising the VH antigen-binding domain and the CH2 and CH3 constant domains.

[0318] In one embodiment, the antibody of the invention is a heavy chain-only antibody composed of a variable region antigen-binding domain composed of framework 1, CDR1, framework 2, CDR2, framework 3, CDR3, and framework 4.

[0319] In another embodiment, the antibody of the invention is a heavy chain-only antibody composed of an antigen-binding domain, at least part of a hinge region and CH1, CH2 and CH3 domains. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and CH2 and CH3 domains. In another embodiment, the antibody of the invention is a heavy chain-only antibody composed of an antigen-binding domain, at least part of a hinge region and a CH1 domain. In another embodiment, the antibody of the invention is a heavy chain-only antibody composed of an antigen-binding domain, at least part of a hinge region and a CH2 domain. In a further embodiment, the antibody of the invention is a heavy chain-only antibody composed of an antigen-binding domain, at least part of a hinge region and a CH3 domain. In a further embodiment, the antibody of the invention is a heavy chain composed of an antigen binding domain, and at least one CH (CH1, CH2, CH3, or CH4) domain but no hinge region.

[0320] In some embodiments, the antibody of the invention is a heavy chain-only antibody in the form of a dimer, in which two heavy chains are disulfide bonded or otherwise, covalently or non-covalently, attached with each other.

[0321] In some embodiments, the antibody of the invention is a heavy chain-only antibody which belongs to the IgG, IgM, IgA, IgD or IgE subclass antibodies.

[0322] In some embodiments, the antibody of the invention is a heavy chain-only antibody of the IgG1, IgG2, IgG3, or IgG4 subtype, in particular the IgG1 or IgG4 subtype. [0323] In one embodiment, the antibody of the invention is a heavy-chain antibody of the IgG1 or IgG4 subtype, wherein one or more of the CH domains is modified to alter an effector function of the antibody.

[0324] The antibody disclosed herein can be an intact antibody or the antigen binding fragment thereof. The antigen binding fragment can be any fragments of the antibody that retain the ability to specifically bind to ROR1. Examples of antigen binding fragments include but are not limited to a Fab fragment; a F(ab')<sub>2</sub> fragment; a Fab' fragment; a Fd fragment; a Fd' fragment; a dAb fragment; an isolated complementarity determining region (CDR); a nanobody; a linear antibody comprising a pair of tandem Fd segments (VH-CH1-VH-CH1), and a modified version of any of the foregoing fragments, which retains antigen binding activity.

[0325] In some embodiments, the antigen binding fragment can be selected from the group consisting of HCAb, VHH, nanobody, Fab, Fab', F(ab')<sub>2</sub>, Fd, Fd', and dAb.

[0326] In some embodiments, the antibody of the invention is a chimeric antibody, a humanized antibody, or a human antibody.

[0327] In some embodiments, the antibody of the invention is a monoclonal antibody, a bi-specific or a multi-specific antibody.

[0328] In some embodiments, the antibody is monovalent, bivalent or multivalent.

[0329] In some embodiments, the antibody or antigen binding fragment of the invention is attached to a fluorescent label, radiolabel or cytotoxic agent.

#### Bi-Specific Antibody

[0330] In a second aspect, the present application provides a bi-specific or a multi-specific antibody. In some embodiments, the antibody is a bi-specific antibody which further comprises a second antigen binding region binding to a second antigen. In some embodiments, the second antigen can be a tumor associated antigen, an immune checkpoint molecule or an immune cell antigen.

[0331] Many tumor associated antigens associated with specific cancers have been identified in the art. In some embodiments, tumor-associated antigens are antigens that can potentially stimulate an obvious tumor-specific immune response. Some of these antigens are encoded by normal cells, but not necessarily expressed by normal cells. These antigens can be characterized as those that are usually silent (i.e., not expressed) in normal cells, those that are expressed only during certain stages of differentiation, and those that are expressed over time, such as embryonic and fetal antigens. Other cancer antigens are encoded by mutant cell genes such as oncogenes (e.g. activated ras oncogene), suppressor genes (e.g. mutant p53), and fusion proteins produced by internal deletions or chromosomal translocations. Other cancer antigens can be encoded by viral genes, such as those carried on RNA and DNA tumor viruses. Many other tumor associated antigens and antibodies against them are known and/or commercially available, and can also be produced by those skilled in the art.

[0332] Examples of tumor associated antigens include but are not limited to 5T4, alphafetoprotein, CA-125, carcinoembryonic antigen, CD19, CD20, CD22, CD23, CD30, CD33, CD40, CD56, CD79, CD78, CD123, CD138, c-Met,

CSPG4, IgM, C-type lectin-like molecule 1 (CLL-1), EGFR, EGFRvIII, epithelial tumor antigen, ERBB2, FLT3, folate binding protein, GD2, GD3, HIV-1 envelope glycoprotein gp41, HIV-1 envelope glycoprotein gp120, melanoma-associated antigen, ROR1, MUC-1, mutated p53, mutated ras, ROR1, VEGFR2, and combinations thereof.

[0333] In some embodiments, the second antigen is an immune cell antigen. In some embodiments, the T-cell antigen can be selected from the group consisting of T cell receptor (TCR), CD3, CD4, CD8, CD16, CD25, CD28, CD44, CD62L, CD69, ICOS, 41-BB (CD137), and NKG2D or any combination thereof. Preferably, the second antigen is CD3.

[0334] In some embodiments, the second antigen is an immune checkpoint molecule. In some embodiments, the immune checkpoint molecule can be selected from the group consisting of PD-1, PD-L1, CTLA-4, and the like.

[0335] In some embodiments, the bi-specific antibody comprises a single polypeptide chain comprising the first antigen binding region and the second antigen binding region, and optionally an Fc region. The Fc region may be of any isotype, including, but not limited to, IgG1, IgG2, IgG3 and IgG4, and may comprise one or more mutations or modifications. In one embodiment, the Fc region is of IgG1 isotype or derived therefrom, optionally with one or more mutations or modifications.

[0336] In one embodiment, the Fc region is effector-function-deficient. For example, the Fc region may be of an IgG1 isotype, or a non-IgG1 type, e.g. IgG2, IgG3 or IgG4, which has been mutated such that the ability to mediate effector functions, such as ADCC, has been reduced or even eliminated. Such mutations have e.g. been described in Dall'Acqua W F et al., J Immunol. 177(2):1129-1138 (2006) and Hezareh M, J Virol.; 75(24):12161-12168 (2001).

[0337] In one embodiment, the Fc region comprises a mutation removing the acceptor site for Asn-linked glycosylation or is otherwise manipulated to change the glycosylation properties. For example, in an IgG1 Fc region, an N297Q mutation can be used to remove an Asn-linked glycosylation site. Accordingly, in a specific embodiment, Fc region comprise an IgG1 wildtype sequence with an N297Q mutation. For example, in an IgG1 Fc region, an N297Q mutation can be used to remove an Asn-linked glycosylation site. Accordingly, in a specific embodiment, Fc region comprise an IgG1 wildtype sequence with an N297Q mutation.

[0338] In a further embodiment, the Fc region is glyco-engineered to reduce fucose and thus enhance ADCC, e.g. by addition of compounds to the culture media during antibody production as described in US2009317869 or as described in van Berkel et al. (2010) Biotechnol. Bioeng. 105:350 or by using FUT8 knockout cells, e.g. as described in Yamane-Ohnuki et al. (2004) Biotechnol. Bioeng. 87:614. ADCC may alternatively be optimized using the method described by Umana et al. (1999) Nature Biotech 17:176. In a further embodiment, the Fc region has been engineered to enhance complement activation, e.g. as described in Natsume et al. (2009) Cancer Sci. 100:2411.

#### Nucleic Acids

[0339] In a third aspect, the invention provides a nucleic acid comprising a nucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof

disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein.

[0340] The term "polynucleotide" or "nucleic acid" includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the nucleic acid can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoreselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranimidate and phosphoroamidate.

[0341] For example, the invention provides nucleic acid molecules encoding any one of the heavy chain variable region sequences disclosed herein. The invention also provides nucleic acid molecules that are at least 90%, at least 95%, at least 98% or at least 99% identical to nucleic acids encoding any one of the heavy chain variable region sequences disclosed herein.

[0342] For example, the invention provides nucleic acid molecules encoding any one of the light chain variable region sequences disclosed herein. The invention also provides nucleic acid molecules that are at least 90%, at least 95%, at least 98% or at least 99% identical to nucleic acids encoding any one of the light chain variable region sequences disclosed herein.

[0343] For example, the invention provides nucleic acid molecules encoding: (i) any one of the heavy chain variable region sequences disclosed herein and (ii) any one of the light chain variable region sequences disclosed herein. The invention also provides nucleic acid molecules that are at least 90%, at least 95%, at least 98% or at least 99% identical to nucleic acids encoding: (i) any one of the heavy chain variable region sequences disclosed herein and (ii) any one of the light chain variable region sequences disclosed herein.

[0344] In some embodiments, the nucleic acid is ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). In some embodiments, the invention provides a ribonucleic acid (RNA) comprising a nucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein. In some embodiments, the invention provides a deoxyribonucleic acid (DNA) comprising a deoxynucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein.

[0345] Accordingly, the deoxyribonucleic acid (DNA) comprising a deoxynucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein is used for treating a disease. In some embodiments, the disease is a cancer, preferably is a ROR1 positive cancer. In some embodiments, the cancer is selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

[0346] Accordingly, the ribonucleic acid (RNA) comprising a deoxynucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein may be used for treating a disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is selected from the group consisting of a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

[0347] In some embodiments, the deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) may be introduced into the cells of a human body in vivo. In some embodiments, the deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) of the invention is comprised in a vector or a delivering agent. In some embodiments, the deoxyribonucleic acid (DNA) of the invention is integrated into the genome of a cell.

#### Vectors

[0348] In the fourth aspect, the invention further provides a vector, which comprises the nucleic acid comprising a nucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein.

[0349] In some embodiments, the vector is a recombinant expression vector capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-ROR1 antibody. For example, the invention provides recombinant expression vectors comprising any of the nucleic acid molecules mentioned above.

[0350] Any vector may be suitable for the present disclosure. In some embodiments, the vector is a viral vector. In some embodiments, the vector is a retroviral vector, a DNA vector, a murine leukemia virus vector, an SFG vector, a plasmid, an RNA vector, an adenoviral vector, a baculoviral vector, an Epstein Barr viral vector, a papavaviral vector, a vaccinia viral vector, a herpes simplex viral vector, an adenovirus associated vector (AAV), a lentiviral vector, or any combination thereof. Suitable exemplary vectors include e.g., pGAR, pBABE-puro, pBABE-neo largeTcDNA, pBABE-hygro-hTERT, pMKO.1 GFP, MSCV-IRES-GFP, pMSCV PIG (Puro IRES GFP empty plasmid), pMSCV-loxp-dsRed-loxp-eGFP-Puro-WPRE, MSCV IRES Luciferase, pMIG, MDH1-PGK-GFP\_2.0, TtRMPVIR, pMSCV-IRES-mCherry FP, pRetroX GFP T2A Cre, pRXTN, pLncEXP, and pLXIN-Luc.

[0351] A recombinant expression vector may be any suitable recombinant expression vector. Suitable vectors com-

prise those designed for propagation and expansion or for expression or both, such as plasmids and viruses. For example, a vector may be selected from the pUC series (Fermentas Life Sciences, Glen Burnie, Md.), the pBlue-script series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as  $\lambda$ GT10,  $\lambda$ GT11,  $\lambda$ ZapII (Stratagene),  $\lambda$ EMBL4, and  $\lambda$ NM1149, also may be used. Examples of plant expression vectors useful in the context of the disclosure comprise pBI01, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors useful in the context of the disclosure comprise pcDNA, pEUK-Cl, pMAM, and pMAMneo (Clontech).

**[0352]** Recombinant expression vectors may be prepared using standard recombinant DNA techniques described in, for example, Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 2001; and Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates and John Wiley & Sons, NY, 1994. Constructs of expression vectors, which are circular or linear, may be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems may be derived, e.g., from ColEl, 2 $\mu$  plasmid,  $\lambda$ , SV40, bovine papilloma virus, and the like.

**[0353]** Accordingly, the vector may be used for treating a disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is selected from the group consisting of a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer. The vector of the invention may be introduced into a cell. In some embodiments, the vector of the invention may be introduced into a cell *in vitro* or *ex vivo*. Optionally, the cell introduced with the vector may subsequently be administered into the body of a subject. In some embodiments, the vector of the invention may be introduced into a cell *in vivo*.

**[0354]** For example, the vector may be an adenoviral vector comprising a nucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein. The vector may be administered into the body of a subject, and then enter into a cell of the subject *in vivo*, thereby the nucleotide sequence encoding the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein or the bi-specific antibody or the antigen binding fragment thereof disclosed herein is integrated into the genome of the cell, and subsequently the cell expresses the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein so as to treat the diseases disclosed herein.

## Host Cells

**[0355]** In the fifth aspect, the invention further provides a host cell comprising the nucleic acid disclosed herein or the vector disclosed herein.

**[0356]** Any cell may be used as a host cell for the nucleic acids or the vectors of the present disclosure. In some embodiments, the cell can be a prokaryotic cell, fungal cell, yeast cell, or higher eukaryotic cells such as a mammalian cell. Suitable prokaryotic cells include, without limitation, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteaceae such as *Escherichia*, e.g., *E. coli*; *Enterobacter*; *Erwinia*; *Klebsiella*; *Proteus*; *Salmonella*, e.g., *Salmonella typhimurium*; *Serratia*, e.g., *Serratia marcescens*, and *Shigella*; Bacilli such as *B. subtilis* and *B. licheniformis*; *Pseudomonas* such as *P. aeruginosa*; and *Streptomyces*. In some embodiments, the cell is a human cell. In some embodiments, the cell is an immune cell. In some embodiments, host cells include, for example, CHO cells, such as CHOS cells and CHO-K1 cells, or HEK293 cells, such as HEK293A, HEK293T and HEK293FS.

**[0357]** The host cell of the invention is prepared by introducing the vector disclosed herein or the nucleic acid disclosed herein *in vitro* or *ex vivo*. The host cell of the invention may be administered into the body of a subject, and the host cell expresses the anti-ROR1 antibody or the antigen binding fragment thereof disclosed herein *in vivo* so as to treat the diseases disclosed herein.

**[0358]** The invention further provides host cells into which any of the vectors mentioned above have been introduced. The invention further provides methods of producing the antibodies and antibody fragments of the invention by culturing the host cells under conditions permitting production of the antibodies or antibody fragments and recovering the antibodies and antibody fragments so produced.

## Antibody-Drug Conjugate

**[0359]** In the sixth aspect, the invention provides an antibody-drug conjugate (ADC), comprising the antibody or the antigen-binding fragment thereof of the first aspect of the invention or the bi-specific antibody of the second aspect of the invention.

**[0360]** In the context of the present disclosure, a “conjugate” is an antibody or antibody fragment (such as an antigen-binding fragment) covalently linked to an effector molecule or a second protein (such as a second antibody). The effector molecule can be, for example, a drug, toxin, therapeutic agent, detectable label, protein, nucleic acid, lipid, nanoparticle, carbohydrate or recombinant virus. An antibody conjugate is often referred to as an “immunoconjugate.” When the conjugate comprises an antibody linked to a drug (e.g., a cytotoxic agent), the conjugate is often referred to as an “antibody-drug conjugate” or “ADC.” Other antibody conjugates include, for example, multi-specific (such as bi-specific or trispecific) antibodies.

**[0361]** In some embodiments, the effector molecule can be a detectable label or an immunotoxin. Specific, non-limiting examples of toxins include, but are not limited to, abrin, ricin, *Pseudomonas* exotoxin (PE, such as PE35, PE37, PE38, and PE40), diphtheria toxin (DT), botulinum toxin, or modified toxins thereof, or other toxic agents that directly or indirectly inhibit cell growth or kill cells. For example, PE and DT are highly toxic compounds that typically bring

about death through liver toxicity. PE and DT, however, can be modified into a form for use as an immunotoxin by removing the native targeting component of the toxin (such as the domain 1a of PE and the B chain of DT) and replacing it with a different targeting moiety, such as an antibody. The term "conjugated" or "linked" may refer to making two polypeptides into one contiguous polypeptide molecule. In one embodiment, an antibody is joined to an effector molecule. In another embodiment, an antibody joined to an effector molecule is further joined to a lipid or other molecule to a protein or peptide to increase its half-life in the body. The linkage can be either by chemical or recombinant means. In one embodiment, the linkage is chemical, wherein a reaction between the antibody moiety and the effector molecule has produced a covalent bond formed between the two molecules to form one molecule. A peptide linker (short peptide sequence) can optionally be included between the antibody and the effector molecule.

[0362] The invention provides immunoconjugates that include a monoclonal antibody or antigen-binding fragment disclosed herein and an effector molecule. In some embodiments, the effector molecule is a toxin, such as, but not limited to, *Pseudomonas* exotoxin or a variant thereof. In other embodiments, the effector molecule is a detectable label, such as, but not limited to, a fluorophore, an enzyme or a radioisotope.

[0363] The disclosed monoclonal antibodies can be conjugated to a therapeutic agent or effector molecule. Immunoconjugates include, but are not limited to, molecules in which there is a covalent linkage of a therapeutic agent to an antibody. A therapeutic agent is an agent with a particular biological activity directed against a particular target molecule or a cell bearing a target molecule. One of skill in the art will appreciate that therapeutic agents can include various drugs such as vinblastine, daunomycin and the like, cytotoxins such as native or modified *Pseudomonas* exotoxin or diphtheria toxin, encapsulating agents (such as liposomes) that contain pharmacological compositions, radioactive agents such as  $^{125}\text{I}$ ,  $^{32}\text{P}$ ,  $^{14}\text{C}$ ,  $^3\text{H}$  and  $^{35}\text{S}$  and other labels, target moieties and ligands.

[0364] The choice of a particular therapeutic agent depends on the particular target molecule or cell, and the desired biological effect. Thus, for example, the therapeutic agent can be a cytotoxin that is used to bring about the death of a particular target cell (such as a tumor cell). Conversely, where it is desired to invoke a non-lethal biological response, the therapeutic agent can be conjugated to a non-lethal pharmacological agent or a liposome containing a non-lethal pharmacological agent.

[0365] With the therapeutic agents and antibodies described herein, one of skill can readily construct a variety of clones containing functionally equivalent nucleic acids, such as nucleic acids which differ in sequence but which encode the same effector moiety or antibody sequence. Thus, the present disclosure provides nucleic acids encoding antibodies and conjugates and fusion proteins thereof.

[0366] Effector molecules can be linked to an antibody of interest using any number of means known to those of skill in the art. Both covalent and noncovalent attachment means may be used. The procedure for attaching an effector molecule to an antibody varies according to the chemical structure of the effector. Polypeptides typically contain a variety of functional groups; such as carboxylic acid (COOH), free amine ( $-\text{NH}_2$ ) or sulfhydryl ( $-\text{SH}$ ) groups,

which are available for reaction with a suitable functional group on an antibody to result in the binding of the effector molecule. Alternatively, the antibody is derivatized to expose or attach additional reactive functional groups. The derivatization may involve attachment of any of a number of known linker molecules. The linker can be any molecule used to join the antibody to the effector molecule. The linker is capable of forming covalent bonds to both the antibody and to the effector molecule. Suitable linkers are well known to those of skill in the art and include, but are not limited to, straight or branched-chain carbon linkers, heterocyclic carbon linkers, or peptide linkers. Where the antibody and the effector molecule are polypeptides, the linkers may be joined to the constituent amino acids through their side groups (such as through a disulfide linkage to cysteine) or to the alpha carbon amino and carboxyl groups of the terminal amino acids.

[0367] In some circumstances, it is desirable to free the effector molecule from the antibody when the immunoconjugate has reached its target site. Therefore, in these circumstances, immunoconjugates will comprise linkages that are cleavable in the vicinity of the target site.

[0368] Cleavage of the linker to release the effector molecule from the antibody may be prompted by enzymatic activity or conditions to which the immunoconjugate is subjected either inside the target cell or in the vicinity of the target site.

[0369] In view of the large number of methods that have been reported for attaching a variety of radiodiagnostic compounds, radiotherapeutic compounds, labels (such as enzymes or fluorescent molecules), drugs, toxins, and other agents to antibodies one skilled in the art will be able to determine a suitable method for attaching a given agent to an antibody or other polypeptide.

[0370] The antibodies disclosed herein can be derivatized or linked to another molecule (such as another peptide or protein). In general, the antibodies or portion thereof is derivatized such that the binding to the target antigen is not affected adversely by the derivatization or labeling. For example, the antibody can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (for example, a bi-specific antibody or a diabody), a detection agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a strep tavidin core region or a polyhistidine tag).

[0371] One type of derivatized antibody is produced by cross-linking two or more antibodies (of the same type or of different types, such as to create bi-specific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (such as m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (such as succinimidyl suberate). Such linkers are commercially available.

[0372] The antibody can be conjugated with a detectable marker; for example, a detectable marker capable of detection by ELISA, spectrophotometry, flow cytometry, microscopy or diagnostic imaging techniques (such as computed tomography (CT), computed axial tomography (CAT) scans, magnetic resonance imaging (MRI), nuclear magnetic resonance imaging (NMRI), magnetic resonance tomography (MTR), ultrasound, fiberoptic examination, and laparo-

scopic examination). Specific, non-limiting examples of detectable markers include fluorophores, chemiluminescent agents, enzymatic linkages, radioactive isotopes and heavy metals or compounds (for example super paramagnetic iron oxide nanocrystals for detection by MRI). For example, useful detectable markers include fluorescent compounds, including fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-naphthalenesulfonyl chloride, phycoerythrin, lanthanide phosphors and the like. Bioluminescent markers are also of use, such as luciferase, green fluorescent protein (GFP) and yellow fluorescent protein (YFP). An antibody or antigen binding fragment can also be conjugated with enzymes that are useful for detection, such as horseradish peroxidase,  $\beta$ -galactosidase, luciferase, alkaline phosphatase, glucose oxidase and the like. When an antibody or antigen binding fragment is conjugated with a detectable enzyme, it can be detected by adding additional reagents that the enzyme uses to produce a reaction product that can be discerned. For example, when the agent horseradish peroxidase is present the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is visually detectable. An antibody or antigen binding fragment may also be conjugated with biotin, and detected through indirect measurement of avidin or streptavidin binding. It should be noted that the avidin itself can be conjugated with an enzyme or a fluorescent label.

[0373] An antibody may be fused to a self-labelling protein tag (e.g. HaloTag). For example, the protein tag could be cloned at the end of a constant region. HaloTag is a self-labelling protein tag derived from a bacterial enzyme (a haloalkane dehalogenase), designed to covalently bind to a synthetic ligand. In some instances, the synthetic ligand comprises a chloroalkane linker attached to a fluorophore, such as a near-infrared fluorophore (Los et al. (2008) ACS Chem Biol. 3(6):373-82).

[0374] An antibody may be labeled with a magnetic agent, such as gadolinium. Antibodies can also be labeled with lanthanides (such as europium and dysprosium), and manganese.

[0375] Paramagnetic particles such as superparamagnetic iron oxide are also of use as labels. An antibody may also be labeled with a predetermined polypeptide epitopes recognized by a secondary reporter (such as leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0376] An antibody can also be labeled with a radiolabeled amino acid. The radiolabel may be used for both diagnostic and therapeutic purposes. For instance, the radiolabel may be used to detect expression of a target antigen by x-ray, emission spectra, or other diagnostic techniques. Examples of labels for polypeptides include, but are not limited to, the following radioisotopes or radionucleotides:  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{99}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ .

[0377] An antibody can also be derivatized with a chemical group such as polyethylene glycol (PEG), a methyl or ethyl group, or a carbohydrazide group. These groups may be useful to improve the biological characteristics of the antibody, such as to increase serum half-life or to increase tissue binding.

[0378] Toxins can be employed with the monoclonal antibodies described herein to produce immunotoxins. Exemplary toxins include ricin, abrin, diphtheria toxin and sub-

units thereof, as well as botulinum toxins A through F. These toxins are readily available from commercial sources (for example, Sigma Chemical Company, St. Louis, MO). Contemplated toxins also include variants of the toxins described herein (see, for example, see, U.S. Pat. Nos. 5,079,163 and 4,689,401). In one embodiment, the toxin is *Pseudomonas* exotoxin (PE) (U.S. Pat. No. 5,602,095).

[0379] The antibodies described herein can also be used to target any number of different diagnostic or therapeutic compounds to cells expressing the tumor or viral antigen on their surface. Thus, an antibody of the present disclosure can be attached directly or via a linker to a drug that is to be delivered directly to cells expressing cell-surface antigen. This can be done for therapeutic, diagnostic or research purposes. Therapeutic agents include such compounds as nucleic acids, proteins, peptides, amino acids or derivatives, glycoproteins, radioisotopes, lipids, carbohydrates, or recombinant viruses. Nucleic acid therapeutic and diagnostic moieties include antisense nucleic acids, derivatized oligonucleotides for covalent cross-linking with single or duplex DNA, and triplex forming oligonucleotides.

[0380] Alternatively, the molecule linked to an antibody can be an encapsulation system, such as a nanoparticle, liposome or micelle that contains a therapeutic composition such as a drug, a nucleic acid (for example, an antisense nucleic acid), or another therapeutic moiety that is preferably shielded from direct exposure to the circulatory system. Means of preparing liposomes attached to antibodies are well known to those of skill in the art (see, for example, U.S. Pat. No. 4,957,735; Connor et al., Pharm. Ther. 28:341-365, 1985).

[0381] Antibodies described herein can also be covalently or non-covalently linked to a detectable label. Detectable labels suitable for such use include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels include magnetic beads, fluorescent dyes (for example, fluorescein isothiocyanate, Texas red, rhodamine, green fluorescent protein, and the like), radiolabels (for example,  $^3\text{H}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^{32}\text{P}$ ), enzymes (such as horseradish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (such as polystyrene, polypropylene, latex, and the like) beads.

[0382] Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted illumination. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

[0383] The ADCs disclosed herein can be used for the treatment of a cancer alone or in combination with another therapeutic agent and/or in combination with any standard therapy for the treatment of cancer (such as surgical resection of the tumor, chemotherapy or radiation therapy), wherein the cancer is responsive to decreasing, inhibiting and/or blocking immune regulatory function or activity mediated by ROR1.

### Pharmaceutical Compositions

[0384] In the seventh aspect, the invention provides a pharmaceutical composition comprising (i) the antibody or the antigen binding fragment thereof of the first aspect of the invention, or the bi-specific antibody of the second aspect of the invention, or the nucleic acid of the third aspect of the invention, or the vector of the fourth aspect of the invention, or the host cell of the fifth aspect of the invention, or the ADC of the sixth aspect of the invention; and optionally (ii) a pharmaceutically acceptable carrier or excipient.

[0385] The invention provides pharmaceutical composition comprising an antibody of the invention. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" includes any and all solvents, buffers, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g. by injection or infusion). For example, in some embodiments, a composition for intravenous administration typically is a solution in sterile isotonic aqueous buffer.

[0386] The antibodies or agents of the invention (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the antibody or agent and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0387] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydrox-

ide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0388] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0389] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0390] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as

sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0391] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0392] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0393] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0394] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0395] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention is dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0396] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0397] The invention provides therapeutic compositions comprising the anti-ROR1 antibodies or antigen-binding fragments thereof of the present invention. Therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company,

Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTINTM), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

#### Methods of Production

[0398] Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

[0399] The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, (1986) pp. 59-103) Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

[0400] Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, Calif. and the American Type Culture Collection, Manassas, Va. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. (See Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, Marcel Dekker, Inc., New York, (1987) pp. 51-63)).

[0401] The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Mun-

son and Pollard, Anal. Biochem., 107:220 (1980). Moreover, in therapeutic applications of monoclonal antibodies, it is important to identify antibodies having a high degree of specificity and a high binding affinity for the target antigen. [0402] After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. (See Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

[0403] The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[0404] Monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (see U.S. Pat. No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

[0405] Fully human antibodies are antibody molecules in which the entire sequence of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "humanized antibodies", "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by using trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72); and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

[0406] In addition, humanized antibodies can be produced in transgenic plants, as an inexpensive production alternative to existing mammalian systems. For example, the

transgenic plant may be a tobacco plant, i.e., *Nicotiana benthamiana*, and *Nicotiana tabaccum*. The antibodies are purified from the plant leaves. Stable transformation of the plants can be achieved through the use of *Agrobacterium tumefaciens* or particle bombardment. For example, nucleic acid expression vectors containing at least the heavy and light chain sequences are expressed in bacterial cultures, i.e., *A. tumefaciens* strain BLA4404, via transformation. Infiltration of the plants can be accomplished via injection. Soluble leaf extracts can be prepared by grinding leaf tissue in a mortar and by centrifugation. Isolation and purification of the antibodies can readily be performed by many of the methods known to the skilled artisan in the art. Other methods for antibody production in plants are described in, for example, Fischer et al., Vaccine, 2003, 21:820-5; and Ko et al, Current Topics in Microbiology and Immunology, Vol. 332, 2009, pp. 55-78. As such, the present invention further provides any cell or plant comprising a vector that encodes the antibody of the present invention, or produces the antibody of the present invention.

[0407] In addition, an (human) antibody of interest may be produced in fungi. For example, the fungus may be *Myceliophthora thermophila* (e.g. *Myceliophthora thermophila* strain C1; Visser et al. (2011) Industrial Biotechnology 7(3):214-223). Other examples include *Aspergillus* species (e.g. *A. oryzae* (Huynh et al. (2020) Fungal Biology and Biotechnology 7:7), *A. niger* (Ward et al. (2004) Environ. Microbiol. 70:2567-76), or *A. awamori* (Joosten et al. (2003) Microb. Cell Fact 2:1)) and *Trichoderma* species (e.g. *T. reesei* (Nyyssönen et al. (1993) Biotechnology 11:591-595)). In other instances, the fungus may be a yeast, such as *Saccharomyces cerevisiae*, *Candida boidinii*, *Hansenula polymorpha*, *Pichia methanolica*, *Pichia pastoris*, *Yarrowia lipolytica*, *Kluyveromyces lactis* or *Ogataea minuta* (Joosten et al. (2003); Suzuki et al. (2017) J Biosci Bioeng. 124:156-63).

[0408] In addition, human antibodies can also be produced using additional techniques, including phage display libraries. (See Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in WO 2006/008548, WO 2007/096779, WO 2010/109165, WO 2010/070263, WO 2014/141189 and WO 2014/141192.

[0409] One method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Pat. No. 5,916,771. This method includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

[0410] In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen and a correlative method for selecting an anti-

body that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

[0411] The antibody can be expressed by a vector containing a DNA segment encoding the single chain antibody described above.

[0412] These can include vectors, liposomes, naked DNA, adjuvant-assisted DNA, gene gun, catheters, etc. Vectors include chemical conjugates such as described in WO 93/64701, which has targeting moiety (e.g., a ligand to a cellular surface receptor), and a nucleic acid binding moiety (e.g., polylysine), viral vector (e.g., a DNA or RNA viral vector), fusion proteins such as described in PCT/US 95/02140 (WO 95/22618) which is a fusion protein containing a target moiety (e.g., an antibody specific for a target cell) and a nucleic acid binding moiety (e.g., a protamine), plasmids, phage, etc. The vectors can be chromosomal, non-chromosomal or synthetic.

[0413] Preferred vectors include viral vectors, fusion proteins and chemical conjugates. Retroviral vectors include Moloney murine leukemia viruses. DNA viral vectors are preferred. These vectors include pox vectors such as a herpes simplex I virus (HSV) vector (see Geller, A. I. et al., *J. Neurochem.*, 64:487 (1995); Lim, F., et al., in *DNA Cloning: Mammalian Systems*, D. Glover, Ed. (Oxford Univ. Press, Oxford England) (1995); Geller, A. I. et al., *Proc Natl. Acad. Sci.: U.S.A.* 90:7603 (1993); Geller, A. I., et al., *Proc Natl. Acad. Sci USA* 87:1149 (1990), Adenovirus Vectors (see LeGal LaSalle et al., *Science*, 259:988 (1993); Davidson, et al., *Nat. Genet.* 3:219 (1993); Yang, et al., *J. Virol.* 69:2004 (1995) and Adeno-associated Virus Vectors (see Kaplitt, M. G. et al., *Nat. Genet.* 8:148 (1994).

[0414] Pox viral vectors introduce the gene into the cell cytoplasm. Avipox virus vectors result in only a short-term expression of the nucleic acid. Adenovirus vectors, adeno-associated virus vectors and herpes simplex virus (HSV) vectors are preferred for introducing the nucleic acid into neural cells. The adenovirus vector results in a shorter-term expression (about 2 months) than adeno-associated virus (about 4 months), which in turn is shorter than HSV vectors. The particular vector chosen will depend upon the target cell and the condition being treated. The introduction can be by standard techniques, e.g., infection, transfection, transduction or transformation. Examples of modes of gene transfer include e.g., naked DNA, CaPO<sub>4</sub> precipitation, DEAE dextran, electroporation, protoplast fusion, lipofection, cell microinjection, and viral vectors.

[0415] The vector can be employed to target essentially any desired target cell. For example, stereotaxic injection can be used to direct the vectors (e.g., adenovirus, HSV) to a desired location. Additionally, the particles can be delivered by intracerebroventricular (icv) infusion using a minipump infusion system, such as a SynchroMed Infusion System. A method based on bulk flow, termed convection, has also proven effective at delivering large molecules to extended areas of the brain and may be useful in delivering the vector to the target cell. (See Bobo et al., *Proc. Natl. Acad. Sci. USA* 91:2076-2080 (1994); Morrison et al., *Am. J. Physiol.* 266:292-305 (1994)). Other methods that can be used include catheters, intravenous, parenteral, intraperitoneal and subcutaneous injection, and oral or other known routes of administration.

[0416] These vectors can be used to express large quantities of antibodies that can be used in a variety of ways. For example, to detect the presence of ROR1 in a sample. The antibody can also be used to try to bind to ROR1.

[0417] Methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme linked immunosorbent assay (ELISA) and other immunologically mediated techniques known within the art.

#### Therapeutic Methods

[0418] The antibodies provide herein can be administered to slow or inhibit the progression of a ROR1-positive cancer, and/or inhibit the metastasis of a ROR1-positive cancer. In these applications, a therapeutically effective amount of a composition is administered to a subject in an amount sufficient to inhibit growth, replication or metastasis of cancer cells, or to inhibit a sign or a symptom of the cancer. Suitable subjects may include those diagnosed with a cancer that expresses ROR1, such as B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

[0419] Administration of an antibody disclosed herein can also be accompanied by administration of other anti-cancer agents or therapeutic treatments (such as surgical resection of a tumor). Any suitable anti-cancer agent can be administered in combination with the antibodies disclosed herein. Exemplary anti-cancer agents include, but are not limited to, chemotherapeutic agents, such as, for example, mitotic inhibitors, alkylating agents, antimetabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, anti-survival agents, biological response modifiers, anti-hormones (e.g. anti-androgens) and anti-angiogenesis agents. Other anti-cancer treatments include radiation therapy and other antibodies that specifically target cancer cells.

[0420] In some embodiments, the antibody or the antigen binding fragment thereof, the bi-specific antibody, the nucleic acid, the vector, the host cell, the antibody-drug conjugate, or the pharmaceutical composition of the invention may be administered in combination with an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.

[0421] Another common treatment for some types of cancer is surgical treatment, for example surgical resection of a metastatic tumor. Another example of a treatment is radiotherapy, for example administration of radioactive material or energy (such as external beam therapy) to the tumor site to help eradicate the tumor or shrink it prior to surgical resection.

#### Methods for Diagnosis and Detection

[0422] In an aspect, the invention provides a method for determining a subject suffering from a cancer or having a risk of developing a ROR1 positive cancer, wherein the method comprises:

[0423] (a) obtaining a biological sample from the subject,

[0424] (b) contacting the sample with the antibody or the antigen binding fragment thereof of the invention, and

[0425] (c) detecting binding of the antibody to the sample,

[0426] wherein an increase in binding of the antibody or antigen binding fragment thereof to the sample as compared to binding of the antibody or antigen binding fragment thereof to a control sample identifies the subject as having a ROR1 positive cancer.

[0427] In another aspect, the invention provides a method for imaging a ROR1 positive cancer in a subject, wherein the method comprises:

[0428] (a) administering the antibody or antigen binding fragment thereof of the invention to the subject, wherein the antibody is conjugated to a detectable marker, and

[0429] (b) detecting the presence of the marker

[0430] Methods are provided herein for detecting ROR1 protein in vitro or in vivo. In some cases, ROR1 expression is detected in a biological sample. The sample can be any sample, including, but not limited to, tumor samples, blood samples, tissue from biopsies, autopsies and pathology specimens. Biological samples also include sections of tissues, for example, frozen sections taken for histological purposes. Biological samples further include body fluids, such as blood, serum, plasma, sputum, spinal fluid or urine. A biological sample is typically obtained from a mammal, such as a human or non-human primate.

[0431] Provided herein is a method of determining if a subject has a cancer by contacting a sample from the subject with a ROR1-specific monoclonal antibody disclosed herein; and detecting binding of the antibody to the sample. An increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having a cancer.

[0432] In another embodiment, provided is a method of diagnosing of a cancer in a subject by contacting a sample from a subject diagnosed with a cancer with a ROR1-specific monoclonal antibody disclosed herein; and detecting binding of the antibody to the sample. An increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample confirms the diagnosis of a cancer in the subject.

[0433] In some examples of the disclosed methods, the monoclonal antibody is directly labeled.

[0434] In other examples, the methods further include contacting a second antibody that specifically binds the monoclonal antibody with the sample; and detecting the binding of the second antibody. An increase in binding of the second antibody to the sample as compared to binding of the second antibody to a control sample detects a cancer in the subject or confirms the diagnosis of a cancer in the subject.

[0435] In some cases, the cancer is a ROR1 positive cancer, preferably selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic can-

cer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.

[0436] In some examples, the control sample is a sample from a subject without cancer. In particular examples, the sample is a blood or tissue sample.

[0437] In some embodiments of the methods of diagnosis and detection, the anti-ROR1 antibody is directly labeled with a detectable label. In another embodiment, the anti-ROR1 antibody (the first antibody) is unlabeled and a second antibody or other molecule that can bind the first is labeled. As is well known to one of skill in the art, a secondary antibody is chosen that is able to specifically bind the specific species and class of the first antibody. For example, if the first antibody is a human IgG, then the secondary antibody may be an anti-human-IgG. Other molecules that can bind to antibodies include, without limitation, Protein A and Protein G, both of which are available commercially.

[0438] Suitable labels for the antibody or secondary antibody include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, magnetic agents and radioactive materials. Non-limiting examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase. Non-limiting examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin. Non-limiting examples of suitable fluorescent materials include umbellifluorone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin. A non-limiting exemplary luminescent material is luminol; a non-limiting exemplary a magnetic agent is gadolinium, and non-limiting exemplary radioactive labels include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

[0439] In an alternative embodiment, ROR1 can be assayed in a biological sample by a competition immunoassay utilizing ROR1 protein standards labeled with a detectable substance and an unlabeled anti-ROR1 antibody. In this assay, the biological sample, the labeled ROR1 protein standards and the anti-ROR1 antibody are combined and the amount of labeled ROR1 protein standard bound to the unlabeled antibody is determined. The amount of ROR1 in the biological sample is inversely proportional to the amount of labeled ROR1 protein standard bound to the anti-ROR1 antibody.

[0440] The immunoassays and methods disclosed herein can be used for a number of purposes. In one embodiment, the anti-ROR1 antibody may be used to detect the production of ROR1 in cells in cell culture. In another embodiment, the antibody can be used to detect the amount of ROR1 in a biological sample, such as a tumor sample, a tissue sample, or a blood or serum sample. In some examples, the ROR1 is cell-surface ROR1. In other examples, the ROR1 protein is soluble (e.g. in a cell culture supernatant or in a body fluid sample, such as a blood or serum sample).

[0441] In one embodiment, a kit is provided for detecting ROR1 in a biological sample, such as a tumor sample, a blood sample or tissue sample. For example, to confirm a cancer diagnosis in a subject, a biopsy can be performed to obtain a tissue sample for histological examination. Kits for detecting a polypeptide will typically comprise a monoclonal anti-ROR1 antibody, such as any of the monoclonal

antibodies disclosed herein. In a further embodiment, the antibody is labeled (for example, with a fluorescent, radioactive, or an enzymatic label).

**[0442]** In one embodiment, a kit includes instructional materials disclosing means of use of an anti-ROR1 antibody. The instructional materials may be written, in an electronic form (such as a computer diskette or compact disk) or may be visual (such as video files). The kits may also include additional components to facilitate the particular application for which the kit is designed. Thus, for example, the kit may additionally contain means of detecting a label (such as enzyme substrates for enzymatic labels, filter sets to detect fluorescent labels, appropriate secondary labels such as a secondary antibody, or the like). The kits may additionally include buffers and other reagents routinely used for the practice of a particular method. Such kits and appropriate contents are well known to those of skill in the art.

**[0443]** In one embodiment, the diagnostic kit comprises an immunoassay. Although the details of the immunoassays may vary with the particular format employed, the method of detecting ROR1 in a biological sample generally includes the steps of contacting the biological sample with an anti-ROR1 antibody. The antibody is allowed to specifically bind under immunologically reactive conditions to form an immune complex, and the presence of the immune complex (bound antibody) is detected directly or indirectly.

**[0444]** The antibodies disclosed herein can also be utilized in immunoassays, such as, but not limited to radioimmunoassays (RIAs), ELISA, or immunohistochemical assays. The antibodies can also be used for fluorescence activated cell sorting (FACS). FACS employs a plurality of color channels, low angle and obtuse light-scattering detection channels, and impedance channels, among other more sophisticated levels of detection, to separate or sort cells (see U.S. Pat. No. 5,061,620). Any of the monoclonal antibodies that bind ROR1, as disclosed herein, can be used in these assays. Thus, the antibodies can be used in a conventional immunoassay, including, without limitation, an ELISA, an RIA, FACS, tissue immunohistochemistry, Western blot or immunoprecipitation.

## EXAMPLES

### Example 1 Preparation of Antigen and Stable Cell Lines

#### 1.1. Preparation of Antigens and Other Proteins

**[0445]** Recombinant human ROR1 ECD Fc-tag protein (Catalog #RO1-H5250) and Human ROR1-ECD-his (abbreviated as hROR1-ECD-his) were purchased from Acro biosystemns (Cat #: RO1-H522y).

#### 1.2. Preparation of Stable Cell Lines

**[0446]** HEK293T-hROR1 (human ROR1) was purchased from Kyinno (Cat #: KC-1018). CHO-K1-cynoROR1 (cy-nomolgus ROR1) and CHO-K1-huROR1 (human ROR1) stable cell lines were prepared as follows. Inoculated CHO-K1 cell suspension with 2 mL/well at a density of 50000/ml into 6-well plates, incubated overnight, then added Polybrene (Shanghai Jikai Gene, REVG0001, 10 mg/ml) to make the final concentration 4 µg/mL, mixed and added 10 µL virus (LV-CynoROR1, Purchased from Shanghai Genechem, 42582-1, titer 1E9/mL, 50 µl/vial), mixed and incubated at 37° C. for 8 hours, then supernatant was

discarded and replaced with fresh medium, and cultured at 37° C. After 24 h digestion, the cells were re-suspended in complete medium containing 8 µg/mL puromycin (Thermo, A1113803), cells were diluted to 5/mL and cultured at 37° C. for 10 days with 100 µL/well 10 96-well plates. Monoclonals were selected for FACS verification. After verification, the verified clones were further expanded and cultured for freezing storage.

### Example 2 Animal Immunization Schemes

**[0447]** In order to obtain ROR1-specific antibodies, Harbour HCAb transgenic mice (<https://harbourantibodies.com/>) were immunised through different approaches. These immunisations yielded a number of HCAb antibodies that bind ROR1 extracellular (ECD) proteins or ROR1-expressing cells.

#### 2.1 Immunization by Injection of ROR1 Proteins

**[0448]** Recombinant human ROR1 ECD Fc-tag protein (Acro Biosystem, Catalog #RO1-H5250) was used as the immunogen to immunize Harbour HCAb transgenic mice.

**[0449]** The immunization scheme for Harbour HCAb mice immunization cohorts is listed in Table 5 below. In brief, each mouse was administrated with 50 µg of the immunogen for the first boost via i.p. with adjuvant (Sigma, F5881), and 25 µg for following boosts via i.p. with adjuvant (Sigma, S6322). The immunization was conducted bi-weekly for a total of 5 times. Final immunization was conducted with immunogen diluted in PBS via i.p. Serum titers were tested against human recombinant human ROR1 ECD His-tag protein (Acro Biosystem, Catalog #RO1-H522y) using ELISA and against ROR1-expressing cell line using FACS.

TABLE 5

Immunogen	Immunization scheme				
	Animal No.	Strain	Route	Adjuvant	Dosage (ug/animal)
huROR1-ECD-huFc	10 2.1	HCAb (250 ul)	i.p. (250 ul)	CFA/Ribi/Ribi/ Ribi/Ribi	50/25/25/ 25/25 ug

#### 2.2 Immunization by Injection of ROR1 Cells

**[0450]** HEK293T-hROR1 was used as the immunogen to immunize Harbour HCAb transgenic mice. The immunization scheme for Harbour HCAb mice immunization cohorts is listed in Table 6 below.

**[0451]** In brief, each mouse was intraperitoneally (i.p.) injected with  $1.0 \times 10^7$  HEK293T-hROR1 cells resuspended in PBS for primary immunization. For booster immunization,  $1.0 \times 10^7$  HEK293T-hROR1 cells were resuspended in PBS and intraperitoneally injected into mice. The interval between the primary immunization and the first booster immunization was 2 weeks. For the following booster immunization  $1.0 \times 10^7$  HEK293T-hROR1 cells were intraperitoneally injected into mice every three weeks with a total of 5 times. Seven days after each booster immunization, the blood was taken, and serum titers were tested against recombinant human ROR1 ECD His-tag protein (Acro Biosystem, Catalog #RO1-H522y) using ELISA and against ROR1-expressing cell line using FACS.

TABLE 6

Immunization scheme					
Immunogen	Animal No.	Strain	Route	Adjuvant	Dosage (cells/animal)
HEK293T-huROR1	10 2.1	HCAb (250 ul)	i.p. (250 ul)	—	1.0 × 10 <sup>7</sup> cells

### Example 3 Screening for ROR1-Specific HCAb Antibodies

#### 3.1 HEK293-pCAG-HCAb Directed Cloning Screening for HCAb Antibodies

[0452] In this example, lymph nodes from mice with high antibody titers were harvested to prepare cDNA. The variable regions of HCAb cDNA were amplified by PCR using specific primers (5'-GGTGTCCAGTGT-SAGGTGCAGCTG-3' (SEQ ID NO: 262), 5'-AATCCCTGGGCACTGAAGAGACGGTGACC-3' (SEQ ID NO: 263)) and cloned on mammalian expression vector (pCAG) which contains human immunoglobulin heavy chain Fe part of the IgG1 subclass, named as pCAG-HCAb libraries. The plasmids of pCAG-HCAb libraries were prepared and transfected into HEK293 cells (ATCC, CRL-1573) on 96-well plates for expression, then the supernatants of HEK293-pCAG-HCAb were harvested and transferred to different 96-well plates for screening by *in vitro* binding assay. Binding to stable cell line CHO-K1-huROR1 expressing human ROR1, and to stable cell line CHO-K1-cynoROR1 expressing cynomolgus monkey ROR1 were tested by Mirrorball (SPT Labtech). HEK293 cell supernatants which exhibited binding to both CHO-K1-huROR1 and CHO-K1-cynoROR1 were selected for subsequently FACS screening.

[0453] Finally, multiple HCAb clones were selected for the further characterization.

#### 3.2 Single B-Cell Screening for HCAb Antibodies

[0454] The Beacon® Optofluidic system was used for single B cell screening. The system uses optical-electric positioning (OEPTM) technology to move individual cells, and allow simultaneous biological function tests, experimental analysis, positive clone selection and other operations under cell culture conditions. The Beacon platform can perform these tasks in a massively parallel, automated manner on thousands of cells.

[0455] In this example, a plasma cell discovery workflow was used. In each experiment, up to 14,000 individual plasma cells were screened for secretion of ROR1-specific antibodies. Then, plasma cells that secreted antigen-specific antibodies were transferred to 96-well plates for subsequent single B cell sequencing to identify the heavy chain of the antibody produced by a single B cell (monoclonal). FIG. 1 shows the screening strategy and process.

[0456] The example used a single B cell sequencing method to obtain the sequences of heavy chain of the antibody from a single plasma cell. General procedures include extraction and purification of the total RNA from single plasma cell lysate, reverse transcription synthesis of cDNA, amplification and purification of cDNA, amplification of the DNA sequences encoding heavy chain of an antibody, cloning and transfection, and Sanger sequencing.

Uniqueness and cluster analysis on the obtained sequences was performed, and then DNA sequences encoding the heavy chain of the antibody were synthesized.

### Example 4. Antibody Production and Purification

[0457] The recombinant plasmids encoding target antibodies were transiently transfected into HEK293-6E cells (National Research Council) using PEI (Polyscience, 24885). After transfection, the cells were incubated at 37° C. with 5% CO<sub>2</sub> and shaking at 120 rpm. The cell culture supernatants containing target antibodies were harvested 6-7 days post transfection by centrifugation and filtration. Monoclonal antibodies were purified using Protein A magnetic beads (AmMag Protein A Magnetic Beads, Genscript, L00695).

[0458] The purity of the antibodies was tested by SEC-HPLC (Agilent 1260 Infinity II HPLC with Welch Xtimate SEC-300 Column, 1×PBS pH 7.4 as mobile phase) and SDS-PAGE (SurePAGE, Bis-Tris, 10×8, 4-12%, 12 wells, Genscript, M00653). Recombinant antibodies were successfully expressed and purified for further characterization.

[0459] By Examples 1-4, HCAb antibody PR005337, PR005338, PR005339, PR005340, PR005341, PR005342, PR005343, PR005344, PR005345, PR005346, PR005347, PR005348, PR005349, PR005350, PR005351, PR005352, PR303125, PR303189, PR303191, PR303199, PR303201, PR303145, PR303147, and PR303155 were obtained. The amino acid sequences of these antibodies were listed in Tables 1-3 above.

[0460] In the meantime, anti-ROR1 antibody PR000374 was produced following the procedures showed above with sequence information from international patent application No. WO2016/094873 (which is incorporated herein by reference). PR000374 is a rabbit to human ROR1 Ab from Patent WO2016/094873.

### Example 5. Binding Activity of Antibodies

#### 5.1 Binding Activity to ROR1 Expressing Cells

[0461] Binding of recombinant anti-ROR1 antibodies to human or cynomolgus ROR1-overexpressing cells was tested by flow cytometry. In this example, ROR1-expressing cell lines are HEK293T cell lines that had been transfected to express human ROR1 on the surface (HEK293T-huROR1, KYINNO BIOTECHNOLOGY CO., LTD, Catalog #KC-1018), CHO-K1 cell lines that had been transfected to express cynomolgus ROR1 (CHOK1-cyno ROR1), PANC-1 (ATCC, catalog: CRL-1469) or A549 cell lines (Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences).

[0462] In brief, anti-ROR1 antibodies were serially diluted in staining buffer (PBS containing 2% FBS). Antibody solution was incubated with 1×10<sup>5</sup> cells at 4° C. for 1 hour. The cells were washed twice with staining buffer (PBS containing 2% FBS), and 100 µL of 1:1000 diluted fluorescent labeled anti-human IgG antibody (Alexa Fluor 647 AffiniPure Goat Anti-Human IgG Fc, Jackson ImmunoResearch, Catalog 109-605-098 or Alexa Fluor® 488 AffiniPure Goat Anti-Human IgG(H+L), Jackson ImmunoResearch, 109-545-088) was added into each well. After 1-hour incubation at 4° C., cells were washed twice with staining buffer and subjected to flow cytometry. PR000374 (Bench

marker 1) and non-relevant IgG isotype control (Crownbio) were used as positive and negative controls, respectively.

**[0463]** The results for PR005337, PR005338, PR005339, PR005340, PR005341, PR005342, PR005343, PR005344, PR005345, PR005346, PR005347, PR005348, PR005349, PR005350, PR005351, and PR005352 are shown in FIGS. 2A, 2B, 3A, 3B, 3C and Tables 7-8 below. The results showed that the HCAb antibodies had a good binding activity to PANC-1 cells and strong binding activity to CHO-K1-cynoROR1 cells, indicating that these HCAb antibodies had cross-reactivity with cynoROR1.

TABLE 7

Binding of anti-ROR1 HCAb antibodies to CHO-K1-cyno ROR1 cells		
Antibody ID	EC50	Max
PR005337	18.18	31123
PR005339	4.40	34835
PR005340	3.44	36398
PR005341	3.22	32905
PR005342	7.27	34495
PR005343	3.62	34069
PR005347	13.49	32745
PR000374	5.20	25195
PR005338	8.042	33279
PR005344	15.09	30737
PR005345	22.37	24571
PR005346	10.38	26634
PR005348	73.37	27989
PR005350	79.08	14394
PR005351	20.1	27464
PR000374	3.883	23157

TABLE 8-continued

Binding of anti-ROR1 HCAb antibodies to PANC-1 cells		
Antibody ID	EC50	Max
PR005341	2.13	16531
PR005342	4.30	16681
PR005343	2.24	18287
PR005347	8.08	16428
PR000374	5.47	10681
PR005338	6.70	12711
PR005344	20.01	12390
PR005345	45.04	9714
PR005346	8.28	10167
PR005348	112.80	10198
PR005350	190.30	4248
PR005351	20.95	10899
PR000374	7.51	8935
PR005349	10.5	27100
PR005352	9.297	23316

**[0464]** The results for HCAb antibodies PR303125, PR303189, PR303191, PR303199, PR303201, PR303145, PR303147, and PR303155 are shown in FIGS. 2C, 3D, 4, 5 and Table 9 below. The results indicate that HCAb antibodies showed strong binding activity to both human and cynomolgus ROR1 expressing cells. These results indicate that the anti-ROR1 HCAb antibodies are capable of binding to human and cynomolgus ROR1 on cell membrane with high affinity.

TABLE 9

Binding of anti-ROR1 HCAb antibodies to cell surface ROR1 by FACS								
Antibody ID	HEK293T-hROR1		CHO-K1-cynoROR1		PANC-1		A549	
	EC50 ( $\mu$ g/ml)	MAX(MFI)						
PR303125	0.273	1.50E+07	0.222	8.27E+06	0.463	8.83E+05	0.16	6.68E+05
PR303189	0.085	1.46E+07	7.525	5.30E+06	+/-	2.40E+05	—	9.01E+03
PR303191	0.044	1.40E+07	0.030	9.24E+06	+/-	3.64E+05	0.01	6.50E+05
PR303199	0.191	1.53E+07	1.427	6.85E+06	11.320	4.62E+05	6.79	4.08E+05
PR303201	0.066	1.55E+07	0.057	1.07E+07	+/-	9.35E+05	0.08	1.23E+06
PR303145	0.158	1.35E+07	0.474	1.04E+07	0.654	6.53E+05	0.93	8.75E+05
PR303147	0.325	1.46E+07	1.257	3.67E+06	7.773	2.91E+05	6.46	4.12E+05
PR303155	0.267	1.49E+07	0.804	1.10E+07	1.069	5.52E+05	1.32	7.91E+05
Isotype	—	—	—	—	—	—	—	—
PR000374	0.506	1.49E+07	0.314	1.05E+07	0.905	4.42E+05	0.61	6.95E+05

TABLE 8

Binding of anti-ROR1 HCAb antibodies to PANC-1 cells		
Antibody ID	EC50	Max
PR005337	17.10	14706
PR005339	1.75	16194
PR005340	1.81	17527

## 5.2 Binding Activity to hu-ROR1-ECD-his

**[0465]** Binding of recombinant anti-ROR1 antibodies to hu-ROR1-ECD-his was tested by ELISA. In brief, 1  $\mu$ g/mL hu-ROR1-ECD-his was added to the 96-well plate, 100  $\mu$ L each well, incubated at 4°C overnight, washing the plates with 1×PBST 3 times, 300  $\mu$ L/well, blocking the plates with 2% BSA in 1×PBST, 200  $\mu$ L/well at 37°C for 1 hour, anti-ROR1 antibodies were serially diluted in staining buffer (PBS containing 2% BSA). Antibody solution was added to

the plate and incubates at 37° C. for 1 hour, washing the plates with 1×PBST 3 times, 300 ul/well, adding secondary antibody 100 ul/well and incubate at 37° C. for 1 hour, washing the plates with 1×PBST 3 times, 300 ul/well and then add 100 ul/well TMB for about 5 min, stop the reaction by adding 100 ul/well 2M H<sub>2</sub>SO<sub>4</sub>, read the plates with Molecular device spectra max plus384 at 450 nm and 570 nm.

[0466] The results for HCAb antibodies are shown in FIG. 6 and Table 10 below. The results indicate that HCAb antibodies showed strong binding activity to hu-ROR1-ECD-his. These results indicate that the anti-ROR1 HCAb antibodies are capable of binding to human ROR1 with high affinity.

TABLE 10

Binding of anti-ROR1 HCAb antibodies to hu-ROR1-ECD-his by ELISA	
Antibody ID	EC50 (μg/ml)
PR303125	0.002
PR303189	0.002
PR303191	0.001
PR303199	0.006
PR303201	0.004
PR303145	0.002
PR303147	0.023
PR303155	0.002
Isotype	X
PR000374	0.001

## Example 6 PR005340 Affinity Maturation

[0467] The affinity maturation of PR005340 was conducted by Yeast surface display with BD FACS AriaII sorting machine. Firstly, the sequence of PR005340 was analyzed by Kabat numbering and the CDRs regions were also defined. Site saturation and CDR walking strategies were applied for this HCAb affinity maturation. Four mutagenesis libraries were constructed and named as 5340-H1L, 5340-H2L, 5340-H3L and 5340-H2WL, respectively. Two rounds of sorting and screening were performed as follows.

[0468] In the 1st round sorting and screening, 5340-H1L, 5340-H2L and 5340-H3L were sorted and screened by BD FACS AriaII; the 5340-H2WL library was subjected to MACS enrichment and FACS sorting and screening. For each library, the populations with high binding were gated and sorted out; then sorted yeast cells were also cultured and picked out for sequencing and analysis; the unique hits were also characterized by FACS. Based on the FACS result, several hotspots were selected and combined to a combo mutagenesis library.

[0469] In the 2nd round, the combo library was designed and constructed. The library was also subjected to gating and sorting; sorted populations with high binding were also cultured and picked out for sequencing and analysis, all unique hits were characterized by FACS.

[0470] Finally, 15 monovalent form (VH-Flag-His) variants (PR009810, PR009811, P009812, PR009813, PR009814, PR009815, PR009816, PR009817, PR009818, PR009819, PR009820, PR009821, PR009822, PR009823, and PR009824) and 17 bivalent form (HCAb) variants (PR007408, PR007409, PR007410, PR007411, PR007412, PR007413, PR007414, PR007415, PR007416, PR007417, R007418, PR007419, PR007420, PR007421, PR007422,

PR007423, and PR007424) were screened and synthesized. The amino acid sequences of these variants were listed in Tables 1-3 above.

[0471] Binding activity of the variants to PANC-1 cells were tested using the same method described in example 5.1. The results were shown in FIGS. 7-8 and Table 11 and Table 12. As shown, most of the variants showed significant binding enhancement compared to PR005340.

TABLE 11

Binding of PR005340 monovalent form variants to PANC-1 cells		
Antibody ID	EC50	Max
PR009810	0.3132	3988
PR009811	0.3651	4082
PR009812	0.3235	3481
PR009813	0.4616	3493
PR009814	0.3595	3330
PR009815	0.2569	3232
PR009816	0.3707	3201
PR009817	0.2067	4672
PR009818	0.1537	4518
PR009819	0.1083	4376
PR009820	0.09228	4600
PR009821	0.1013	4524
PR009822	0.1861	4335
PR009823	1.026	4909
PR009824	1.461	4622

TABLE 12

Binding of PR005340 bivalent form variants to PANC-1 cells		
FACS BINDING TO PANC-1		
ANTIBODY ID	TOP	EC50
PR005340	84867	2.65
PR007408	87015	0.37
PR007409	87438	0.8
PR007410	80302	0.76
PR007411	81434	0.65
PR007412	77181	0.55
PR007413	89837	0.584
PR007414	88874	0.496
PR007415	82756	0.3652
PR007416	87637	0.7235
PR007417	83758	0.7836
PR007418	81348	0.3941
PR007419	75713	0.7909
PR007420	79539	0.7015
PR007421	86578	0.7776
PR007422	73634	0.5903
PR007423	74531	0.4087
PR007424	70766	0.5504

## Example 7 Binding Activity of Antibodies to Soluble ROR1 Protein by BLI Method

[0472] In the example, binding kinetics of anti-ROR1 antibodies to soluble ROR1 protein were analyzed by using Bio-Layer Interferometry (BLI) analysis on Fortebio Octet Red384 instrument (ForteBio).

7.1 Binding Affinity of Antibodies to ROR1 Protein by Using HIS1K Sensor

[0473] In BLI analysis, recombinant anti-ROR1 antibodies were serially diluted with 10× kinetics buffer (ForteBio). Human ROR1-His proteins were diluted to 20 nM. Then the

diluted antibodies, ROR1 proteins and regeneration buffer (10 mM glycine HCl pH 1.5) were added to 96-well plates (Greiner). Rate constants for association and dissociation were measured using HIS1K sensor (ForteBio). The sensor surface was regenerated after each binding experiment with regeneration buffer. The traces were processed using Octet Data Analysis Software (version 11.0, Pall ForteBio, CA, USA).

**[0474]** The binding kinetics parameters for anti-ROR1 HCAb antibodies binding to human ROR1 are summarized in Table 13. As shown in Table 13, in Octet analysis, the HCAb antibodies showed high binding affinity to soluble ROR1.

TABLE 13

Binding of anti-ROR1 HCAb antibodies to soluble human ROR1				
Antibody ID	K <sub>D</sub> (M)	k <sub>on</sub> (1/Ms)	k <sub>dis</sub> (1/s)	Full R <sup>2</sup>
PR303125	<1.0E-12	1.65E+05	<1.0E-07	0.64
PR303189	6.234E-10	6.46E+06	4.03E-03	0.83
PR303191	3.95E-11	2.90E+06	1.15E-04	0.98
PR303199	1.409E-08	1.23E+05	1.73E-03	0.90
PR303201	4.891E-09	1.28E+06	6.26E-03	0.98
PR303145	1.11E-08	2.78E+05	3.10E-03	0.99
PR303147	1.12E-08	1.47E+06	1.65E-02	0.70
PR303155	6.83E-09	4.92E+05	3.36E-03	0.99

## 7.2 Binding Affinity of Antibodies to ROR1 Protein by Using AHC Sensor

**[0475]** In BLI analysis, Antibodies were diluted to 5 µg/mL using freshly prepared 1× kinetic buffer (10× kinetic buffer (ForteBio, #18-1105) was diluted with PBS (BBI Life Sciences, #E607016-0500)) and captured on the surface of anti-human Fc (AHC) Octet biosensors (ForteBio, #18-5060) to reach capture levels between 0.6-1.0 nm. The captured biosensors were then dipped in wells containing 2-fold serial dilutions of antigen proteins to detect association signals, followed by dissociation steps in wells containing 1× kinetic buffer. Human ROR1 hits-tagged protein (Acrobiosystems, #RO1-H522y) was diluted from 80 nM to 5 nM; the association phase was 180 seconds, and the dissociation phase was 600 seconds. The sensograms were recorded and the reference signals were subtracted before curve fitting using ForteBio Data Analysis 11.0 software. Association rates (k<sub>on</sub>) and dissociation rates (k<sub>dis</sub>) were calculated using a simple one-to-one Langmuir binding model. The equilibrium dissociation constant (K<sub>D</sub>) was calculated as the ratio of k<sub>dis</sub>/k<sub>on</sub>. The binding kinetics parameters for anti-ROR1 HCAb antibodies binding to human ROR1 are summarized in Table 14.

TABLE 14

Binding of anti-ROR1 antibodies to soluble human ROR1						
Antibody ID	Antigen	Antigen Concentration (nM)	KD (M)	k <sub>on</sub> (1/Ms)	k <sub>dis</sub> (1/s)	Full R <sup>2</sup>
PR005338	Human	5-80	2.40E-09	1.32E+05	3.16E-04	0.9954
PR005340	ROR1, His	5-80	1.20E-09	1.43E+05	1.71E-04	0.9968
PR007417	Tag	5-80	1.80E-10	2.71E+05	4.86E-05	0.9952
PR007424		5-80	1.01E-09	2.81E+05	2.84E-04	0.9955

## Example 8. Antibody Specificity Validation

### 8.1 Binding of Antibodies to Human ROR2 Tested by ELISA.

**[0476]** 1 µg/mL hu-ROR2-ECD-his (Acrobiosystems, RO2-H52E5) was added to the 96-well plate, 100 µL each well, incubated at 4° C. overnight, washing the plates with 1×PBST 3 times, 300 µl/well, blocking the plates with 2% BSA in 1×PBST, 200 µl/well at 37° C. for 1 hour, anti-ROR1 antibodies were serially diluted in staining buffer (PBS containing 2% BSA). Antibody solution was added to the plate and incubates at 37° C. for 1 hour, washing the plates with 1×PBST 3 times, 300 µl/well, adding secondary antibody 100 µl/well and incubate at 37° C. for 1 hour, washing the plates with 1×PBST 3 times, 300 µl/well and then add 100 µl/well TMB for about 5 min, stop the reaction by adding 100 µl/well 2M H<sub>2</sub>SO<sub>4</sub>, read the plates with Molecular device spectra max plus384 at 450 nm and 570 nm.

**[0477]** The results for HCAb antibodies are shown in FIG. 9. The results indicate that HCAb antibodies showed no binding activity to hu-ROR2-ECD-his. These results indicate that the anti-ROR1 HCAb antibodies specifically binds to ROR1.

### 8.2 Binding of Antibodies to Human ROR2 Tested by BLI Method

**[0478]** In the example, binding kinetics of anti-ROR1 antibodies to soluble ROR2 protein were analyzed by using Bio-Layer Interferometry (BLI) analysis on ForteBio Octet Red384 instrument (ForteBio). In BLI analysis, Antibodies were diluted to 5 µg/mL using freshly prepared 1× kinetic buffer (10× kinetic buffer (ForteBio, #18-1105) was diluted with PBS (BBI Life Sciences, #E607016-0500)) and captured on the surface of anti-human Fc (AHC) Octet biosensors (ForteBio, #18-5060) to reach capture levels between 0.6-1.0 nm. The captured biosensors were then dipped in wells containing 2-fold serial dilutions of antigen proteins to detect association signals, followed by dissociation steps in wells containing 1× kinetic buffer. Human ROR2 his-tagged protein (Acrobiosystems, #RO2-H52E5) was diluted from 600 nM to 37.5 nM; the association phase was 180 seconds, and the dissociation phase was 180 seconds. The sensograms were recorded and the reference signals were subtracted before curve fitting using ForteBio Data Analysis 11.0 software. Association rates (k<sub>on</sub>) and dissociation rates (k<sub>dis</sub>) were calculated using a simple one-to-one Langmuir binding model. The equilibrium dissociation constant (K<sub>D</sub>) was calculated as the ratio of k<sub>dis</sub>/k<sub>on</sub>.

**[0479]** The binding kinetics parameters for anti-ROR1 HCAb antibodies binding to human ROR2 are summarized in Table 15. The results show that HCAb antibodies have no binding activity to ROR2, suggesting that the anti-ROR1 HCAb antibodies specifically bind to ROR1.

TABLE 15

Binding of anti-ROR1 antibodies to soluble human ROR2						
Antibody ID	Antigen	Antigen	Concentration	KD	kon	kdis
		(nM)	(M)	(1/Ms)	(1/s)	R'2
PR005338	Human	37.5-600		No binding		
PR005340	ROR2,	37.5-600		No binding		
PR007417	His Tag	37.5-600		No binding		
PR007424		37.5-600		No binding		

software. The inhibition rate is calculated by the following formula:

$$\text{Inhibition rate (\%)} = \frac{(A-B)}{A} * 100$$

**[0481]** A: 100% signal of each antibody;

**[0482]** B: the signals of second antibody binding steps.

**[0483]** If the obtained inhibition rate is greater than 80(%), it indicates that the epitopes of the two antibodies completely overlap; if the inhibition rate is less than 40(%), it indicates that the epitopes of the two antibodies are different or far away from each other.

**[0484]** As shown in Tables 16 and 17, HCAb antibodies PR005338, PR005340, PR007417 and PR007424 shared almost identical binding epitopes on human ROR1, but completely different to that of reference antibody PR000374. HCAb antibodies PR303189, PR303199, PR303145, PR303147, PR303155, PR303125, PR303191, PR303201 showed different binding epitopes to that of PR000374; among them, PR303125, PR303191, PR303201 shared similar or overlapped epitopes, but different to other HCAb antibodies.

TABLE 16

The inhibition rates of antibodies in the epitope competition assay						
		2 <sup>nd</sup> Ab				
Inhibition (%)		PR005338	PR005340	PR007417	PR007424	PR000374
1 <sup>st</sup> Ab	PR005338	103.62%	107.73%	107.80%	102.42%	-3.02%
	PR005340	106.23%	109.38%	108.72%	106.11%	-0.17%
	PR007417	113.69%	116.43%	112.59%	111.34%	10.25%
	PR007424	107.56%	111.11%	111.27%	106.82%	-0.73%
	PR000374	-7.76%	-7.48%	-10.49%	-8.53%	111.00%

TABLE 17

The inhibition rates of antibodies in the epitope competition assay									
Inhibition (%)	PR303189	PR303199	PR303145	PR303147	PR303155	PR303125	PR303191	PR303201	PR000374
PR303191	-99%	-57%	-70%	-60%	-62%	80%	80%	57%	-38%
PR303125	-24%	-48%	-41%	-88%	-62%	104%	109%	86%	-24%
PR000374	-52%	-61%	-61%	-72%	-67%	-45%	-34%	-63%	109%

#### Example 9. Epitope Binning of Antibodies by Competition Assay

**[0480]** To determine if anti-ROR1 antibodies bind to human ROR1 on different or approximate binding epitopes, the ForteBio Octet® RED96e platform was used to perform epitope competition experiments on the anti-ROR1 antibodies. Human ROR1 protein (Acrobiosystems, #R01-H522y) was biotinylated and then captured onto SA biosensors (ForteBio, #18-5020) to reach loading level of 0.3-0.4 nm. The in-tandem competition assay format was applied and it contains two association steps. Firstly, the antigen-loaded biosensors bind to each antibody (a.k.a, First antibody, 1<sup>st</sup> Ab) with a saturating concentration of 200 nM for 180 seconds to reach equilibrium and then secondly bind to the competing antibodies (a.k.a, Second antibody, 2<sup>nd</sup> Ab) of 200 nM for 180 seconds. The second binding signals were recorded as the 100% signal of each antibody when the first antibodies were replaced by kinetics buffer. All the binding data were analyzed using ForteBio Data Analysis 11.0

#### Example 10. Antibody Internalization by ROR1 Expressing Cells

##### 10.1 Antibody Internalization by HEK293T-hROR1 Cells by Ab-MMAF Cytotoxicity Method

**[0485]** 12000 cells/90 ul of HEK293T-hROR1 cells were added to flat bottom 96-well plates, incubated overnight in 37° C., 5% CO<sub>2</sub> incubator. Antibodies at 10<sup>x</sup> concentration (100 nM) in complete medium were prepared. The dilution factor is 5 and 6 doses (10, 2, 0.4, 0.08, 0.016, 0.0032) were prepared. 10 ul of each complex dilution was transferred to the cells in duplicate to final volume of 100 ul for all assay well. aHFc-CL-MMAF at concentration of 50 ug/ml (50<sup>x</sup>) was prepared and added with 2 ul to the wells, the final concentration is 1 ug/ml. Cells were incubated for 120 h at 37° C, 5% CO<sub>2</sub>. Add 100 ul of Cell Titer-Glo Reagent equal to the volume of cell culture medium present in each well. Contents were mixed for 2 minutes on an orbital shaker to induce cell lysis. The plate was incubated at room tempera-

ture for 10 minutes to stabilize the luminescent signal. Luminescence was recorded using PE Enspire.

**[0486]** The results of internalization rate of anti-ROR1 HCAbs are shown in FIG. 10. HCAbs showed better internalization activity on ROR1 overexpressing 293T cells than PR000374.

#### 10.2 Antibody Internalization by PANC-1 Cells by pHAb Kit

**[0487]** In this example, pHAb Amine Reactive Dye (Pro-mega, Cat #G9845) was used to determine the antigen-based internalization of anti-ROR1 antibodies into PANC-1 cells. pHAb Dyes are pH sensor dyes that have very low fluorescence at pH>7 and a dramatic increase in fluorescence when the pH of the solution becomes acidic. When an antibody labelled with pHAb dyes binds outside membrane of cells in neutral pH, no or very low fluorescence could be monitored. After internalization, the fluorescence will become stronger in lower pH environments in endosomes and lysosomes.

**[0488]** Antibodies were labelled with pHAb Dyes and calculated for DARs following the kit instructions. The labelled antibodies were then incubated with PANC-1 at 4° C. (the internalization activity at this temperature is very low, which was used as background control) or 37° C. for 24 hours. Then a fluorescence with excitation maxima (Ex) at 532 nm and emission maxima (Em) at 560 nm was detected. The final normalized results are shown as the fluorescence intensity under 37° C. subtracting the fluorescence intensity at background under 4° C. and then divided by DARs of pHAb Dye of the antibody. A higher value indicates a higher internalization activity.

**[0489]** The results of internalization rate of anti-ROR1 HCAb antibodies detected at 7<sup>th</sup> hour and 24<sup>th</sup> hour are separately shown in FIGS. 11A-11B. The results indicate that HCAb clones PR303155, PR303191 and PR303199 show good internalization by PANC-1 cells.

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	mol_type = protein
	organism = synthetic construct
SEQUENCE: 42	
SNNGST	6
SEQ ID NO: 43	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 43	
SSSGSS	6
SEQ ID NO: 44	moltype = AA length = 6

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FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 44	
SNSST	6
SEQ ID NO: 45	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 45	
SNSSS	6
SEQ ID NO: 46	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 46	
SKNGFT	6
SEQ ID NO: 47	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 47	
STTGST	6
SEQ ID NO: 48	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 48	
SRSGST	6
SEQ ID NO: 49	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 49	
SSSGNT	6
SEQ ID NO: 50	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 50	
DTNGST	6
SEQ ID NO: 51	moltype = AA length = 6
FEATURE	Location/Qualifiers
REGION	1..6
source	note = Synthetic
	1..6
	mol_type = protein
	organism = synthetic construct

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SEQUENCE: 51		
SSGGGS		6
SEQ ID NO: 52	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 52		
SSSGSY		6
SEQ ID NO: 53	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 53		
SSSGSW		6
SEQ ID NO: 54	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 54		
NTRGSP		6
SEQ ID NO: 55	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 55		
DSSGRP		6
SEQ ID NO: 56	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 56		
SGSGDS		6
SEQ ID NO: 57	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 57		
SGSGRT		6
SEQ ID NO: 58	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
source	note = Synthetic	
	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 58		
NSDGSS		6
SEQ ID NO: 59	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	

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source          note = Synthetic
               1..6
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 59
SSNGST                                     6

SEQ ID NO: 60      moltype = AA  length = 6
FEATURE          Location/Qualifiers
REGION           1..6
note = Synthetic
source          1..6
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 60
SGTGGN                                     6

SEQ ID NO: 61      moltype = AA  length = 6
FEATURE          Location/Qualifiers
REGION           1..6
note = Synthetic
source          1..6
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 61
SGSGDK                                     6

SEQ ID NO: 62      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 62
TWYASWVKGR FTISRDDSKS IAYLQMNSLK TEDTAVYYCA R           41

SEQ ID NO: 63      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 63
IHYADSVKGR FTVSRDNAKN SLYLQMNSLR TEDTAVYYCA R           41

SEQ ID NO: 64      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 64
IHYADSVKGR FTISRDNNAKN SLYLQMNSLR TEDTAVYYCA R           41

SEQ ID NO: 65      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 65
IHYADSVKGR FTISRDNNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 66      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 66
IHYADSVKGR FTISRDNNAKN SLYLQMNSLR AEDTAIYYCA R           41

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SEQ ID NO: 67      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 67
IYYAESVKGR FTISRDNAKN SLYLQMNRLR AEDTALYYCA R               41

SEQ ID NO: 68      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 68
IYYADSVKGR FTISRDNAKN SLYLQMSRLR AEDTAMYCYCA R               41

SEQ ID NO: 69      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 69
KNYANSVKGR FTISRDNAKN SLYLQMNSLR AEDTAAYYCA R               41

SEQ ID NO: 70      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 70
ISYANSVKGR FTVSRDANKN SLYLQMNSLR AEDTALYYCA R               41

SEQ ID NO: 71      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 71
IHYSDSVKGR FTISRDNAKN SLYLQMNSLR AEDTAVYYCA R               41

SEQ ID NO: 72      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 72
IYYAESVKGR FTVSRDANKN SLYLQMNSLR AEDTAIYYCA R               41

SEQ ID NO: 73      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 73
KNYANSVKGR FTISRDNAKS SLYLQMNSLR AEDTAAYYCA R               41

SEQ ID NO: 74      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41

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mol_type = protein
organism = synthetic construct
SEQUENCE: 74
KYYADSVKGR PTISRDNAKN SLYLQMNSLR AEDTAVYYCA R           41

SEQ ID NO: 75      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 75
IYYGDSVKGR PTISRDNAKN SLFLQMNSLR AEDTAVYYCA R           41

SEQ ID NO: 76      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 76
RYYAESVKGR PTLSRDNVKN SLNLQMNGLR AEDTALYYCA R           41

SEQ ID NO: 77      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 77
IYYADSVKGR FTISRDNAKN SLYLQMNRRL AEDTALYYCA R           41

SEQ ID NO: 78      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 78
IGYADSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 79      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 79
RYYADSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 80      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 80
LAYADSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 81      moltype = AA length = 41
FEATURE          Location/Qualifiers
REGION           1..41
source            note = Synthetic
                 1..41
mol_type = protein
organism = synthetic construct
SEQUENCE: 81
IHYAHSVVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 82      moltype = AA length = 41

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FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 82	
IHYSGSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 83	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 83	
IHYSHSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 84	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 84	
IHYSSSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 85	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 85	
IHYSPSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 86	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 86	
IHYSASVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 87	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 87	
IHYSTSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 88	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 88	
IHYAGSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R	41
SEQ ID NO: 89	moltype = AA length = 41
FEATURE	Location/Qualifiers
REGION	1..41
source	note = Synthetic
	1..41
	mol_type = protein
	organism = synthetic construct

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SEQUENCE: 89
IHYATSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 90      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 90
IHYASSVKGR FTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 91      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 91
THYAASVKGR FTISRDN SKN TLYLQMNSLR AEDTAVYYCE T           41

SEQ ID NO: 92      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 92
IYYAESVKGR FTISRDNAKN SLYLQMNSLR AEDTAMYYCA R           41

SEQ ID NO: 93      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 93
TNYADSVKGR FTISRDNAKN TLYLQMNSLR VEDTAVYSCA R           41

SEQ ID NO: 94      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 94
IYYADSVKGR FTISRDNARN SLYLQMNSLR AEDTALYYCA R           41

SEQ ID NO: 95      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 95
IYYADSVKGR FTVS RDNAKN SLYLQMNHLR AEDTALYYCA R           41

SEQ ID NO: 96      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source            1..41
mol_type = protein
organism = synthetic construct

SEQUENCE: 96
TYYADSVKGR FTISRDN SKN TLYLQMNSLR AEDTAVYFCE R           41

SEQ ID NO: 97      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41

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source          note = Synthetic
               1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 97
IYYADSVKGR PTISRDNAKN SLYLQMNSLR AEDTAIYYCA R           41

SEQ ID NO: 98      moltype = AA  length = 41
FEATURE          Location/Qualifiers
REGION           1..41
note = Synthetic
source          1..41
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 98
TYYAASVKGR PTISRDNNSNN TVYLQMNSLR AEDTAVYYC K           41

SEQ ID NO: 99      moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Synthetic
source          1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 99
GYSTYYRDFN I           11

SEQ ID NO: 100     moltype = AA  length = 16
FEATURE          Location/Qualifiers
REGION           1..16
note = Synthetic
source          1..16
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 100
DPPTSNSDWV SLHFDH           16

SEQ ID NO: 101     moltype = AA  length = 16
FEATURE          Location/Qualifiers
REGION           1..16
note = Synthetic
source          1..16
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 101
DAPSSNSDWV SLQFDY           16

SEQ ID NO: 102     moltype = AA  length = 12
FEATURE          Location/Qualifiers
REGION           1..12
note = Synthetic
source          1..12
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 102
DFNNGWYEDF DY           12

SEQ ID NO: 103     moltype = AA  length = 16
FEATURE          Location/Qualifiers
REGION           1..16
note = Synthetic
source          1..16
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 103
DIPSSSSDWV SLQFDY           16

SEQ ID NO: 104     moltype = AA  length = 14
FEATURE          Location/Qualifiers
REGION           1..14
note = Synthetic
source          1..14
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 104
TPPSSSDNWYE DFDY           14

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SEQ ID NO: 105 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Synthetic 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 105 DTTNGWYEDF DY		12
SEQ ID NO: 106 FEATURE REGION source	moltype = AA length = 14 Location/Qualifiers 1..14 note = Synthetic 1..14 mol_type = protein organism = synthetic construct	
SEQUENCE: 106 VPPYNASWYE DFDY		14
SEQ ID NO: 107 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Synthetic 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 107 SPRGAFYEDF DY		12
SEQ ID NO: 108 FEATURE REGION source	moltype = AA length = 16 Location/Qualifiers 1..16 note = Synthetic 1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 108 DTPSSSSDWV SLQFDY		16
SEQ ID NO: 109 FEATURE REGION source	moltype = AA length = 11 Location/Qualifiers 1..11 note = Synthetic 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 109 DSSGHWSEFD Y		11
SEQ ID NO: 110 FEATURE REGION source	moltype = AA length = 14 Location/Qualifiers 1..14 note = Synthetic 1..14 mol_type = protein organism = synthetic construct	
SEQUENCE: 110 VPPSNASWYE DFDY		14
SEQ ID NO: 111 FEATURE REGION source	moltype = AA length = 16 Location/Qualifiers 1..16 note = Synthetic 1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 111 DAPSSNSDWV SLHFDH		16
SEQ ID NO: 112 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Synthetic 1..12	

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	mol_type = protein
	organism = synthetic construct
SEQUENCE: 112	
SPRSAFYEDF DY	12
SEQ ID NO: 113	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
source	note = Synthetic
	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 113	
VPPSSSNWYE DFDI	14
SEQ ID NO: 114	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
source	note = Synthetic
	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 114	
IPSYTSSWYE DFDH	14
SEQ ID NO: 115	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
source	note = Synthetic
	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 115	
TPPSSNNWYE DFDY	14
SEQ ID NO: 116	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 116	
DMPSSSSDWV DLQFDY	16
SEQ ID NO: 117	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 117	
DIPSSSSDWV DLQFDY	16
SEQ ID NO: 118	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 118	
DMPSSSSDWV SLQFDY	16
SEQ ID NO: 119	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 119	
DMPSSSEDWV DLQFDY	16
SEQ ID NO: 120	moltype = AA length = 16

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FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 120	
DMPSSSIDWV ELQFDY	16
SEQ ID NO: 121	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 121	
DMPSSSKDWV DLQFDY	16
SEQ ID NO: 122	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 122	
DMPSSSIDWV DLQFDY	16
SEQ ID NO: 123	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 123	
DMPSSSEDWV ELQFDY	16
SEQ ID NO: 124	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 124	
DMPSSSSDWV ELQFDY	16
SEQ ID NO: 125	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Synthetic
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 125	
DMPSSSEDWV MLQFDY	16
SEQ ID NO: 126	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = Synthetic
	1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 126	
LLRFLESLGN DGFKI	15
SEQ ID NO: 127	moltype = AA length = 12
FEATURE	Location/Qualifiers
REGION	1..12
source	note = Synthetic
	1..12
	mol_type = protein
	organism = synthetic construct

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SEQUENCE: 127 DLSSGWYEDF DY	12
SEQ ID NO: 128 FEATURE REGION source	moltype = AA length = 11 Location/Qualifiers 1..11 note = Synthetic 1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 128 EGSGWYEDFD Y	11
SEQ ID NO: 129 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Synthetic 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 129 DVSSGWYEDF DY	12
SEQ ID NO: 130 FEATURE REGION source	moltype = AA length = 12 Location/Qualifiers 1..12 note = Synthetic 1..12 mol_type = protein organism = synthetic construct
SEQUENCE: 130 DCVIGIRD DS DI	12
SEQ ID NO: 131 FEATURE REGION source	moltype = AA length = 14 Location/Qualifiers 1..14 note = Synthetic 1..14 mol_type = protein organism = synthetic construct
SEQUENCE: 131 GITHGVVII PPDY	14
SEQ ID NO: 132 FEATURE REGION source	moltype = AA length = 13 Location/Qualifiers 1..13 note = Synthetic 1..13 mol_type = protein organism = synthetic construct
SEQUENCE: 132 EYYGSENYDH FDY	13
SEQ ID NO: 133 FEATURE REGION source	moltype = AA length = 9 Location/Qualifiers 1..9 note = Synthetic 1..9 mol_type = protein organism = synthetic construct
SEQUENCE: 133 GAFRTTMDY	9
SEQ ID NO: 134 FEATURE REGION source	moltype = AA length = 11 Location/Qualifiers 1..11 note = Synthetic 1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 134 WGQGTLVTVS S	11
SEQ ID NO: 135 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11

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source          note = Synthetic
               1..11
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 135
WGQGALVTVS S                                         11

SEQ ID NO: 136      moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Synthetic
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 136
WGGGTPVTVS S                                         11

SEQ ID NO: 137      moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Synthetic
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 137
WGQGTMVTVS S                                         11

SEQ ID NO: 138      moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Synthetic
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 138
RGQGTLVTVS S                                         11

SEQ ID NO: 139      moltype = AA  length = 23
FEATURE          Location/Qualifiers
REGION           1..23
note = Synthetic
1..23
mol_type = protein
organism = synthetic construct
SEQUENCE: 139
DIQMTQSPSS LSASVGDRV INC                           23

SEQ ID NO: 140      moltype = AA  length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Synthetic
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 140
QASQSIDSNL A                                         11

SEQ ID NO: 141      moltype = AA  length = 15
FEATURE          Location/Qualifiers
REGION           1..15
note = Synthetic
1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 141
WFQQKPGQPP KLLIY                                     15

SEQ ID NO: 142      moltype = AA  length = 7
FEATURE          Location/Qualifiers
REGION           1..7
note = Synthetic
1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 142
RASNLAS

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SEQ ID NO: 143      moltype = AA  length = 32
FEATURE
REGION
1..32
note = Synthetic
source
1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 143
GVPDRFSGSG SGTDFTLTIS SLEAEDVATY YC                                32

SEQ ID NO: 144      moltype = AA  length = 12
FEATURE
REGION
1..12
note = Synthetic
source
1..12
mol_type = protein
organism = synthetic construct
SEQUENCE: 144
LGGVGAVSYR TS                                              12

SEQ ID NO: 145      moltype = AA  length = 10
FEATURE
REGION
1..10
note = Synthetic
source
1..10
mol_type = protein
organism = synthetic construct
SEQUENCE: 145
FGGGTKVEIK                                              10

SEQ ID NO: 146      moltype = AA  length = 119
FEATURE
REGION
1..119
note = Synthetic
source
1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 146
EVQLVESGGG LVQPGRSLRL SCTASGSDIN DYPITWVRQA PGQGLEWIGF INSGGSTWYA  60
SWVKGRFTIS RDDSKSIAYL QMNSLKTEDT AVYYCARGYS TYYRDFNIWG QGTLTVSS  119

SEQ ID NO: 147      moltype = AA  length = 125
FEATURE
REGION
1..125
note = Synthetic
source
1..125
mol_type = protein
organism = synthetic construct
SEQUENCE: 147
EVOLVESGGG LVKPGGSLRL SCAASGFIFS DYYSMSWIRQA PGKGLEWVSY ISSSGSTIHY 60
ADSVKGRFTV SRDNAKNSLY LQMNSLRTE D TAVYYCARDP PTSNSDWVSL HFDHWGQGTL 120
VTVSS                                              125

SEQ ID NO: 148      moltype = AA  length = 125
FEATURE
REGION
1..125
note = Synthetic
source
1..125
mol_type = protein
organism = synthetic construct
SEQUENCE: 148
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DYYSMSWIRQA PGKGLEWISY ISSSGTTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRTE D TAVYYCARDA PSSNSDWVSL QFDYWGQGTL 120
VTVSS                                              125

SEQ ID NO: 149      moltype = AA  length = 121
FEATURE
REGION
1..121
note = Synthetic
source
1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 149
EVQLVESGGG LVKPGGSLKL SCAASGFTFS DYYSMSWIRQA PGKGVEWISY ISNNNGSTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARDF NNGWYEDFDY WGQGTLTVS  120

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S		121
SEQ ID NO: 150	moltype = AA length = 125	
FEATURE	Location/Qualifiers	
REGION	1..125	
	note = Synthetic	
source	1..125	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 150		
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISSSGSTIHY	60	
ADSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSDWVSL QFDYWGQGTL	120	
VTVSS	125	
SEQ ID NO: 151	moltype = AA length = 123	
FEATURE	Location/Qualifiers	
REGION	1..123	
	note = Synthetic	
source	1..123	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 151		
EVQLVESGGG LVKPGGSLRL SCVASGFTFS DYYMSWIRQA PGKGLEWISY ISSSGSSIYY	60	
AESVKGRFTI SRDNAKNSLY LQMNRRLAED TALYYCARTP PSSDNWYEDF DYWGQGALVT	120	
VSS	123	
SEQ ID NO: 152	moltype = AA length = 121	
FEATURE	Location/Qualifiers	
REGION	1..121	
	note = Synthetic	
source	1..121	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 152		
EVQLVESGGG LVKPGGSLRL SCAASGFNFS DYYMSWIRQA PGKGLEWISY ISNSSSTIYY	60	
ADSVVKGRFTI SRDNAKNSLY LQMSRLRAED TAMYYCARDT TNGWYEDFDY WGQGTLVTS	120	
S	121	
SEQ ID NO: 153	moltype = AA length = 123	
FEATURE	Location/Qualifiers	
REGION	1..123	
	note = Synthetic	
source	1..123	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 153		
EVQLVESGGG LVKPGGSLRL SCVASGFTFS DYYMSWIRQA PGKGMEWISY ISSSGSTKNY	60	
ANSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAAYYCARVP PYNASWYEDF DYWGQGTLVT	120	
VSS	123	
SEQ ID NO: 154	moltype = AA length = 121	
FEATURE	Location/Qualifiers	
REGION	1..121	
	note = Synthetic	
source	1..121	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 154		
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISNSSSSISY	60	
ANSVKGRFTV SRDNAKNSLY LQMNSLRAED TALYYCARSP RGAFYEDFDY WGQGTLVTS	120	
S	121	
SEQ ID NO: 155	moltype = AA length = 125	
FEATURE	Location/Qualifiers	
REGION	1..125	
	note = Synthetic	
source	1..125	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 155		
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWIAY ISSSGSTIHY	60	
SDSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARDT PSSSDWVSL QFDYWGQGTP	120	
VTVSS	125	
SEQ ID NO: 156	moltype = AA length = 120	
FEATURE	Location/Qualifiers	

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REGION          1..120
source          note = Synthetic
                1..120
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 156
EVQLVESGGG LVKPGGSLRL SCAASGFTLS DYYSMSWIROA PGKGLEWVSN ISKNGFTIYY 60
AESVKGRFTV SRDNAKNSLY LQMNSLRAED TAIYYCARDS SGWYSEFDYW GQGTLTVSS 120

SEQ ID NO: 157      moltype = AA length = 123
FEATURE          Location/Qualifiers
REGION           1..123
source            note = Synthetic
                1..123
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 157
EVQLVESGGG LVKPGGSLRL SCVTSGFTFS DYYSMSWIROA PGKGMEWISY ISTTGSTKNY 60
ANSVKGRFTI SRDNNAKSSLY LQMNSLRAED TAAYYCARVP PSNASWYEDF DYWGQGTLVT 120
VSS              123

SEQ ID NO: 158      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                1..125
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 158
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYSMSWIROQT PGKGLEWVSY ISRSGSTKYY 60
ADSVKGRFTI SRDNNAKNSLY LQMNSLRAED TAVYYCARDA PSSNSDWVSL HFDHWGQGTL 120
VTSS              125

SEQ ID NO: 159      moltype = AA length = 121
FEATURE          Location/Qualifiers
REGION           1..121
source            note = Synthetic
                1..121
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 159
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYSMSWIROA PGKGLEWISY ISNSSSSISY 60
ANSVKGRFTV SRDNNAKNSLY LQMNSLRAED TALYYCARSP RSAFYEDFDY WGQGTLTVS 120
S                 121

SEQ ID NO: 160      moltype = AA length = 123
FEATURE          Location/Qualifiers
REGION           1..123
source            note = Synthetic
                1..123
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 160
EVQLVESGGG LVKPGGSLRL SCAASGFTLS DSQMSWIROA PGKGVEWVSY ISSSGNTIYY 60
GDSVKGRFTI SRDNNAKNSLF LQMNSLRAED TAVYYCARVP PSSSNWYEDF DIWGQGTLVT 120
VSS              123

SEQ ID NO: 161      moltype = AA length = 123
FEATURE          Location/Qualifiers
REGION           1..123
source            note = Synthetic
                1..123
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 161
QVQLVESGGG LVKPGGSLRL SCAASGFKLS DFQMSWIROA PGKGLEWVAY IDTNGSTRYY 60
AESVKGRFTL SRDNVKNSLN LQMNLRAED TALYYCARIP SYTSSWYEDF DHWGQGTLVT 120
VSS              123

SEQ ID NO: 162      moltype = AA length = 123
FEATURE          Location/Qualifiers
REGION           1..123
source            note = Synthetic
                1..123
                mol_type = protein
                organism = synthetic construct

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SEQUENCE: 162
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGGSIYY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARTP PSSNNWYEDF DYWGQGALVT 120
VTVSS 123

SEQ ID NO: 163      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 163
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSYIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 164      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 164
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 165      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 165
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSYIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 166      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 166
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 167      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 167
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 168      moltype = AA length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source            note = Synthetic
                 1..125
                 mol_type = protein
                 organism = synthetic construct

SEQUENCE: 168
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY INTRGSPIGY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL 120
VTVSS 125

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SEQ ID NO: 169      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 169
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 170      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 170
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 171      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 171
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY INTRGSPIGY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 172      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 172
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 173      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 173
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 174      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 174
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY INTRGSPIGY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 175      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125

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source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 175
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 176      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 176
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 177      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 177
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 178      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 178
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 179      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 179
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 180      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 180
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
AHVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVSL QFDYWGQGTL 120
VTVSS                                     125

SEQ ID NO: 181      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

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SEQUENCE: 181
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SGSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 182      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 182
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SHSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 183      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 183
EVOLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SSSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVEL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 184      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 184
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SPSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSKDWVDL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 185      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 185
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SPSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVEL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 186      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 186
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SASVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVEL QFDYWGQGTL 120
VTVSS 125

SEQ ID NO: 187      moltype = AA length = 125
FEATURE           Location/Qualifiers
REGION            1..125
source             note = Synthetic
1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 187
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
STSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSDWVDL QFDYWGQGTL 120
VTVSS 125

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SEQ ID NO: 188      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 188
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SSSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVEL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 189      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 189
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SSSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVLD QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 190      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 190
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
AGSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVEL QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 191      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 191
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
SSSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVML QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 192      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 192
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ATSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVLD QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 193      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125
note = Synthetic
source            1..125
mol_type = protein
organism = synthetic construct

SEQUENCE: 193
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ASSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVLD QFDYWGQGTL 120
TVSS                           125

SEQ ID NO: 194      moltype = AA  length = 125
FEATURE          Location/Qualifiers
REGION           1..125

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source          note = Synthetic
               1..125
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 194
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
STSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVDL QFDYWGQGTL 120
TVSS                                     125

SEQ ID NO: 195      moltype = AA  length = 124
FEATURE          Location/Qualifiers
REGION           1..124
source          note = Synthetic
               1..124
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 195
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SHAMSWVRQA PGKGLEWVSA ISGSGDSTHY 60
AASVKGRFTI SRDNNSKNTLY LQMNSLRAED TAVYYCETLL RFLESLGNNDG FKIWGQGTMV 120
TVSS                                     124

SEQ ID NO: 196      moltype = AA  length = 121
FEATURE          Location/Qualifiers
REGION           1..121
source          note = Synthetic
               1..121
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 196
QVQLVESGGG LVKPGGSLRI SCAASGFTFS NYNMSWIRQA PGKGVEWVSH ISGSGRTIYY 60
AESVKGRFTI SRDNAKNSLY LQMNSLRAED TAMYYCARDL SSGWYEDFDY WGQGTLVTVS 120
S                                         121

SEQ ID NO: 197      moltype = AA  length = 120
FEATURE          Location/Qualifiers
REGION           1..120
source          note = Synthetic
               1..120
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 197
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NFWMYWVRQA PGKGLVVCSR INSDGSSSTNY 60
ADSVKGRFTI SRDNAKNTLY LQMNSLRVED TAVYSCAREG SGWYEDFDYWG QGQGTLVTVS 120

SEQ ID NO: 198      moltype = AA  length = 121
FEATURE          Location/Qualifiers
REGION           1..121
source          note = Synthetic
               1..121
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 198
EVQLVESGGG LVKPGGSLRL SCAASGFTLS DYYSWIRQA PGKGLEWISY ISSNGSTIYY 60
ADSVKGRFTI SRDNARNNSLY LQMNSLRAED TALYYCARDV SSGWYEDFDYWG QGQGTLVTVS 120
S                                         121

SEQ ID NO: 199      moltype = AA  length = 121
FEATURE          Location/Qualifiers
REGION           1..121
source          note = Synthetic
               1..121
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 199
EVQLVESGGG LVKPGGSLRL SCAASGFNLDS YMSWIRQA PGKGLEWVSC ISSSGSTIYY 60
ADSVKGRFTV SRDNAKNSLY LQMNHHLRAED TALYYCARDV VIGIRDDSDI WGQGTMVTVS 120
S                                         121

SEQ ID NO: 200      moltype = AA  length = 123
FEATURE          Location/Qualifiers
REGION           1..123
source          note = Synthetic
               1..123
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 200

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EVQLLESGGG LVQPGGSLRL SCAASGFIFG SYAMSWVRQA PGKGLEWVG ISGTGGNTYY 60	
ADSVKGRFTI SRDNNSKNTLY LQMNSLRAED TAVYFCERGI TIHGVVIIIPP DYRGQQGTLVT 120	
VSS	123
SEQ ID NO: 201	moltype = AA length = 122
FEATURE	Location/Qualifiers
REGION	1..122
source	note = Synthetic
	1..122
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 201	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWIAY ISSSGSTIYY 60	
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCAREY YGSENYDHFD YWGQQGTLVT 120	
SS	122
SEQ ID NO: 202	moltype = AA length = 118
FEATURE	Location/Qualifiers
REGION	1..118
source	note = Synthetic
	1..118
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 202	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS GNAMSWVRQA PGKGLEWVA ISGSGDKTYY 60	
AASVKGRFTI SRDNNNTVY LQMNSLRAED TAVYYCEKGA FRTTMDYWGQ GTLTVSS 118	
SEQ ID NO: 203	moltype = AA length = 110
FEATURE	Location/Qualifiers
REGION	1..110
source	note = Synthetic
	1..110
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 203	
DIGMTQSPSS LSASVGDRVT INCQASQSID SNLAWFQQKQ GPQQPKLLIYR ASNLASGVPD 60	
RFSGSGSGTD FTLTISSEA EDVATYYCLG GVGAVSYRTS FGGGTKVEIK 110	
SEQ ID NO: 204	moltype = AA length = 449
FEATURE	Location/Qualifiers
REGION	1..449
source	note = Synthetic
	1..449
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 204	
EVQLVESGGG LVQPGRSLRL SCTASGSDIN DYPITWVRQA PGQGLEWIGF INSGGSTWYA 60	
SWVKGRFTIS RDDSKSIAYL QMNSLKTEDT AVYYCARGYS TYYRDFNIWG QGTLVTVSSA 120	
STKGPSVPPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG 180	
LYSLSSVVTV PSSSLGTQTY ICNVNHNKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP 240	
SVELFPPKPK DTLMISRTPE VTCVVVDVSH EDEPEVKFNWY VGDGVEVHNAK TKPREEQYNS 300	
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTKISK AKGQPREPQV YTLPPSREEM 360	
TKNQVSLSLCL VKGFYPSDIA WEVESNGQPE NNYKTTTPVVL DSDGSFFLYS KLTVDKSRWQ 420	
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK 449	
SEQ ID NO: 205	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
source	note = Synthetic
	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 205	
EVQLVESGGG LVKPGGSLRL SCAASGFIFS DYYMSWIRQA PGKGLEWVSY ISSSGSTIHY 60	
ADSVKGRFTV SRDNAKNSLY LQMNSLRTED TAVYYCARPD PTSNSDWVSL HFDHWGQQGTL 120	
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 180	
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240	
PIEKTISKAK GQPREPQVYT LPSSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQOPENN 300	
YKTTTPPVLDs DGSFFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357	
SEQ ID NO: 206	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
source	note = Synthetic
	1..357
	mol_type = protein

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SEQUENCE: 206          organism = synthetic construct
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISSSGTTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNLSRTEAD TAVYYCARDP PSSNSDWVSL QFDYWQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNKEYK CKVSNKALPA 240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 207          moltype = AA length = 353
FEATURE               Location/Qualifiers
REGION                1..353
source                 note = Synthetic
                      1..353
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 207          moltype = AA length = 353
EVQLVESGGG LVKPGGSLKL SCAASGFTFS DYYMSWIRQA PGKGVEWISY ISNNNGSTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAVYYCARDP NNGWYEDFDY WGQGTLVTVS 120
SEPKSSDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMS RTPEVTCVVV DVSHEDPEVK 180
FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK 240
TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 300
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMEHALHN HYTQKSLSLSPGK 353

SEQ ID NO: 208          moltype = AA length = 357
FEATURE               Location/Qualifiers
REGION                1..357
source                 note = Synthetic
                      1..357
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 208          moltype = AA length = 357
EVQLVESGGG LVKPGGSLKL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISSSGSTIHY 60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDP PSSSSDWVSL QFDYWQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNKEYK CKVSNKALPA 240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 209          moltype = AA length = 355
FEATURE               Location/Qualifiers
REGION                1..355
source                 note = Synthetic
                      1..355
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 209          moltype = AA length = 355
EVQLVESGGG LVKPGGSLRL SCVASGFTFS DYYMSWIRQA PGKGLEWISY ISSSGSSIYY 60
AESVKGRFTI SRDNAKNSLY LQMNRRLRAED TALYYCARDP PSSDNWYEDF DYWGOGALVT 120
VSSEPKSSDK THTCPPCPAP ELLGGPSVFL FPPPKPKDTLM ISRTPEVTCV VVDVSHEDPE 180
VKEPNWYVDG EVHNNAKTKPREE EQYNSTYRV VSVLTVLHQDWL WLNGKEYKCK VSNKALPAPI 240
EKTISKAKGQ PRPQVYTLPPS PSREEMTKNQ VSLTCLVKGF SNGPENNYK 300
TTPPVLDSDG SFFLYSKLT DKSRSRQGNV FSCEVMEHALHN HYTQKSLSLSPGK 355

SEQ ID NO: 210          moltype = AA length = 353
FEATURE               Location/Qualifiers
REGION                1..353
source                 note = Synthetic
                      1..353
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 210          moltype = AA length = 353
EVQLVESGGG LVKPGGSLRL SCAASGFNFS DYYMSWIRQA PGKGLEWISY ISNSSSTIYY 60
ADSVKGRFTI SRDNAKNSLY LQMSRLRAED TAMYYCARDP TNGWYEDFDY WGQGTLVTVS 120
SEPKSSDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMS RTPEVTCVVV DVSHEDPEVK 180
FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK 240
TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 300
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMEHALHN HYTQKSLSLSPGK 353

SEQ ID NO: 211          moltype = AA length = 355
FEATURE               Location/Qualifiers
REGION                1..355
source                 note = Synthetic
                      1..355
                      mol_type = protein
                      organism = synthetic construct

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SEQUENCE: 211  
 EVQLVESGGG LVKPGGSLRL SCVASGFTFS DYYMSWIRQA PGKGMEWISY ISSSGSTKNY 60  
 ANSVKGRFTI SRDNAKNSLY LQMNLSRAED TAAYYCARVP PYNASWYEDF DYWGQGTIVT 120  
 VSSEPKSSDK THTCPCPAP ELLGGPSVFL FPPKPDTLM ISRTPEVTCV VVDVSHEDPE 180  
 VKFNWYVGDGV EVHNAKTAKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 240  
 EKTISKAKGQ PREPVYTLPPS PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYK 300  
 TPPVLDSDG SFFLYSKLT DKSRSRQGNV FSCSVMHEAL HNHYTQKSLS LSPGK 355

SEQ ID NO: 212 moltype = AA length = 353  
 FEATURE Location/Qualifiers  
 REGION 1..353  
 note = Synthetic  
 source 1..353  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 212  
 EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISNSSSSISY 60  
 ANSVKGRFTV SRDNAKNSLY LQMNLSRAED TALYYCARSP RGAFYEDFDY WGQGTIVTWS 120  
 SEPSSDKTH TCPCPAP ELLGGPSVFL PPKDTLMIS RTPEVTCVV DVSHEDEVK 180  
 FNWYVGDGEV HNAKTAKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCVS NKALPAPIK 240  
 TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYPS SDIAVEWESN GQPENNYKTT 300  
 PVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK 353

SEQ ID NO: 213 moltype = AA length = 357  
 FEATURE Location/Qualifiers  
 REGION 1..357  
 note = Synthetic  
 source 1..357  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 213  
 EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY ISSLGFTIHY 60  
 SDSVKGRFTI SRDNAKNSLY LQMNLSRAED TAVYYCARDT PSSSSDWVSL QFDYWQGTP 120  
 VTVSSEPKSS DKTHTCPCPAP APPELLGGPSV FLPPPKPDT LMISRTPEVT CVVVDVSHED 180  
 PEVKFNWYVGDGV EVHNAKTAKPR PREEQYNSTY RVVSVLTVLHQ DWLNGKEYK CKVSNKALPA 240  
 PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300  
 YTTPVLDSDGSFF DGSSFLY SKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLS LSPGK 357

SEQ ID NO: 214 moltype = AA length = 352  
 FEATURE Location/Qualifiers  
 REGION 1..352  
 note = Synthetic  
 source 1..352  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 214  
 EVQLVESGGG LVKPGGSLRL SCAASGFTLS DYYMSWIRQA PGKGLEWVSN ISKNGFTIYY 60  
 AESVKGRFTV SRDNAKNSLY LQMNLSRAED TAIYYCARDS SGWYSEPDYWGQGTIVTSS 120  
 EPKSSDKTH CTPCPCAP ELLGGPSVFL PPKDTLMISR TPEVTCVV DVSHEDEVK 180  
 NWYVGDGEVH NAKTAKPREEQ YNSTYRVVS LTVLHQDWLN GKEYKCVSN KALPAPIK 240  
 ISKAKGOPRE PQVYTLPPSR EEMTKNQVS LTCLVKGFYPS DIAVEWESNQ PENNYKTT 300  
 PVLDSDGSFF LYSKLTVDK RWQQGNVFS SVMHEALHNH YTQKSLSLSP GK 352

SEQ ID NO: 215 moltype = AA length = 355  
 FEATURE Location/Qualifiers  
 REGION 1..355  
 note = Synthetic  
 source 1..355  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 215

EVQLVESGGG LVKPGGSLRL SCVTSGFTFS DYYMSWIRQA PGKGMEWISY ISTTGSTKNY 60  
 ANSVKGRFTI SRDNAKSSLY LQMNLSRAED TAAYYCARVP PSNASWYEDF DYWGQGTIVT 120  
 VSSEPKSSDK THTCPCPAP ELLGGPSVFL FPPKPDTLM ISRTPEVTCV VVDVSHEDPE 180  
 VKFNWYVGDGV EVHNAKTAKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 240  
 EKTISKAKGQ PREPVYTLPPS PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYK 300  
 TPPVLDSDG SFFLYSKLT DKSRSRQGNV FSCSVMHEAL HNHYTQKSLS LSPGK 355

SEQ ID NO: 216 moltype = AA length = 357  
 FEATURE Location/Qualifiers  
 REGION 1..357  
 note = Synthetic  
 source 1..357  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 216

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EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DYYMSWIRQT	PGKGLEWVSY	ISRGSGSTKYY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNSLRAED	TAVYYCARDA	PSSNSDWSSL	HFDHWGQGTL	120
VTVSSEPKSS	DKTHTCPPCP	APELLGGGPSV	FLFPPPKPKDT	LMISRTPEVT	CVVVDVSHED	180
PEVKFNWYVVD	GVEVHNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNKEYK	CKVSNKALPA	240
PIEKTKISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSDIAVE	WESNGQPENN	300
YKTTPPVLDLS	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO:	217	moltype = AA	length = 353
FEATURE		Location/Qualifiers	
REGION	1..353	note = Synthetic	
source	1..353	mol_type = protein	
		organism = synthetic construct	

SEQUENCE:	217					
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DYYMSWIRQA	PGKGLEWISY	ISNNSSSSIY	60
ANSVKGRFTV	SRDNAKNSLY	LQMNSLRAED	TALYYCARSP	RSAFYEDFDY	WGQGTLVTVS	120
SEPKSSDKTH	TCPPCPAPEL	LGGGPSVFLP	PKPKDITLMS	RTPEVTCVVV	DVSHDPEVK	180
FNWYVWDGVEV	HNAKTKPREE	EEQYNSTYRV	VSLTVLHQDWL	NGKEYKCKVS	NKALPAPIEK	240
EKTISKAKGQ	PREPVYTLPPS	PSREEMTKNQ	LTCVLVKGFP	YPSDIAVEWE	SNGQPENNYKTT	300
PPVLDSDG	FLYSKLTVDK	SRWQQGNVFS	CSVMHEALHN	HYTQKSLSL	PKG	353

SEQ ID NO:	218	moltype = AA	length = 355
FEATURE		Location/Qualifiers	
REGION	1..355	note = Synthetic	
source	1..355	mol_type = protein	
		organism = synthetic construct	

SEQUENCE:	218					
EVQLVESGGG	LVKPGGSLRL	SCAASGFTLS	DSQMSWIRQA	PGKGVEWVSY	ISSSGNTIYY	60
GDSVKGRFTI	SRDNAKNSLF	LQMNSLRAED	TAVYYCARVP	PSSSNWYEDF	DIWGQGTLVT	120
VSSEPKSSDK	THTCPPCPAP	ELLGGPSVFL	FPPPKPKDTLM	ISRTPEVTCV	VVDVSHEDPE	180
VKNWYVWDGVEV	HNAKTKPREE	EEQYNSTYRV	VSLTVLHQDWL	NGKEYKCK	VSNKALPAPI	240
EKTISKAKGQ	PREPVYTLPPS	PSREEMTKNQ	VSLTCVLVKG	YPSDIAVEWE	SNGQPENNYK	300
TPPPVLDSDG	FFFLYSKLT	DKSRWQQGNV	FSCSVMHEAL	HNHYTQKS	LSPGK	355

SEQ ID NO:	219	moltype = AA	length = 355
FEATURE		Location/Qualifiers	
REGION	1..355	note = Synthetic	
source	1..355	mol_type = protein	
		organism = synthetic construct	

SEQUENCE:	219					
EVQLVESGGG	LVKPGGSLRL	SCAASGFKLS	DFQMSWIRQA	PGKGLEWVAY	IDTNGSTRYY	60
AESVKGRFTL	SRDNVKNNSLN	LQMNSLRAED	TALYYCARPD	SYTSSWYEDF	DHWGQGTLVT	120
VSSEPKSSDK	THTCPPCPAP	ELLGGPSVFL	FPPPKPKDTLM	ISRTPEVTCV	VVDVSHEDPE	180
VKNWYVWDGVEV	HNAKTKPREE	EEQYNSTYRV	VSLTVLHQDWL	NGKEYKCK	VSNKALPAPI	240
EKTISKAKGQ	PREPVYTLPPS	PSREEMTKNQ	VSLTCVLVKG	YPSDIAVEWE	SNGQPENNYK	300
TPPPVLDSDG	FFFLYSKLT	DKSRWQQGNV	FSCSVMHEAL	HNHYTQKS	LSPGK	355

SEQ ID NO:	220	moltype = AA	length = 355
FEATURE		Location/Qualifiers	
REGION	1..355	note = Synthetic	
source	1..355	mol_type = protein	
		organism = synthetic construct	

SEQUENCE:	220					
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DYYMSWIRQA	PGKGLEWISY	ISSSGGSIYY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNRSLRAED	TALYYCARPT	PSSNNWYEDF	DYWGQGALVT	120
VSSEPKSSDK	THTCPPCPAP	ELLGGPSVFL	FPPPKPKDTLM	ISRTPEVTCV	VVDVSHEDPE	180
VKNWYVWDGVEV	HNAKTKPREE	EEQYNSTYRV	VSLTVLHQDWL	NGKEYKCK	VSNKALPAPI	240
EKTISKAKGQ	PREPVYTLPPS	PSREEMTKNQ	VSLTCVLVKG	YPSDIAVEWE	SNGQPENNYK	300
TPPPVLDSDG	FFFLYSKLT	DKSRWQQGNV	FSCSVMHEAL	HNHYTQKS	LSPGK	355

SEQ ID NO:	221	moltype = AA	length = 357
FEATURE		Location/Qualifiers	
REGION	1..357	note = Synthetic	
source	1..357	mol_type = protein	
		organism = synthetic construct	

SEQUENCE:	221					
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	ISSSGSYIHY	60

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ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDM	PSSSDWVDL	QFDYWGQGTL	120
VTSSSEPSS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSCHED	180
PEVKFNWYVD	GVEVHNNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	240
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSPDIAVE	WESNGQPENN	300
YKTPPVLDs	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO: 222	moltype = AA	length = 357				
FEATURE	Location/Qualifiers					
REGION	1..357					
	note = Synthetic					
source	1..357					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 222						
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	ISSSGSWIHY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDI	PSSSDWVDL	QFDYWGQGTL	120
VTSSSEPSS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSCHED	180
PEVKFNWYVD	GVEVHNNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	240
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSPDIAVE	WESNGQPENN	300
YKTPPVLDs	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO: 223	moltype = AA	length = 357				
FEATURE	Location/Qualifiers					
REGION	1..357					
	note = Synthetic					
source	1..357					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 223						
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	ISSSGSYIHY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDI	PSSSDWVDL	QFDYWGQGTL	120
VTSSSEPSS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSCHED	180
PEVKFNWYVD	GVEVHNNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	240
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSPDIAVE	WESNGQPENN	300
YKTPPVLDs	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO: 224	moltype = AA	length = 357				
FEATURE	Location/Qualifiers					
REGION	1..357					
	note = Synthetic					
source	1..357					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 224						
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	ISSSGSTIHY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDM	PSSSDWVDL	QFDYWGQGTL	120
VTSSSEPSS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSCHED	180
PEVKFNWYVD	GVEVHNNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	240
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSPDIAVE	WESNGQPENN	300
YKTPPVLDs	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO: 225	moltype = AA	length = 357				
FEATURE	Location/Qualifiers					
REGION	1..357					
	note = Synthetic					
source	1..357					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 225						
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	ISSSGSWIHY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDM	PSSSDWVSL	QFDYWGQGTL	120
VTSSSEPSS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSCHED	180
PEVKFNWYVD	GVEVHNNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	240
PIEKTISKAK	GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSPDIAVE	WESNGQPENN	300
YKTPPVLDs	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSSLSPGK	357

SEQ ID NO: 226	moltype = AA	length = 357				
FEATURE	Location/Qualifiers					
REGION	1..357					
	note = Synthetic					
source	1..357					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 226						
EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	DFYMSWIRQA	PGKGLEWISY	INTRGSPIGY	60
ADSVKGRFTI	SRDNAKNSLY	LQMNLSRAED	TAIYYCARDM	PSSSDWVDL	QFDYWGQGTL	120

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SEQ ID NO: 227	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
	note = Synthetic
source	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 227	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY	60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL	120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSCHED	180
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA	240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 228	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
	note = Synthetic
source	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 228	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY	60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSSDWVDL QFDYWGQGTL	120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSCHED	180
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA	240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 229	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
	note = Synthetic
source	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 229	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY INTRGSPIGY	60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL	120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSCHED	180
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA	240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 230	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
	note = Synthetic
source	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 230	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY	60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL	120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSCHED	180
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA	240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 231	moltype = AA length = 357
FEATURE	Location/Qualifiers
REGION	1..357
	note = Synthetic
source	1..357
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 231	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY	60
ADSVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDI PSSSSDWVDL QFDYWGQGTL	120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSCHED	180

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PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240
PIEKTISKAK QOPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 232      moltype = AA length = 357
FEATURE           Location/Qualifiers
REGION            1..357
note = Synthetic
source             1..357
mol_type = protein
organism = synthetic construct

SEQUENCE: 232
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY INTRGSPIGY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240
PIEKTISKAK QOPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 233      moltype = AA length = 357
FEATURE           Location/Qualifiers
REGION            1..357
note = Synthetic
source             1..357
mol_type = protein
organism = synthetic construct

SEQUENCE: 233
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSTRYY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240
PIEKTISKAK QOPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 234      moltype = AA length = 357
FEATURE           Location/Qualifiers
REGION            1..357
note = Synthetic
source             1..357
mol_type = protein
organism = synthetic construct

SEQUENCE: 234
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSSDWVSL QFDYWGQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240
PIEKTISKAK QOPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 235      moltype = AA length = 357
FEATURE           Location/Qualifiers
REGION            1..357
note = Synthetic
source             1..357
mol_type = protein
organism = synthetic construct

SEQUENCE: 235
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240
PIEKTISKAK QOPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 357

SEQ ID NO: 236      moltype = AA length = 357
FEATURE           Location/Qualifiers
REGION            1..357
note = Synthetic
source             1..357
mol_type = protein
organism = synthetic construct

SEQUENCE: 236
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWISY IDSSGRPLAY 60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDI PSSSSDWVSL QFDYWGQGTL 120
VTVSSEPKSS DKTHTCPPCP APELLGGPSV FLFPPPKPKDT LMISRTPEVT CVVVDVSHED 180
PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 240

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PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMH ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 237 moltype = AA length = 357	
FEATURE Location/Qualifiers	
REGION 1..357	
note = Synthetic	
source 1..357	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 237	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSDWVSL QFDYWGQGTL	120
VTSSSEPSS DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED	180
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA	240
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN	300
YKTPPVLDs DGSFFLYSKL TVDKSRWQQG NVFSCSVMH ALHNHYTQKS LSLSPGK	357
SEQ ID NO: 238 moltype = AA length = 145	
FEATURE Location/Qualifiers	
REGION 1..145	
note = Synthetic	
source 1..145	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 238	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
AHSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVDL QFDYWGQGTL	120
VTVSSQGGSD YKDDDDKASH HHHHH	145
SEQ ID NO: 239 moltype = AA length = 145	
FEATURE Location/Qualifiers	
REGION 1..145	
note = Synthetic	
source 1..145	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 239	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
SGSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSDWVDL QFDYWGQGTL	120
VTVSSQGGSD YKDDDDKASH HHHHH	145
SEQ ID NO: 240 moltype = AA length = 145	
FEATURE Location/Qualifiers	
REGION 1..145	
note = Synthetic	
source 1..145	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 240	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
SHSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSEDWVDL QFDYWGQGTL	120
VTVSSQGGSD YKDDDDKASH HHHHH	145
SEQ ID NO: 241 moltype = AA length = 145	
FEATURE Location/Qualifiers	
REGION 1..145	
note = Synthetic	
source 1..145	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 241	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
SSSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSIDWVEL QFDYWGQGTL	120
VTVSSQGGSD YKDDDDKASH HHHHH	145
SEQ ID NO: 242 moltype = AA length = 145	
FEATURE Location/Qualifiers	
REGION 1..145	
note = Synthetic	
source 1..145	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 242	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60
SPSVVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCARDM PSSSKDWVDL QFDYWGQGTL	120

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SEQ ID NO: 243	moltype = AA length = 145		145
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 243			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
SASVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSIDWVLD QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 244	moltype = AA length = 145		
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 244			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
SASVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSIDWVEL QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 245	moltype = AA length = 145		
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 245			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
STSVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSDWVLD QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 246	moltype = AA length = 145		
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 246			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
SSSVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSEDWVEL QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 247	moltype = AA length = 145		
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 247			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
AGSVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSSDWVLD QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 248	moltype = AA length = 145		
FEATURE	Location/Qualifiers		
REGION	1..145		
	note = Synthetic		
source	1..145		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 248			
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY	60		
AGSVVKGRFTI SRDNAKNSLY LQMNLSRAED TAIYYCARDM PSSSSDWVEL QFDYWGQGTL	120		
VTVSSQGGSD YKDDDDKASH HHHHH	145		
SEQ ID NO: 249	moltype = AA length = 145		
FEATURE	Location/Qualifiers		

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REGION          1..145
source          note = Synthetic
                1..145
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 249
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ASSVKGRFTI SRDANKNSLY LQMNLSRAED TAIYYCARDM PSSSEDWVML QFDYWQGTL 120
VTVSSQGGSD YKDDDDKASH HHHHHH 145

SEQ ID NO: 250      moltype = AA length = 145
FEATURE          Location/Qualifiers
REGION          1..145
source          note = Synthetic
                1..145
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 250
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ATSVKGRFTI SRDANKNSLY LQMNLSRAED TAIYYCARDM PSSSIDWVDL QFDYWQGTL 120
VTVSSQGGSD YKDDDDKASH HHHHHH 145

SEQ ID NO: 251      moltype = AA length = 145
FEATURE          Location/Qualifiers
REGION          1..145
source          note = Synthetic
                1..145
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 251
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
ASSVKGRFTI SRDANKNSLY LQMNLSRAED TAIYYCARDM PSSSSDWVDL QFDYWQGTL 120
VTVSSQGGSD YKDDDDKASH HHHHHH 145

SEQ ID NO: 252      moltype = AA length = 145
FEATURE          Location/Qualifiers
REGION          1..145
source          note = Synthetic
                1..145
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 252
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DFYMSWIRQA PGKGLEWISY ISSSGSWIHY 60
STSVKGRFTI SRDANKNSLY LQMNLSRAED TAIYYCARDM PSSSIDWVDL QFDYWQGTL 120
VTVSSQGGSD YKDDDDKASH HHHHHH 145

SEQ ID NO: 253      moltype = AA length = 356
FEATURE          Location/Qualifiers
REGION          1..356
source          note = Synthetic
                1..356
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 253
EVOLVESGGG LVQPGGSLRL SCAASGFTFS SHAMSWVRQA PGKGLEWVSA ISGSGDSTHY 60
AASVKGRFTI SRDNSKNTRY LQMNLSRAED TAVYYCETLL RFLESLGNNDG FKIWGQGTMV 120
TVSSSEPCKSD KTHTCPCKPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVVDVSHEPD 180
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP 240
IEKTISKAKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSPDIAVEW ESNQOPENNY 300
KTPPPVLDSD GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK 356

SEQ ID NO: 254      moltype = AA length = 353
FEATURE          Location/Qualifiers
REGION          1..353
source          note = Synthetic
                1..353
                mol_type = protein
                organism = synthetic construct
SEQUENCE: 254
QVQLVESGGG LVKPGGSLRI SCAASGFTFS NYNMSWIRQA PGKGVEWVSH ISGSGRTIYY 60
AESVKGRFTI SRDANKNSLY LQMNLSRAED TAMYYCARDL SSGWYEDFDY WGQGTIVTWS 120
SEPKSSDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK 180
FNVYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCVS NKALPAPIEK 240
TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN QQPENNYKTT 300
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMEALHN HYTQKSLSLGS PKG 353

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SEQ ID NO: 255	moltype = AA length = 352
FEATURE	Location/Qualifiers
REGION	1..352
note = Synthetic	
source	1..352
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 255	
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NFWMYWVRQA PGKGLVVCSR INSDGSSTNY	60
ADSVKGRFTI SRDNAKNTLY LQMNSLRVED TAVYSCAREG SGWYEDFDYW GQGTLVTVSS	120
EPKSSDKTHT CPPCPAPELL GGPSVFLFP PKPKDTLMISR TPEVTCVVVD VSHEDEPEVK	180
NWYVVDGVEVH NAKTKPREEQ YNSTYRVVSV LTIVLHQDWLNGKEYKCKVSN KALPAPIEK	240
TISKAKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTT	300
PPVLDSDGSF LYSLKLTVDKS RWQQGNVFSC SVMHEALHN YTQKSLSLSP GK	352
SEQ ID NO: 256	moltype = AA length = 353
FEATURE	Location/Qualifiers
REGION	1..353
note = Synthetic	
source	1..353
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 256	
EVQLVESGGG LVKPGGSLRL SCAASGFTLS DYMSWIRQA PGKGLEWISY ISSNGSTIYY	60
ADSVKGRFTI SRDNARNSLY LQMNSLRAED TALYYCARDV SSGWYEDFDY WGQGTLVTVS	120
SEPKSSDKTH TCPPCPAPEL LGGPSPVFLFP PKPKDTLMISR RTPEVTCVVVD DVSHEDPEVK	180
FNWYVVDGVEVH NAKTKPREEQ YNSTYRVVSV LTIVLHQDWLNGKEYKCKVSN KALPAPIEK	240
TISKAKGQPRE PQVYTLPPSR REEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTT	300
PPVLDSDGSF FLYSLKLTVDK SRWQQGNVFS CSVMHEALHN YTQKSLSLSP PGK	353
SEQ ID NO: 257	moltype = AA length = 353
FEATURE	Location/Qualifiers
REGION	1..353
note = Synthetic	
source	1..353
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 257	
EVQLVESGGG LVKPGGSLRL SCAASGFNLDS SYMSWIRQA PGKGLEWVSC ISSSGSTIYY	60
ADSVKGRFTV SRDNAKNSLY LQMNHILRAED TALYYCARDV VIGIRDDSDI WGQGTMVTVS	120
SEPKSSDKTH TCPPCPAPEL LGGPSPVFLFP PKPKDTLMISR RTPEVTCVVVD DVSHEDPEVK	180
FNWYVVDGVEVH NAKTKPREEQ YNSTYRVVSV LTIVLHQDWLNGKEYKCKVSN KALPAPIEK	240
TISKAKGQPRE PQVYTLPPSR REEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTT	300
PPVLDSDGSF FLYSLKLTVDK SRWQQGNVFS CSVMHEALHN YTQKSLSLSP PGK	353
SEQ ID NO: 258	moltype = AA length = 355
FEATURE	Location/Qualifiers
REGION	1..355
note = Synthetic	
source	1..355
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 258	
EVQLLESGGG LVQPGGSLRL SCAASGFIFG SYAMSWVRQA PGKGLEWVSG ISGTGGNTYY	60
ADSVKGRFTI SRDNNSKNTLY LQMNSLRAED TAVYFCERGI TIHGVIIPD DYRGOGTLVT	120
VSEPKSSDKTHTCPPCPAPELLGGPSVFLFP PPKPKDTLMISR RTPEVTCVVVDVSHEDEPE	180
VKNWYVVDGVEVH NAKTKPREEQ YNSTYRVVSV LTIVLHQDWLNGKEYKCKVSN KALPAPIEK	240
EKTISKAKGQPRE PQVYTLPPSR REEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTT	300
TPPVLDSDGSF FFLYSLKLTVDK DKSRWQQGNVFS CSVMHEALHN YTQKSLSLSP PGK	355
SEQ ID NO: 259	moltype = AA length = 354
FEATURE	Location/Qualifiers
REGION	1..354
note = Synthetic	
source	1..354
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 259	
EVQLVESGGG LVKPGGSLRL SCAASGFTFS DYMSWIRQA PGKGLEWIAY ISSSGSTIYY	60
ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAIYYCAREY YGSENYDHFD YWGQGTLVTV	120
SSEPKSSDKTH TCPPCPAPELLGGPSVFLFP PPKPKDTLMISR RTPEVTCVVVDVSHEDEPE	180
KFNWYVVDGVEVH NAKTKPREEQ YNSTYRVVSV LTIVLHQDWLNGKEYKCKVSN KALPAPIEK	240
EKTISKAKGQPRE PQVYTLPPSR REEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTT	300
TPPVLDSDGSF FFLYSLKLTVDK KSRWQQGNVFS CSVMHEALHN YTQKSLSLSP PGK	354
SEQ ID NO: 260	moltype = AA length = 350

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FEATURE	Location/Qualifiers
REGION	1..350
	note = Synthetic
source	1..350
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 260	
EVOLLESGGG LVQPGGSSLRL SCAASGFTFS GNAMSWVRQA PGKGLEWVSA ISGSGDKTYY 60	
AASVKGRFTI SRDNSNNTVY LQMNSLRAED TAVYYCEKGA FRTTMDYWQ GTLTVSSEP 120	
KSSDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTTP EVTCVVVDVS HEDPEVKFNW 180	
YVDGVEVHNA STYRVSVLT VLHQDWLNKG EYKCKVSNKA LPAPIEKTI 240	
KAKGQPREGPQ VYTLPSPREE MTKNQVSLTC LVKGFYPDSI AVEWESENQGP ENNYKTPPV 300	
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPKG 350	
SEQ ID NO: 261	moltype = AA length = 217
FEATURE	Location/Qualifiers
REGION	1..217
	note = Synthetic
source	1..217
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 261	
DIQMTQSPSS LSASVGDRVT INCQASQSID SNLAWFQQKP GQPPKLLIYR ASNLASGVPD 60	
RFSGSGSGTD FTLTISLEA EDVATYYCLG GVGAVSYRTS FGGGTKEIK RTVAAPSVFI 120	
FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS 180	
TTLTSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC 217	
SEQ ID NO: 262	moltype = DNA length = 24
FEATURE	Location/Qualifiers
misc_feature	1..24
	note = Primer
source	1..24
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 262	
gggttccagt gtsaggtgca gctg	24
SEQ ID NO: 263	moltype = DNA length = 29
FEATURE	Location/Qualifiers
misc_feature	1..29
	note = Primer
source	1..29
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 263	
aatccctggg cactgaagag acgggtgacc	29

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1. An antibody that specifically binds to ROR1, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region (VH), and wherein the VH comprises HCDRs 1-3 of a VH having the amino acid sequence set forth in any one of SEQ ID NOS: 150, 180-194, 163-179, 147-149, 151-162, and 195-202.

2. The antibody or antigen binding fragment thereof according to claim 1, wherein the VH comprises HCDRs 1-3 having the amino acid sequences set forth in:

SEQ ID NOS: 12, 40, 103 respectively,  
 SEQ ID NOS: 17, 53, 119 respectively,  
 SEQ ID NOS: 17, 53, 116 respectively,  
 SEQ ID NOS: 17, 53, 120 respectively,  
 SEQ ID NOS: 17, 53, 121 respectively,  
 SEQ ID NOS: 17, 53, 122 respectively,  
 SEQ ID NOS: 17, 53, 123 respectively,  
 SEQ ID NOS: 17, 53, 124 respectively,  
 SEQ ID NOS: 17, 53, 125 respectively,  
 SEQ ID NOS: 17, 52, 116 respectively,  
 SEQ ID NOS: 17, 53, 117 respectively,  
 SEQ ID NOS: 17, 52, 117 respectively,  
 SEQ ID NOS: 17, 40, 116 respectively,  
 SEQ ID NOS: 17, 53, 118 respectively,

SEQ ID NOS: 17, 54, 116 respectively,  
 SEQ ID NOS: 17, 55, 116 respectively,  
 SEQ ID NOS: 17, 54, 117 respectively,  
 SEQ ID NOS: 17, 40, 117 respectively,  
 SEQ ID NOS: 17, 55, 117 respectively,  
 SEQ ID NOS: 17, 54, 118 respectively,  
 SEQ ID NOS: 17, 40, 118 respectively,  
 SEQ ID NOS: 17, 55, 118 respectively,  
 SEQ ID NOS: 17, 55, 103 respectively,  
 SEQ ID NOS: 12, 55, 117 respectively,  
 SEQ ID NOS: 12, 55, 118 respectively,  
 SEQ ID NOS: 11, 40, 100 respectively,  
 SEQ ID NOS: 12, 41, 101 respectively,  
 SEQ ID NOS: 12, 42, 102 respectively,  
 SEQ ID NOS: 12, 43, 104 respectively,  
 SEQ ID NOS: 13, 44, 105 respectively,  
 SEQ ID NOS: 12, 40, 106 respectively,  
 SEQ ID NOS: 12, 45, 107 respectively,  
 SEQ ID NOS: 12, 40, 108 respectively,  
 SEQ ID NOS: 14, 46, 109 respectively,  
 SEQ ID NOS: 12, 47, 110 respectively,  
 SEQ ID NOS: 12, 48, 111 respectively,  
 SEQ ID NOS: 12, 45, 112 respectively,

SEQ ID NOs: 15, 49, 113 respectively,  
 SEQ ID NOs: 16, 50, 114 respectively,  
 SEQ ID NOs: 12, 51, 115 respectively,  
 SEQ ID NOs: 18, 56, 126 respectively,  
 SEQ ID NOs: 21, 40, 130 respectively,  
 SEQ ID NOs: 22, 60, 131 respectively,  
 SEQ ID NOs: 12, 40, 132 respectively,  
 SEQ ID NOs: 23, 61, 133 respectively,  
 SEQ ID NOs: 19, 57, 127 respectively,  
 SEQ ID NOs: 20, 58, 128 respectively, or  
 SEQ ID NOs: 14, 59, 129 respectively.

**3.** The antibody or antigen binding fragment thereof according to claim 1, wherein the VH comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to any one of SEQ ID NOs: 150, 180-194, 163-179, 147-149, 151-162, and 195-202.

**4.** (canceled)

**5.** The antibody or antigen binding fragment thereof according to claim 1, wherein the antibody comprises a heavy chain (HC), and wherein the HC comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to any one of SEQ ID NOs: 208, 238-252, 221-237, 205-207, 209-220, and 253-260.

**6.** The antibody or antigen binding fragment thereof according to claim 1, wherein the antibody does not comprise a light chain.

**7.** (canceled)

**8.** The antibody or antigen binding fragment thereof of claim 1, wherein the antibody is a chimeric antibody, a humanized antibody, or a human antibody.

**9.** The antibody or the antigen binding fragment thereof according to claim 1, wherein the antibody is of an isotype selected from the group consisting of IgG, IgA, IgM, IgE and IgD.

**10.** The antibody or the antigen binding fragment thereof according to claim 1, wherein the antibody is of a subtype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.

**11.** The antibody or the antigen binding fragment thereof according to claim 1, wherein the antigen binding fragment is selected from the group consisting of HCAb, VH<sub>H</sub>, nanobody, Fab, Fab', F(ab')<sub>2</sub>, Fd, Fd', and dAb.

**12.** The antibody or the antigen binding fragment thereof according to claim 1, wherein the antibody is a monoclonal antibody, a bi-specific or a multi-specific antibody and/or, the antibody is monovalent, bivalent or multivalent.

**13.** (canceled)

**14.** The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment is attached to a fluorescent label, radiolabel or cytotoxic agent.

**15.** A bi-specific antibody, comprising the antibody or antigen-binding fragment thereof according to claim 1 and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen, or binding to CD3.

**16.** A nucleic acid comprising a nucleotide sequence encoding the antibody or the antigen binding fragment thereof according to claim 1 or a bi-specific antibody

comprising the antibody or the antigen binding fragment thereof according to claim 1 and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen.

**17.** (canceled)

**18.** (canceled)

**19.** An antibody-drug conjugate (ADC), comprising the antibody or the antigen binding fragment thereof according to claim 1 or a bi-specific antibody comprising the antibody or the antigen binding fragment thereof according to claim 1 and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen.

**20.** A pharmaceutical composition comprising (i) the antibody or the antigen binding fragment thereof according to claim 11, a bi-specific antibody comprising the antibody or the antigen binding fragment thereof according to claim 1 and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen, or an antibody-drug conjugate comprising the antibody or the antigen binding fragment thereof according to claim 1; and (ii) a pharmaceutically acceptable carrier or excipient.

**21.** The pharmaceutical composition according to claim 20, wherein the composition further comprises a second therapeutic agent selected from the group consisting of an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.

**22.** A method of treating a cancer in a subject, comprising administering to the subject an effective amount of the antibody or the antigen binding fragment thereof according to claim 1, a bi-specific antibody comprising the antibody or the antigen binding fragment thereof according to claim 1 and a second antigen binding region specifically binding to a tumor associated antigen or an immune cell antigen, comprising the antibody or the antigen binding fragment thereof according to claim 1, or a pharmaceutical composition comprising the antibody or the antigen binding fragment thereof according to claim 1.

**23.** The method according to claim 22, wherein the cancer is a ROR1 positive cancer.

**24.** The method according to claim 22, further comprising administering to the subject a second therapeutic agent, wherein the second therapeutic agent is selected from an antibody, a chemotherapeutic agent, a siRNA, an antisense oligonucleotide, a polypeptide, and a small molecule drug.

**25-35.** (canceled)

**36.** The method according to claim 22, wherein the cancer is selected from the group consisting of B-cell leukemia, lymphoma, acute myeloid leukemia (AML), Burkitt lymphoma, mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), breast cancer, renal cancer, ovarian cancer, gastric cancer, liver cancer, lung cancer, colorectal cancer, pancreatic cancer, skin cancer, bladder cancer, testicular cancer, uterine cancer, prostate cancer, non-small cell lung cancer (NSCLC), neuroblastoma, brain cancer, colon cancer, squamous cell carcinoma, melanoma, myeloma, cervical cancer, thyroid cancer, head and neck cancer, and adrenal cancer.