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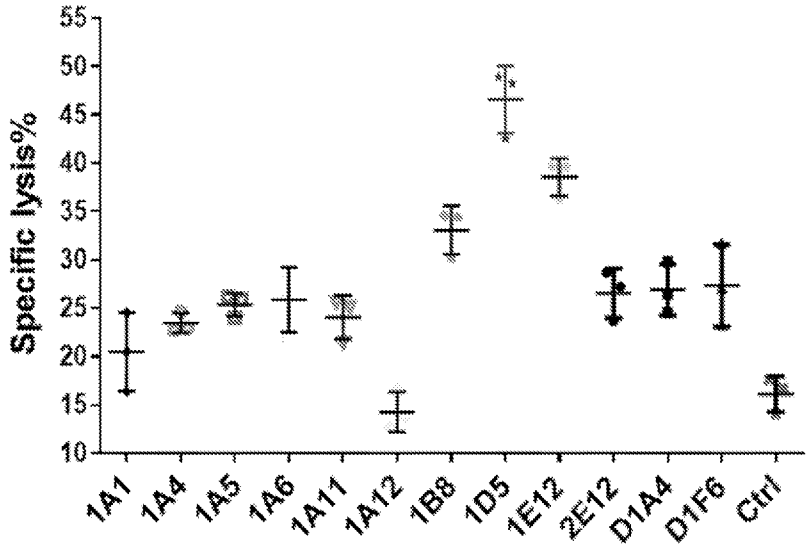
(54) Title: IL1RAP ANTIBODIES

FIG. 4



(57) Abstract: Provided herein are, *inter alia*, Interleukin-1 receptor accessory protein (IL1RAP) antibodies and fragments thereof which may form part of chimeric antigen receptors or bispsecific antibodies and are useful for treating IL1RAP-expressing cancers.

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IL1RAP ANTIBODIES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to US Application No. 62/885,724 filed August 12, 2019, the disclosure of which is incorporated by reference herein in its entirety.

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

[0002] The Sequence Listing written in file 048440-720001WO_Sequence Listing_ST25.TXT, created on August 7, 2020, 70,043 bytes, machine format IBM-PC, MS Windows operating system, is incorporated herein by reference.

BACKGROUND

[0003] Acute myeloid leukemia (AML) is a devastating hematopoietic malignancy that can lead to hematopoiesis failure and death. Despite increasing knowledge of the disease, current treatment options benefit only a minority of AML patients. The limited success of treatments is believed to be at least partially due to the inability of chemotherapy and/or other molecular targeting therapeutics to eliminate so-called leukemia stem cells (LSCs). Thus, there is a need in the art for treatments, which specifically eliminate LSCs while sparing normal hematopoietic stem cells.

[0004] Immunotherapeutic approaches hold promise as an effective means of treating patients suffering from AML. In order to be successful, however, immunotherapy must allow for the selective targeting and destruction of LSCs. Provided herein are compositions and methods which cure this and other needs in the art.

BRIEF SUMMARY

[0005] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

[0006] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the

heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

[0007] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

[0008] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0009] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0010] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38, and a CDR L3 as set forth in SEQ ID NO:39.

[0011] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0012] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45.

[0013] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0014] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

[0015] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

[0016] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

[0017] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

[0018] In an aspect, an isolated nucleic acid encoding an antibody provided herein including embodiments thereof is provided.

[0019] In another aspect, a pharmaceutical composition including a therapeutically effective amount of an antibody provided herein including embodiments thereof and a pharmaceutically acceptable excipient is provided.

[0020] In another aspect, a method of treating cancer in a subject in need thereof is provided. The method includes administering to a subject a therapeutically effective amount of an antibody provided herein including embodiments thereof, thereby treating cancer in the subject.

[0021] In an aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6; and (ii) a transmembrane domain.

[0022] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12; and (ii) a transmembrane domain.

[0023] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24; and (ii) a transmembrane domain.

[0024] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30; and (ii) a transmembrane domain.

[0025] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set

forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36; and (ii) a transmembrane domain.

[0026] In an aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain.

[0027] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and (ii) a transmembrane domain.

[0028] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45; and (ii) a transmembrane domain.

[0029] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (ii) a transmembrane domain.

[0030] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51; and (ii) a transmembrane domain.

[0031] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54; and (ii) a transmembrane domain.

[0032] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57; and (ii) a transmembrane domain.

[0033] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60; and (ii) a transmembrane domain.

[0034] In another aspect, an isolated nucleic acid encoding a recombinant protein provided herein including embodiments thereof is provided.

[0035] In another aspect, a pharmaceutical composition including a therapeutically effective amount of a recombinant protein provided herein including embodiments thereof and a pharmaceutically acceptable excipient is provided.

[0036] In another aspect, a method of treating cancer in a subject in need thereof is provided. The method includes administering to a subject a therapeutically effective amount of a recombinant protein provided herein including embodiments thereof, thereby treating cancer in the subject.

[0037] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2, and a CDR H3 as set forth in SEQ ID NO:3; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5 and a CDR L3 as set forth in SEQ ID NO:6.

[0038] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8, and a CDR H3 as set forth in SEQ ID NO:9; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11 and a CDR L3 as set forth in SEQ ID NO:12.

[0039] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20, and a CDR H3 as set forth in SEQ ID NO:21; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23 and a CDR L3 as set forth in SEQ ID NO:24.

[0040] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID NO:27; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30.

[0041] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID NO:33; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36.

[0042] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39.

[0043] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42.

[0044] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45.

[0045] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48.

[0046] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light

chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51.

[0047] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54.

[0048] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57.

[0049] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60.

[0050] In another aspect, an isolated nucleic acid encoding a recombinant protein provided herein including embodiments thereof is provided.

[0051] In another aspect, a pharmaceutical composition including a therapeutically effective amount of a recombinant protein provided herein including embodiments thereof and a pharmaceutically acceptable excipient is provided.

[0052] In another aspect, a method of treating cancer in a subject in need thereof is provided. The method includes administering to a subject a therapeutically effective amount of a recombinant protein provided herein including embodiments thereof, thereby treating cancer in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] FIG. 1. Shown are the graphs for determining EC_{50} of the human anti-IL1RAP monoclonal antibody clones 1A1 (upper left) having a CDR L1 sequence of SEQ ID NO:46, a CDR L2 sequence of SEQ ID NO:47, and a CDR L3 sequence of SEQ ID NO:48, 1A4 (upper right) having a CDR L1 sequence of SEQ ID NO:49, a CDR L2 sequence of SEQ ID NO:50, and a CDR L3 sequence of SEQ ID NO:51, 1A5 (lower left) having a CDR L1 sequence of SEQ ID NO:40, a CDR L2 sequence of SEQ ID NO:41, and a CDR L3 sequence of SEQ ID NO:42, and

1A6 (lower right) having a CDR L1 sequence of SEQ ID NO:43, a CDR L2 sequence of SEQ ID NO:44, and a CDR L3 sequence of SEQ ID NO: 45. EC_{50} were determined by ELISA.

[0054] FIG. 2. Shown are the graphs for determining EC_{50} of the human anti-IL1RAP monoclonal antibody clones 1A11, 1A12 (upper right) having a CDR L1 sequence of SEQ ID NO:37, a CDR L2 sequence of SEQ ID NO:38, and a CDR L3 sequence of SEQ ID NO:39, 1B8 (lower left) having a CDR H1 sequence of SEQ ID NO:31, a CDR H2 sequence of SEQ ID NO:32, and a CDR H3 sequence of SEQ ID NO:33, a CDR L1 sequence of SEQ ID NO:34, a CDR L2 sequence of SEQ ID NO:35, and a CDR L3 sequence of SEQ ID NO: 36, and 1E12 (lower right) having a CDR L1 sequence of SEQ ID NO:55, a CDR L2 sequence of SEQ ID NO:56, and a CDR L3 sequence of SEQ ID NO: 57. EC_{50} were determined by ELISA.

[0055] FIG. 3. Shown are the graphs for determining EC_{50} of the human anti-IL1RAP monoclonal antibody clones 2E12 (upper left) having a CDR H1 sequence of SEQ ID NO:19, a CDR H2 sequence of SEQ ID NO:20, and a CDR H3 sequence of SEQ ID NO:21, a CDR L1 sequence of SEQ ID NO:22, a CDR L2 sequence of SEQ ID NO:23, and a CDR L3 sequence of SEQ ID NO: 24, D1A4 (upper right) having a CDR H1 sequence of SEQ ID NO:1, a CDR H2 sequence of SEQ ID NO:2, and a CDR H3 sequence of SEQ ID NO:3, a CDR L1 sequence of SEQ ID NO:4, a CDR L2 sequence of SEQ ID NO:5, and a CDR L3 sequence of SEQ ID NO: 6, and D1F6 (lower left) having a CDR L1 sequence of SEQ ID NO:58, a CDR L2 sequence of SEQ ID NO:59, and a CDR L3 sequence of SEQ ID NO:60. Lower right: Human anti-IL1RAP monoclonal antibody EC_{50} of 12 clones as indicated are shown. The clones tested are 1A1, 1A4, 1A5, 1A6, 1A11, 1A12, 1B8, 1E12, 2E,12, D1A4, D1F6 and 1D5 having a CDR H1 sequence of SEQ ID NO:13, a CDR H2 sequence of SEQ ID NO:14, and a CDR H3 sequence of SEQ ID NO:15, a CDR L1 sequence of SEQ ID NO:16, a CDR L2 sequence of SEQ ID NO:17, and a CDR L3 sequence of SEQ ID NO:18. EC_{50} of the antibodies was determined by ELISA.

[0056] FIG. 4. Antibody-dependent cellular cytotoxicity (ADCC) analysis of exemplary anti-IL1RAP antibodies provided herein. The percentage of specific lysis induced by the twelve clones was determined by ADCC assay.

DETAILED DESCRIPTION

[0057] While various embodiments and aspects of the present invention are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood

that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0058] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

DEFINITIONS

[0059] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, e.g., Singleton et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY 2nd ed., J. Wiley & Sons (New York, NY 1994); Sambrook et al., MOLECULAR CLONING, A LABORATORY MANUAL, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989). Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0060] "Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term "polynucleotide" refers to a linear sequence of nucleotides. The term "nucleotide" typically refers to a single unit of a polynucleotide, *i.e.*, a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA (including siRNA), and hybrid molecules having mixtures of single and double stranded DNA and RNA. Nucleic acid as used herein also refers to nucleic acids that have the same basic chemical structure as a naturally occurring nucleic acid. Such analogues have modified sugars and/or modified ring substituents, but retain the same basic chemical structure as the naturally occurring nucleic acid. A nucleic acid mimetic refers to chemical compounds that have a structure that is different the general chemical structure of a nucleic acid, but that functions in a manner similar to a naturally occurring nucleic acid. Examples of such analogues include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs).

[0061] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0062] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0063] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0064] An amino acid or nucleotide base "position" is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that may be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the

reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0065] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence. An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. For example, a selected residue in a selected antibody (or Fab domain) corresponds to light chain threonine at Kabat position 40, when the selected residue occupies the same essential spatial or other structural relationship as a light chain threonine at Kabat position 40. In some embodiments, where a selected protein is aligned for maximum homology with the light chain of an antibody (or Fab domain), the position in the aligned selected protein aligning with threonine 40 is said to correspond to threonine 40. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the light chain threonine at Kabat position 40, and the overall structures compared. In this case, an amino acid that occupies the same essential position as threonine 40 in the structural model is said to correspond to the threonine 40 residue.

[0066] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, "conservatively modified variants" refers to those nucleic acids that encode identical or essentially identical amino acid sequences. Because of the degeneracy of the genetic code, a number of nucleic acid sequences will encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0067] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0068] The following eight groups each contain amino acids that are conservative substitutions for one another:

1) Alanine (A), Glycine (G);

2) Aspartic acid (D), Glutamic acid (E);

3) Asparagine (N), Glutamine (Q);

4) Arginine (R), Lysine (K);

5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);

6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);

7) Serine (S), Threonine (T); and

8) Cysteine (C), Methionine (M)

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

[0069] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identity over a specified region, e.g., of the entire polypeptide sequences of the invention or individual domains of the polypeptides of the invention), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Such sequences are then said to be "substantially identical." This definition also refers to the complement of a

test sequence. Optionally, the identity exists over a region that is at least about 50 nucleotides in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides in length.

[0070] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0071] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0072] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of, e.g., a full length sequence or from 20 to 600, about 50 to about 200, or about 100 to about 150 amino acids or nucleotides in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat'l. Acad. Sci. USA* 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g.,* Ausubel *et al.*, *Current Protocols in Molecular Biology* (1995 supplement)).

[0073] An example of an algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0074] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0075] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0076] Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. A natural antibody molecule contains two identical pairs of polypeptide chains, each pair having one light chain and one heavy chain. Each light chain and heavy chain in turn consists of two regions: a variable ("V") region, involved in binding the target antigen, and a constant ("C") region that interacts with other components of the immune system. The light and heavy chain variable regions (also referred to herein as light chain variable (VL) domain and heavy chain variable (VH) domain, respectively) come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). Within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called the complementarity determining regions ("CDRs"). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The position and length of the CDRs have been precisely defined by Kabat, E. et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1983, 1987. The part of a variable region not contained in the CDRs is called the framework ("FR"), which forms the environment for the CDRs.

[0077] An "antibody variant" as provided herein refers to a polypeptide capable of binding to an antigen and including one or more structural domains (e.g., light chain variable domain, heavy chain variable domain) of an antibody or fragment thereof. Non-limiting examples of antibody variants include single-domain antibodies or nanobodies, monospecific Fab_2, bispecific Fab_2, trispecific Fab_3, monovalent IgGs, scFv, bispecific antibodies, bispecific diabodies, trispecific triabodies, scFv-Fc, minibodies, IgNAR, V-NAR, hcIgG, VhH, or peptibodies. A "peptibody" as provided herein refers to a peptide moiety attached (through a covalent or non-

covalent linker) to the Fc domain of an antibody. Further non-limiting examples of antibody variants known in the art include antibodies produced by cartilaginous fish or camelids. A general description of antibodies from camelids and the variable regions thereof and methods for their production, isolation, and use may be found in references WO97/49805 and WO 97/49805 which are incorporated by reference herein in their entirety and for all purposes. Likewise, antibodies from cartilaginous fish and the variable regions thereof and methods for their production, isolation, and use may be found in WO2005/118629, which is incorporated by reference herein in its entirety and for all purposes.

[0078] The terms "CDR L1", "CDR L2" and "CDR L3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a CDR L1, a CDR L2 and a CDR L3. Likewise, the terms "CDR H1", "CDR H2" and "CDR H3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a CDR H1, a CDR H2 and a CDR H3.

[0079] The terms "FR L1", "FR L2", "FR L3" and "FR L4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a FR L1, a FR L2, a FR L3 and a FR L4. Likewise, the terms "FR H1", "FR H2", "FR H3" and "FR H4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a FR H1, a FR H2, a FR H3 and a FR H4.

[0080] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one “light” (about 25 kD) and one “heavy” chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL), variable light chain (VL) domain or light chain variable region and variable heavy chain (VH), variable heavy chain (VH) domain or heavy chain variable region refer to these light and heavy chain regions, respectively. The terms

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

[0081] The term "antibody" is used according to its commonly known meaning in the art. Antibodies exist, e.g., as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H-C_{H1} by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized de novo using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty *et al.*, *Nature* 348:552-554 (1990)). The term “antibody” as referred to herein further includes antibodyvariants such as single domain antibodies. Thus, in embodiments an antibody includes a single monomeric variable antibody domain. Thus, in embodiments, the antibody, includes a variable light chain (VL) domain or a variable heavy chain (VH) domain. In embodiments, the antibody is a variable light chain (VL) domain or a variable heavy chain (VH) domain.

[0082] For preparation of monoclonal or polyclonal antibodies, any technique known in the art can be used (*see*, *e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4:72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy* (1985)). "Monoclonal" antibodies (mAb) refer to antibodies derived from a single clone. Techniques for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be

adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies. Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (*see*, *e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990); Marks *et al.*, *Biotechnology* 10:779-783 (1992)).

[0083] The epitope of a mAb is the region of its antigen to which the mAb binds. Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1x, 5x, 10x, 20x or 100x excess of one antibody inhibits binding of the other by at least 30% but preferably 50%, 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans *et al.*, Cancer Res. 50:1495, 1990). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0084] A single-chain variable fragment (scFv) is typically a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of 10 to about 25 amino acids. The linker may usually be rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa.

[0085] For preparation of suitable antibodies of the invention and for use according to the invention, e.g., recombinant, monoclonal, or polyclonal antibodies, many techniques known in the art can be used (see, e.g., Kohler & Milstein, Nature 256:495-497 (1975); Kozbor et al., Immunology Today 4: 72 (1983); Cole et al., pp. 77-96 in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985); Coligan, Current Protocols in Immunology (1991); Harlow & Lane, Antibodies, A Laboratory Manual (1988); and Goding, Monoclonal Antibodies: Principles and Practice (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (see, e.g., Kuby, Immunology (3rd ed. 1997)). Techniques for the production of single chain antibodies or

recombinant antibodies (U.S. Patent 4,946,778, U.S. Patent No. 4,816,567) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (see, e.g., U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks et al., Bio/Technology 10:779-783 (1992); Lonberg et al., Nature 368:856-859 (1994); Morrison, Nature 368:812-13 (1994); Fishwild et al., Nature Biotechnology 14:845-51 (1996); Neuberger, Nature Biotechnology 14:826 (1996); and Lonberg & Huszar, Intern. Rev. Immunol. 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, e.g., McCafferty et al., Nature 348:552-554 (1990); Marks et al., Biotechnology 10:779-783 (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (see, e.g., WO 93/08829, Traunecker et al., EMBO J. 10:3655-3659 (1991); and Suresh et al., Methods in Enzymology 121:210 (1986)). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (see, e.g., U.S. Patent No. 4,676,980 , WO 91/00360; WO 92/200373; and EP 03089).

[0086] Methods for humanizing or primatizing non-human antibodies are well known in the art (e.g., U.S. Patent Nos. 4,816,567; 5,530,101; 5,859,205; 5,585,089; 5,693,761; 5,693,762; 5,777,085; 6,180,370; 6,210,671; and 6,329,511; WO 87/02671; EP Patent Application 0173494; Jones et al. (1986) Nature 321:522; and Verhoyen et al. (1988) Science 239:1534). Humanized antibodies are further described in, e.g., Winter and Milstein (1991) Nature 349:293. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (see, e.g., Morrison et al., PNAS USA, 81:6851-6855 (1984), Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Morrison and Oi, Adv. Immunol., 44:65-92 (1988), Verhoeyen et al., Science 239:1534-1536 (1988) and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992), Padlan, Molec. Immun., 28:489-498 (1991); Padlan, Molec. Immun., 31(3):169-217 (1994)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are

substituted by residues from analogous sites in rodent antibodies. For example, polynucleotides comprising a first sequence coding for humanized immunoglobulin framework regions and a second sequence set coding for the desired immunoglobulin complementarity determining regions can be produced synthetically or by combining appropriate cDNA and genomic DNA segments. Human constant region DNA sequences can be isolated in accordance with well known procedures from a variety of human cells.

[0087] A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. The preferred antibodies of, and for use according to the invention include humanized and/or chimeric monoclonal antibodies.

[0088] Techniques for conjugating therapeutic agents to antibodies are well known (see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery"in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review" in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982)). As used herein, the term "antibody-drug conjugate" or "ADC" refers to a therapeutic agent conjugated or otherwise covalently bound to to an antibody.

[0089] A "therapeutic agent" as referred to herein, is a composition useful in treating or preventing a disease such as cancer (e.g., leukemia). In embodiments, the therpaeutic agent is an anti-cancer agent. "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In embodiments, an anti-cancer agent is a chemotherapeutic. In embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In embodiments, an

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

[0090] The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies can be selected to obtain only a subset of antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, Using Antibodies, A Laboratory Manual (1998) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0091] A "ligand" refers to an agent, e.g., a polypeptide or other molecule, capable of binding to a receptor or antibody, antibody variant, antibody region or fragment thereof.

[0092] The term “IL1RAP” as used herein refers to any recombinant or naturally-occurring forms of interleukin-1 receptor accessory protein (IL1RAP) or variants or homologs thereof that maintain IL1RAP activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to IL1RAP). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 10, 20, 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring IL1RAP polypeptide. In embodiments, IL1RAP is substantially identical to the protein identified by the UniProt reference number Q9NPH3 or a variant or homolog having substantial identity thereto.

[0093] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include 32P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be

made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any appropriate method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego.

[0094] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. antibodies and antigens) to become sufficiently proximal to react, interact, or physically touch. It should be appreciated; however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0095] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be, for example, a pharmaceutical composition as provided herein and a cell. In embodiments contacting includes, for example, allowing a pharmaceutical composition as described herein to interact with a cell.

[0096] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include, but are not limited to, yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells.

[0097] A "stem cell" as provided herein refers to a cell characterized by the ability of self-renewal through mitotic cell division and the potential to differentiate into a tissue or an organ. Among mammalian stem cells, embryonic stem cells (ES cells) and somatic stem cells (e.g., HSC) can be distinguished. Embryonic stem cells reside in the blastocyst and give rise to embryonic tissues, whereas somatic stem cells reside in adult tissues for the purpose of tissue regeneration and repair. In embodiments, the stem cell is a leukemia stem cell (LSC). A "leukemia stem cell or "LSC" as provided herein refers to a cell capable of initiating the disease (leukemia) when transplanted into immunodeficient animals and can self-renew by giving rise to leukemia in serial transplantations and also partially differentiate into non-LSC bulk blasts that resemble the original disease but are unable to self-renew. An LSC may carry a gene mutation

and be able to self-renew through mitotic cell division and differentiate into the hematopoietic lineage carrying said gene mutant or an LSC may remain as immature progenitor cells, also known as blast cells. In embodiments, the LSC expresses CD34.

[0098] The term "CD34" as referred to herein includes any of the recombinant or naturally-occurring forms of the cluster of differentiation 34 protein, or variants or homologs thereof that maintain CD34 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD34). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD34 protein. In embodiments, the CD34 protein is substantially identical to the protein identified by the UniProt reference number P28906 or a variant or homolog having substantial identity thereto.

[0099] The term "recombinant" when used with reference, *e.g.*, to a cell, nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. Transgenic cells and plants are those that express a heterologous gene or coding sequence, typically as a result of recombinant methods.

[0100] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[0101] The term "exogenous" refers to a molecule or substance (*e.g.*, a compound, nucleic acid or protein) that originates from outside a given cell or organism. For example, an "exogenous promoter" as referred to herein is a promoter that does not originate from the cell or organism it

is expressed by. Conversely, the term "endogenous" or "endogenous promoter" refers to a molecule or substance that is native to, or originates within, a given cell or organism.

[0102] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to cell proliferation (e.g., cancer cell proliferation) means negatively affecting (e.g., decreasing proliferation) or killing the cell. In some embodiments, inhibition refers to reduction of a disease or symptoms of disease (e.g., cancer, cancer cell proliferation). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. Similarly an "inhibitor" is a compound or protein that inhibits a receptor or another protein, *e.g.*,, by binding, partially or totally blocking, decreasing, preventing, delaying, inactivating, desensitizing, or down-regulating activity (e.g., a receptor activity or a protein activity).

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

[0104] A "control" or "standard control" refers to a sample, measurement, or value that serves as a reference, usually a known reference, for comparison to a test sample, measurement, or value. For example, a test sample can be taken from a patient suspected of having a given disease (e.g. cancer) and compared to a known normal (non-diseased) individual (e.g. a standard control subject). A standard control can also represent an average measurement or value gathered from a population of similar individuals (e.g. standard control subjects) that do not have a given disease (i.e. standard control population), e.g., healthy individuals with a similar medical background, same age, weight, etc. A standard control value can also be obtained from the same individual, e.g. from an earlier-obtained sample from the patient prior to disease onset. For example, a control can be devised to compare therapeutic benefit based on pharmacological data

(*e.g.*, half-life) or therapeutic measures (*e.g.*, comparison of side effects). Controls are also valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant. One of skill will recognize that standard controls can be designed for assessment of any number of parameters (e.g. RNA levels, protein levels, specific cell types, specific bodily fluids, specific tissues, synoviocytes, synovial fluid, synovial tissue, fibroblast-like synoviocytes, macrophagelike synoviocytes, etc).

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

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

[0107] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including acute myeloid leukemia (AML), ALL, and CML), or multiple myeloma.

[0108] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g., humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include breast cancer, colon cancer, kidney cancer, leukemia, lung cancer, melanoma, ovarian cancer, prostate cancer, pancreatic cancer, brain cancer, liver cancer, gastric cancer or a sarcoma.

[0109] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute myeloid leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0110] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

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

[0112] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous

cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

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

[0114] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g., cancer (e.g. leukemia, acute myeloid leukemia)) means that the disease (e.g., cancer (e.g. leukemia, acute myeloid leukemia)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. Alternatively, the substance (e.g., IL1RAP) may be an indicator of the disease (e.g., cancer (e.g. leukemia, acute myeloid leukemia)). Thus, an associated substance may serve as a means of targeting disease tissue (e.g., cancer cells (e.g., leukemia stem cells, acute myeloid leukemia cells)).

[0115] As used herein, “treating” or “treatment of” a condition, disease or disorder or symptoms associated with a condition, disease or disorder refers to an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can

include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of condition, disorder or disease, stabilization of the state of condition, disorder or disease, prevention of development of condition, disorder or disease, prevention of spread of condition, disorder or disease, delay or slowing of condition, disorder or disease progression, delay or slowing of condition, disorder or disease onset, amelioration or palliation of the condition, disorder or disease state, and remission, whether partial or total. "Treating" can also mean prolonging survival of a subject beyond that expected in the absence of treatment. "Treating" can also mean inhibiting the progression of the condition, disorder or disease, slowing the progression of the condition, disorder or disease temporarily, although in some instances, it involves halting the progression of the condition, disorder or disease permanently. As used herein the terms treatment, treat, or treating refers to a method of reducing the effects of one or more symptoms of a disease or condition characterized by expression of the protease or symptom of the disease or condition characterized by expression of the protease. Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease, condition, or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition. Further, as used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level and such terms can include but do not necessarily include complete elimination.

[0116] The terms "dose" and "dosage" are used interchangeably herein. A dose refers to the amount of active ingredient given to an individual at each administration. The dose will vary depending on a number of factors, including the range of normal doses for a given therapy, frequency of administration; size and tolerance of the individual; severity of the condition; risk of side effects; and the route of administration. One of skill will recognize that the dose can be modified depending on the above factors or based on therapeutic progress. The term "dosage form" refers to the particular format of the pharmaceutical or pharmaceutical composition, and depends on the route of administration. For example, a dosage form can be in a liquid form for

nebulization, e.g., for inhalants, in a tablet or liquid, e.g., for oral delivery, or a saline solution, e.g., for injection.

[0117] By "therapeutically effective dose or amount" as used herein is meant a dose that produces effects for which it is administered (e.g. treating or preventing a disease). The exact dose and formulation will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Remington: The Science and Practice of Pharmacy, 20th Edition, Gennaro, Editor (2003), and Pickar, Dosage Calculations (1999)). For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a standard control. A therapeutically effective dose or amount may ameliorate one or more symptoms of a disease. A therapeutically effective dose or amount may prevent or delay the onset of a disease or one or more symptoms of a disease when the effect for which it is being administered is to treat a person who is at risk of developing the disease.

[0118] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention

can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0119] The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In embodiments, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0120] As used herein, the term "pharmaceutically acceptable" is used synonymously with "physiologically acceptable" and "pharmacologically acceptable". A pharmaceutical composition will generally comprise agents for buffering and preservation in storage, and can include buffers and carriers for appropriate delivery, depending on the route of administration.

[0121] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors,

salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0122] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0123] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0124] The pharmaceutical preparation is optionally in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The unit dosage form can be of a frozen dispersion.

ANTIBODY COMPOSITIONS

[0125] Provided herein are, *inter alia*, antibodies and antibody variants (e.g., single domain antibodies) capable of binding Interleukin-1 receptor accessory protein (IL1RAP). The antibodies provided herein include novel light chain and heavy chain sequences and bind IL1RAP with high efficiency and specificity, thereby effectively targeting IL1RAP expressing cells. The light and heavy chains of the antibodies and antibody variants (e.g., single domain antibodies) provided herein may form part of recombinant proteins (e.g., chimeric antigen receptors or bispecific antibodies). Through the recruitment of effector cells, the anti-ILRAP1

antibodies and antibody variants (e.g., single domain antibodies) provided herein are able to induce cell killing of IL1RAP-expressing cells. IL1RAP is expressed on a variety of cell types, for example, on candidate leukemic stem cells acute myeloid leukemia (AML) patients, but not on normal hematopoietic stem cells. Thus, the anti-IL1RAP antibodies and antibody variants (e.g., single domain antibodies) provided herein are, *inter alia*, useful for the treatment of IL1RAP-expressing cancers such as AML.

[0126] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

[0127] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

[0128] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

[0129] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0130] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a heavy chain variable domain and a light chain variable domain, wherein the

heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0131] As described above, a "light chain variable (VL) domain" as provided herein refers to the variable region of the light chain of an antibody, an antibody variant or fragment thereof. Likewise, the "heavy chain variable (VH) domain" as provided herein refers to the variable region of the heavy chain of an antibody, an antibody variant or fragment thereof. The light chain variable domain and the heavy chain variable domain together form the paratope, which binds an antigen (epitope). The paratope or antigen-binding site is formed at the N-terminus of an antibody, an antibody variant or fragment thereof. In embodiments, the light chain variable (VL) domain includes CDR L1, CDR L2, CDR L3 and FR L1, FR L2, FR L3 and FR L4 (framework regions) of an antibody light chain. In embodiments, the heavy chain variable (VH) domain includes CDR H1, CDR H2, CDR H3 and FR H1, FR H2, FR H3 and FR H4 (framework regions) of an antibody heavy chain. In embodiments, the light chain variable (VL) domain and a light chain constant (CL) domain form part of an antibody light chain. In embodiments, the heavy chain variable (VH) domain and a heavy chain constant (CH1) domain form part of an antibody heavy chain. In embodiments, the heavy chain variable (VH) domain and one or more heavy chain constant (CH1, CH2, or CH3) domains form part of an antibody heavy chain. Thus, in embodiments, the light chain variable (VL) domain forms part of an antibody. In embodiments, the heavy chain variable (VH) domain forms part of an antibody. In embodiments, the light chain variable (VL) domain forms part of a therapeutic antibody. In embodiments, the heavy chain variable (VH) domain forms part of a therapeutic antibody. In embodiments, the light chain variable (VL) domain forms part of a human antibody. In embodiments, the heavy chain variable (VH) domain forms part of a human antibody. In embodiments, the light chain variable (VL) domain forms part of a humanized antibody. In embodiments, the heavy chain variable (VH) domain forms part of a humanized antibody. In embodiments, the light chain variable (VL) domain forms part of a chimeric antibody. In embodiments, the heavy chain variable (VH) domain forms part of a chimeric antibody. In embodiments, the light chain variable (VL) domain forms part of an antibody fragment. In embodiments, the heavy chain variable (VH) domain forms part of an antibody fragment. In embodiments, the light chain variable (VL) domain forms part of an antibody variant. In embodiments, the heavy chain variable (VH) domain forms part of an antibody variant. In

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

[0132] In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:61. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:61. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:62. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:62. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:63. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:63. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:64. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:64. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:67. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:67. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:68. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:68. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:69. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:69. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:70. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:70. In embodiments, the heavy chain variable domain includes the sequence of SEQ ID NO:71. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:71. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:72. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:72.

[0133] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

[0134] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

[0135] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

[0136] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

[0137] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

[0138] In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2; a CDR H3 as set forth in SEQ ID NO:3; a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, a CDR L3 as set forth in SEQ ID NO:6; a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88. In one further embodiment, the antibody is antibody D1A4.

[0139] In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8; a CDR H3 as set forth in SEQ ID NO:9; a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92; and

(ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, a CDR L3 as set forth in SEQ ID NO:12; a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96. In one further embodiment, the antibody is antibody 1C7.

[0140] In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20; a CDR H3 as set forth in SEQ ID NO:21; a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, a CDR L3 as set forth in SEQ ID NO:24; a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112. In one further embodiment, the antibody is antibody 2E12.

[0141] In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26; a CDR H3 as set forth in SEQ ID NO:27; a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, a CDR L3 as set forth in SEQ ID NO:30; a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120. In one further embodiment, the antibody is antibody 1A7.

[0142] In one embodiment, the antibody includes (i) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32; a CDR H3 as set forth in SEQ ID NO:33; a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124; and (ii) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, a CDR L3 as set forth in SEQ ID NO:36; a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128. In one further embodiment, the antibody is antibody 1B8.

[0143] In embodiments, the antibody is an IgG. In embodiments, the antibody is a human IgG. In embodiments, the antibody is an IgG1. In embodiments, the antibody is a human IgG1.

[0144] In embodiments, the antibody is a Fab' fragment. In embodiments, the antibody forms part of a Fab' fragment. In embodiments, the antibody is a single chain antibody (scFv). In embodiments, the light chain variable domain and the heavy chain variable domain form part of an scFv. In embodiments, the antibody is a single domain antibody. In embodiments, the single domain antibody includes a light chain variable domain. In embodiments, the single domain antibody includes a heavy chain variable domain.

[0145] In embodiments, the scFv includes the sequence of SEQ ID NO:61. In embodiments, the scFv includes the sequence of SEQ ID NO:63. In embodiments, the scFv includes the sequence of SEQ ID NO:67. In embodiments, the scFv includes the sequence of SEQ ID NO:69. In embodiments, the scFv includes the sequence of SEQ ID NO:71.

[0146] In embodiments, the scFv includes the sequence of SEQ ID NO:62. In embodiments, the scFv includes the sequence of SEQ ID NO:64. In embodiments, the scFv includes the sequence of SEQ ID NO:68. In embodiments, the scFv includes the sequence of SEQ ID NO:70. In embodiments, the scFv includes the sequence of SEQ ID NO:72.

[0147] In embodiments, the scFv includes the sequence of SEQ ID NO:61 and the sequence of SEQ ID NO:62. In embodiments, the scFv is the sequence of SEQ ID NO:61 and the sequence of SEQ ID NO:62. In embodiments, the scFv includes the sequence of SEQ ID NO:63 and the sequence of SEQ ID NO:64. In embodiments, the scFv is the sequence of SEQ ID NO:63 and the sequence of SEQ ID NO:64. In embodiments, the scFv includes the sequence of SEQ ID NO:67 and the sequence of SEQ ID NO:68. In embodiments, the scFv is the sequence of SEQ ID NO:67 and the sequence of SEQ ID NO:68. In embodiments, the scFv includes the sequence of SEQ ID NO:69 and the sequence of SEQ ID NO:70. In embodiments, the scFv is the sequence of SEQ ID NO:69 and the sequence of SEQ ID NO:70. In embodiments, the scFv includes the sequence of SEQ ID NO:71 and the sequence of SEQ ID NO:72. In embodiments, the scFv is the sequence of SEQ ID NO:71 and the sequence of SEQ ID NO:72.

[0148] The antibodies provided herein may be single domain antibodies. Thus, in an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38, and a CDR L3 as set forth in SEQ ID NO:39.

[0149] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0150] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45.

[0151] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0152] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

[0153] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

[0154] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

[0155] In an aspect is provided an anti-interleukin-1 receptor accessory protein (IL1RAP) antibody including a light chain variable domain, wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

[0156] In embodiments, the single domain antibody includes a light chain variable domain. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:73. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:74. In

embodiments, the single domain antibody includes the sequence of SEQ ID NO:75. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:76. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:77. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:78. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:79. In embodiments, the single domain antibody includes the sequence of SEQ ID NO:80.

[0157] In embodiments, the single domain antibody is a light chain variable domain. In embodiments, the single domain antibody is the sequence of SEQ ID NO:73. In embodiments, the single domain antibody is the sequence of SEQ ID NO:74. In embodiments, the single domain antibody is the sequence of SEQ ID NO:75. In embodiments, the single domain antibody is the sequence of SEQ ID NO:76. In embodiments, the single domain antibody is the sequence of SEQ ID NO:77. In embodiments, the single domain antibody is the sequence of SEQ ID NO:78. In embodiments, the single domain antibody is the sequence of SEQ ID NO:79. In embodiments, the single domain antibody is the sequence of SEQ ID NO:80.

[0158] In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:73. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:74. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:75. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:76. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:77. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:78. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:79. In embodiments, the light chain variable domain includes the sequence of SEQ ID NO:80.

[0159] In embodiments, the light chain variable domain is the sequence of SEQ ID NO:73. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:74. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:75. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:76. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:77. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:78. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:79. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:80.

[0160] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR H3 as set forth in SEQ ID NO:131 and a FR H4 as set forth in SEQ ID NO:132.

[0161] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR H3 as set forth in SEQ ID NO:135 and a FR H4 as set forth in SEQ ID NO:136.

[0162] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR H3 as set forth in SEQ ID NO:139 and a FR H4 as set forth in SEQ ID NO:140.

[0163] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR H3 as set forth in SEQ ID NO:143 and a FR H4 as set forth in SEQ ID NO:144.

[0164] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR H3 as set forth in SEQ ID NO:147 and a FR H4 as set forth in SEQ ID NO:148.

[0165] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR H3 as set forth in SEQ ID NO:151 and a FR H4 as set forth in SEQ ID NO:152.

[0166] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR H3 as set forth in SEQ ID NO:155 and a FR H4 as set forth in SEQ ID NO:156.

[0167] In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR H3 as set forth in SEQ ID NO:159 and a FR H4 as set forth in SEQ ID NO:160.

[0168] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and a FR L1 as set forth in SEQ ID NO: 129, a FR L2 as set forth in SEQ ID NO: 130, a FR L3 as set forth in SEQ ID NO: 131, and a FR L4 as set forth in SEQ ID NO: 132. In one further embodiment, the antibody is antibody 1A12.

[0169] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and a FR L1 as set forth in SEQ ID NO: 133, a FR L2 as set forth in SEQ ID NO: 134, a FR L3 as set forth in SEQ ID NO: 135, and a FR L4 as set forth in SEQ ID NO: 136. In one further embodiment, the antibody is antibody 1A5.

[0170] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45; and a FR L1 as set forth in SEQ ID NO: 137, a FR L2 as set forth in SEQ ID NO: 138, a FR L3 as set forth in SEQ ID NO: 139, and a FR L4 as set forth in SEQ ID NO: 140. In one further embodiment, the antibody is antibody 1A6.

[0171] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and a FR L1 as set forth in SEQ ID NO: 141, a FR L2 as set forth in SEQ ID NO: 142, a FR L3 as set forth in SEQ ID NO: 143, and a FR L4 as set forth in SEQ ID NO: 144. In one further embodiment, the antibody is antibody 1A1.

[0172] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51; and a FR L1 as set forth in SEQ ID NO: 145, a FR L2 as set forth in SEQ ID NO: 146, a FR L3 as set forth in SEQ ID NO: 147, and a FR L4 as set forth in SEQ ID NO: 148. In one further embodiment, the antibody is antibody 1A4.

[0173] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54; and a FR L1 as set forth in SEQ ID NO: 149, a FR L2 as set forth in SEQ ID NO: 150, a FR L3 as set forth in SEQ ID NO: 151, and a FR L4 as set forth in SEQ ID NO: 152. In one further embodiment, the antibody is antibody 1A11.

[0174] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57; and a FR L1 as set forth in SEQ ID NO: 153, a FR L2 as set forth in SEQ ID NO: 154, a FR L3 as set forth in SEQ ID NO: 155, and a FR L4 as set forth in SEQ ID NO: 156. In one further embodiment, the antibody is antibody 1E12.

[0175] In one embodiment, the antibody includes a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60; and a FR L1 as set forth in SEQ ID NO: 157, a FR L2 as set forth in SEQ ID NO: 158, a FR L3 as set forth in SEQ ID NO: 159, and a FR L4 as set forth in SEQ ID NO: 160. In one further embodiment, the antibody is antibody D1F6.

[0176] The ability of an antibody to bind a specific epitope (e.g., IL1RAP) can be described by the equilibrium dissociation constant (K_D). The equilibrium dissociation constant (K_D) as defined herein is the ratio of the dissociation rate (K-off) and the association rate (K-on) of an antibody to IL1RAP. It is described by the following formula: K_D = K-off/K-on. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 21 nM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 21 nM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 80.6 nM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 80.6 nM.

[0177] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1.5-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.5-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3.5-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1.5-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.5-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3-4 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3.5-4 M.

[0178] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-3.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-3 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-2.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-2 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-1.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-3.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-3 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-2.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-2 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-1.5 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 4 M, about 3.5 M, about 3 M, about 2.5 M, about 2 M, about 1.5 M, or about 1 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 4 M, 3.5 M, 3 M, 2.5 M, 2 M, 1.5 M, or 1 M.

[0179] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.899 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.899 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1.402 M. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1.402 M.

[0180] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1.5-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.5-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3.5-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-4 mM. In embodiments, the antibody is

capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1.5-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.5-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3-4 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3.5-4 mM.

[0181] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-3.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-3 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-2.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-2 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-1.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-3.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-3 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-2.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-2 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-1.5 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 4 mM, about 3.5 mM, about 3 mM, about 2.5 mM, about 2 mM, about 1.5 mM, or about 1 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 4 mM, 3.5 mM, 3 mM, 2.5 mM, 2 mM, 1.5 mM, or 1 mM.

[0182] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.71 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.71 mM.

[0183] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 21-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation

constant (K_D) of about 22-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 23-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 24-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 25-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 26-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 27-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 28-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 29-30 mM.

[0184] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 21-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 22-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 23-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 24-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 25-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 26-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 27-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 28-30 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 29-30 mM.

[0185] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-29 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-28 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-27 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-26 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-25 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium

dissociation constant (K_D) of about 20-24 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-23 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-22 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 20-21 mM.

[0186] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-29 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-28 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-27 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-26 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-25 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-24 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-23 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-22 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 20-21 mM.

[0187] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30 mM, about 29 mM, about 28 mM, about 27 mM, about 26 mM, about 25 mM, about 24 mM, about 23 mM, about 22 mM, about 21 mM, or about 20 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30 mM, 29 mM, 28 mM, 27 mM, 26 mM, 25 mM, 24 mM, 23 mM, 22 mM, 21 mM, or 20 mM.

[0188] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 26.95 mM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 26.95 mM.

[0189] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 242-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 244-260 μM. In embodiments, the antibody is capable of binding

IL1RAP with an equilibrium dissociation constant (K_D) of about 246-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 248-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 250-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 252-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 254-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 256-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 258-260 μM.

[0190] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) from 240-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 242-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 244-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 246-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 248-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 250-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 252-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 254-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 256-260 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 258-260 μM.

[0191] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-258 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-256 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-254 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-252 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-250 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-248 μM. In embodiments, the antibody is

capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-246 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 240-242 μM.

[0192] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) from 240-258 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-256 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-254 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-252 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-250 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-248 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-246 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 240-242 μM.

[0193] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 260 μM, about 258 μM, about 256 μM, about 254 μM, about 252 μM, about 250 μM, about 248 μM, about 246 μM, about 244 μM, about 242 μM, or about 240 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 260 μM, 258 μM, 256 μM, 254 μM, 252 μM, 250 μM, 248 μM, 246 μM, 244 μM, 242 μM, or 240 μM.

[0194] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 249.8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 249.8 μM.

[0195] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 31-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 32-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 33-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 34-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 35-40 μM. In embodiments, the antibody is capable of

binding IL1RAP with an equilibrium dissociation constant (K_D) of about 36-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 37-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 38-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 39-40 μM.

[0196] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 31-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 32-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 33-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 34-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 35-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 36-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 37-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 38-40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 39-40 μM.

[0197] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-39 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-38 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-37 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-36 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-35 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-34 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-33 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-32 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30-31 μM.

[0198] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-39 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-38 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-37 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-36 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-35 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-34 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-33 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-32 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30-31 μM.

[0199] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 30 μM, about 31 μM, about 32 μM, about 33 μM, about 34 μM, about 35 μM, about 36 μM, about 37 μM, about 38 μM, about 39 μM, or about 40 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 30 μM, 31 μM, 32 μM, 33 μM, 34 μM, 35 μM, 36 μM, 37 μM, 38 μM, 39 μM, or 40 μM.

[0200] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 35.75 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 35.75 μM.

[0201] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.4-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.6-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.8-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2-8 μM. In embodiments, the antibody

is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 4-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 4.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 5.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 6-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 6.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 7-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 7.5-8 μM.

[0202] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) from 0.2-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.4-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.6-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.8-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 4-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 4.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 5-8 μM. In embodiments, the antibody is capable of binding

IL1RAP with an equilibrium dissociation constant (K_D) of 5.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 6-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 6.5-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 7-8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 7.5-8 μM.

[0203] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-7.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-7 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-6.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-6 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-5.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-4.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-4 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-3.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-3 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-2.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-2 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-1.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-1 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-0.8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-0.6 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.2-0.4 μM.

[0204] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-7.5 μM. In embodiments, the antibody is capable of binding

IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-7 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-6.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-6 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-5.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-4.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-4 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-3.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-3 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-2.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-2 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-1.5 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-1 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-0.8 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-0.6 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.2-0.4 μM.

[0205] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 8 μM, about 7.5 μM, about 7 μM, about 6.5 μM, about 6 μM, about 5.5 μM, about 5 μM, about 4.5 μM, about 4 μM, about 3.5 μM, about 3 μM, about 2.5 μM, about 2 μM, about 1.5 μM, about 1 μM, about 0.8 μM, about 0.6 μM, about 0.4 μM, or about 0.2 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 8 μM, 7.5 μM, 7 μM, 6.5 μM, 6 μM, 5.5 μM, 5 μM, 4.5 μM, 4 μM, 3.5 μM, 3 μM, 2.5 μM, 2 μM, 1.5 μM, 1 μM, 0.8 μM, 0.6 μM, 0.4 μM, or 0.2 μM.

[0206] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 3.07 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 3.07 μM.

[0207] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 2.11 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 2.11 μM.

[0208] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 0.85 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 0.85 μM.

[0209] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 1.4 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 1.4 μM.

[0210] In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of about 6.63 μM. In embodiments, the antibody is capable of binding IL1RAP with an equilibrium dissociation constant (K_D) of 6.63 μM.

[0211] The term "EC50" or "half maximal effective concentration" as used herein refers to the concentration of a molecule (e.g., antibody, chimeric antigen receptor or bispecific antibody) capable of inducing a response which is halfway between the baseline response and the maximum response after a specified exposure time. In embodiments, the EC50 is the concentration of a molecule (e.g., antibody, chimeric antigen receptor or bispecific antibody) that produces 50% of the maximal possible effect of that molecule. In embodiments, the antibody has an EC_{50} of about 21 nM. In embodiments, the antibody has an EC_{50} of 21 nM. In embodiments, the antibody has an EC_{50} of about 80.6 nM. In embodiments, the antibody has an EC_{50} of 80.6 nM.

[0212] In embodiments, the antibody has an EC_{50} of about 1-4 M. In embodiments, the antibody has an EC_{50} of about 1.5-4 M. In embodiments, the antibody has an EC_{50} of about 2-4 M. In embodiments, the antibody has an EC_{50} of about 2.5-4 M. In embodiments, the antibody has an EC_{50} of about 3-4 M. In embodiments, the antibody has an EC_{50} of about 3.5-4 M. In embodiments, the antibody has an EC_{50} of 1-4 M. In embodiments, the antibody has an EC_{50} of 1.5-4 M. In embodiments, the antibody has an EC_{50} of 2-4 M. In embodiments, the antibody has an EC_{50} of 2.5-4 M. In embodiments, the antibody has an EC_{50} of 3-4 M. In embodiments, the antibody has an EC_{50} of 3.5-4 M.

[0213] In embodiments, the antibody has an EC_{50} of about 1-3.5 M. In embodiments, the antibody has an EC_{50} of about 1-3 M. In embodiments, the antibody has an EC_{50} of about 1-2.5

M. In embodiments, the antibody has an EC_{50} of about 1-2 M. In embodiments, the antibody has an EC_{50} of about 1-1.5 M. In embodiments, the antibody has an EC_{50} of 1-3.5 M. In embodiments, the antibody has an EC_{50} of 1-3 M. In embodiments, the antibody has an EC_{50} of 1-2.5 M. In embodiments, the antibody has an EC_{50} of 1-2 M. In embodiments, the antibody has an EC_{50} of 1-1.5 M. In embodiments, the antibody has an EC_{50} of about 4 M, about 3.5 M, about 3 M, about 2.5 M, about 2 M, about 1.5 M, or about 1 M. In embodiments, the antibody has an EC_{50} of 4 M, 3.5 M, 3 M, 2.5 M, 2 M, 1.5 M, or 1 M.

[0214] In embodiments, the antibody has an EC_{50} of about 2.899 M. In embodiments, the antibody has an EC_{50} of 2.899 M. In embodiments, the antibody has an EC_{50} of about 1.402 M. In embodiments, the antibody has an EC_{50} of 1.402 M.

[0215] In embodiments, the antibody has an EC_{50} of about 1-4 mM. In embodiments, the antibody has an EC_{50} of about 1.5-4 mM. In embodiments, the antibody has an EC_{50} of about 2-4 mM. In embodiments, the antibody has an EC_{50} of about 2.5-4 mM. In embodiments, the antibody has an EC_{50} of about 3-4 mM. In embodiments, the antibody has an EC_{50} of about 3.5-4 mM. In embodiments, the antibody has an EC_{50} of 1-4 mM. In embodiments, the antibody has an EC_{50} of 1.5-4 mM. In embodiments, the antibody has an EC_{50} of 2-4 mM. In embodiments, the antibody has an EC_{50} of 2.5-4 mM. In embodiments, the antibody has an EC_{50} of 3-4 mM. In embodiments, the antibody has an EC_{50} of 3.5-4 mM.

[0216] In embodiments, the antibody has an EC_{50} of about 1-3.5 mM. In embodiments, the antibody has an EC_{50} of about 1-3 mM. In embodiments, the antibody has an EC_{50} of about 1-2.5 mM. In embodiments, the the antibody has an EC_{50} of about 1-2 mM. In embodiments, the antibody has an EC_{50} of about 1-1.5 mM. In embodiments, the antibody has an EC_{50} of 1-3.5 mM. In embodiments, the antibody has an EC_{50} of 1-3 mM. In embodiments, the antibody has an EC_{50} of 1-2.5 mM. In embodiments, the antibody has an EC_{50} of 1-2 mM. In embodiments, the antibody has an EC_{50} of 1-1.5 mM. In embodiments, the antibody has an EC_{50} of 4 mM, about 3.5 mM, about 3 mM, about 2.5 mM, about 2 mM, about 1.5 mM, or about 1 mM. In embodiments, the antibody has an EC_{50} of 4 mM, 3.5 mM, 3 mM, 2.5 mM, 2 mM, 1.5 mM, or 1 mM.

[0217] In embodiments, the antibody has an EC_{50} of about 2.71 mM. In embodiments, the antibody has an EC_{50} of of 2.71 mM.

[0218] In embodiments, the antibody has an EC_{50} of about 20-30 mM. In embodiments, the antibody has an EC_{50} of about 21-30 mM. In embodiments, the antibody has an EC_{50} of about

22-30 mM. In embodiments, the antibody has an EC_{50} of about 23-30 mM. In embodiments, the antibody has an EC_{50} of about 24-30 mM. In embodiments, the antibody has an EC_{50} of about 25-30 mM. In embodiments, the antibody has an EC_{50} of about 26-30 mM. In embodiments, the antibody has an EC_{50} of about 27-30 mM. In embodiments, the antibody has an EC_{50} of about 28-30 mM. In embodiments, the antibody has an EC_{50} of about 29-30 mM.

[0219] In embodiments, the antibody has an EC_{50} of 20-30 mM. In embodiments, the antibody has an EC_{50} of 21-30 mM. In embodiments, the antibody has an EC_{50} of 22-30 mM. In embodiments, the antibody has an EC_{50} of 23-30 mM. In embodiments, the antibody has an EC_{50} of of 24-30 mM. In embodiments, the antibody has an EC_{50} of 25-30 mM. In embodiments, the antibody has an EC_{50} of 26-30 mM. In embodiments, the antibody has an EC_{50} of 27-30 mM. In embodiments, the antibody has an EC_{50} of 28-30 mM. In embodiments, the antibody has an EC_{50} of 29-30 mM.

[0220] In embodiments, the antibody has an EC_{50} of about 20-29 mM. In embodiments, the antibody has an EC_{50} of about 20-28 mM. In embodiments, the antibody has an EC_{50} of about 20-27 mM. In embodiments, the antibody has an EC_{50} of about 20-26 mM. In embodiments, the antibody has an EC_{50} of about 20-25 mM. In embodiments, the antibody has an EC_{50} of about 20-24 mM. In embodiments, the antibody has an EC_{50} of about 20-23 mM. In embodiments, the antibody has an EC_{50} of about 20-22 mM. In embodiments, the antibody has an EC_{50} of about 20-21 mM.

[0221] In embodiments, the antibody has an EC_{50} of 20-29 mM. In embodiments, the antibody has an EC_{50} of 20-28 mM. In embodiments, the antibody has an EC_{50} of 20-27 mM. In embodiments, the antibody has an EC_{50} of 20-26 mM. In embodiments, the antibody has an EC_{50} of 20-25 mM. In embodiments, the antibody has an EC_{50} of 20-24 mM. In embodiments, the antibody has an EC_{50} of 20-23 mM. In embodiments, the antibody has an EC_{50} of 20-22 mM. In embodiments, the antibody has an EC_{50} of 20-21 mM.

[0222] In embodiments, the antibody has an EC_{50} of about 30 mM, about 29 mM, about 28 mM, about 27 mM, about 26 mM, about 25 mM, about 24 mM, about 23 mM, about 22 mM, about 21 mM, or about 20 mM. In embodiments, the antibody has an EC_{50} of of 30 mM, 29 mM, 28 mM, 27 mM, 26 mM, 25 mM, 24 mM, 23 mM, 22 mM, 21 mM, or 20 mM.

[0223] In embodiments, the antibody has an EC_{50} of about 26.95 mM. In embodiments, the antibody has an EC_{50} of of 26.95 mM.

[0224] In embodiments, the antibody has an EC_{50} of about 240-260 μM. In embodiments, the antibody has an EC_{50} of about 242-260 μM. In embodiments, the antibody has an EC_{50} of about 244-260 μM. In embodiments, the antibody has an EC_{50} of about 246-260 μM. In embodiments, the antibody has an EC_{50} of about 248-260 μM. In embodiments, the antibody has an EC_{50} of about 250-260 μM. In embodiments, the antibody has an EC_{50} of about 252-260 μM. In embodiments, the antibody has an EC_{50} of about 254-260 μM. In embodiments, the antibody has an EC_{50} of about 256-260 μM. In embodiments, the antibody has an EC_{50} of about 258-260 μM.

[0225] In embodiments, the antibody has an EC_{50} from 240-260 μM. In embodiments, the antibody has an EC_{50} of 242-260 μM. In embodiments, the antibody has an EC_{50} of 244-260 μM. In embodiments, the antibody has an EC_{50} of 246-260 μM. In embodiments, the antibody has an EC_{50} of 248-260 μM. In embodiments, the antibody has an EC_{50} of 250-260 μM. In embodiments, the antibody has an EC_{50} of 252-260 μM. In embodiments, the antibody has an EC_{50} of 254-260 μM. In embodiments, the antibody has an EC_{50} of 256-260 μM. In embodiments, the antibody has an EC_{50} of 258-260 μM.

[0226] In embodiments, the antibody has an EC_{50} of about 240-258 μM. In embodiments, the antibody has an EC_{50} of about 240-256 μM. In embodiments, the antibody has an EC_{50} of about 240-254 μM. In embodiments, the antibody has an EC_{50} of about 240-252 μM. In embodiments, the antibody has an EC_{50} of about 240-250 μM. In embodiments, the antibody has an EC_{50} of about 240-248 μM. In embodiments, the antibody has an EC_{50} of about 240-246 μM. In embodiments, the antibody has an EC_{50} of about 240-242 μM.

[0227] In embodiments, the antibody has an EC_{50} from 240-258 μM. In embodiments, the antibody has an EC_{50} of 240-256 μM. In embodiments, the antibody has an EC_{50} of 240-254 μM. In embodiments, the antibody has an EC_{50} of 240-252 μM. In embodiments, the antibody has an EC_{50} of 240-250 μM. In embodiments, the antibody has an EC_{50} of 240-248 μM. In embodiments, the antibody has an EC_{50} of 240-246 μM. In embodiments, the antibody has an EC_{50} of 240-242 μM.

[0228] In embodiments, the antibody has an EC_{50} of about 260 μM, about 258 μM, about 256 μM, about 254 μM, about 252 μM, about 250 μM, about 248 μM, about 246 μM, about 244 μM, about 242 μM, or about 240 μM. In embodiments, the antibody has an EC_{50} of 260 μM, 258 μM, 256 μM, 254 μM, 252 μM, 250 μM, 248 μM, 246 μM, 244 μM, 242 μM, or 240 μM.

[0229] In embodiments, the antibody has an EC_{50} of about 249.8 μM. In embodiments, the antibody has an EC_{50} of 249.8 μM.

[0230] In embodiments, the antibody has an EC_{50} of about 30-40 μM. In embodiments, the antibody has an EC_{50} of about 31-40 μM. In embodiments, the antibody has an EC_{50} of about 32-40 μM. In embodiments, the antibody has an EC_{50} of about 33-40 μM. In embodiments, the antibody has an EC_{50} of about 34-40 μM. In embodiments, the antibody has an EC_{50} of about 35-40 μM. In embodiments, the antibody has an EC_{50} of about 36-40 μM. In embodiments, the antibody has an EC_{50} of about 37-40 μM. In embodiments, the antibody has an EC_{50} of about 38-40 μM. In embodiments, the antibody has an EC_{50} of about 39-40 μM.

[0231] In embodiments, the antibody has an EC_{50} of 30-40 μM. In embodiments, the antibody has an EC_{50} of 31-40 μM. In embodiments, the antibody has an EC_{50} of 32-40 μM. In embodiments, the antibody has an EC_{50} of 33-40 μM. In embodiments, the antibody has an EC_{50} of 34-40 μM. In embodiments, the antibody has an EC_{50} of 35-40 μM. In embodiments, the antibody has an EC_{50} of 36-40 μM. In embodiments, the antibody has an EC_{50} of 37-40 μM. In embodiments, the antibody has an EC_{50} of 38-40 μM. In embodiments, the antibody has an EC_{50} of 39-40 μM.

[0232] In embodiments, the antibody has an EC_{50} of about 30-39 μM. In embodiments, the antibody has an EC_{50} of about 30-38 μM. In embodiments, the antibody has an EC_{50} of about 30-37 μM. In embodiments, the antibody has an EC_{50} of about 30-36 μM. In embodiments, the antibody has an EC_{50} of about 30-35 μM. In embodiments, the antibody has an EC_{50} of about 30-34 μM. In embodiments, the antibody has an EC_{50} of about 30-33 μM. In embodiments, the antibody has an EC_{50} of about 30-32 μM. In embodiments, the antibody has an EC_{50} of about 30-31 μM.

[0233] In embodiments, the antibody has an EC_{50} of 30-39 μM. In embodiments, the antibody has an EC_{50} of 30-38 μM. In embodiments, the antibody has an EC_{50} of 30-37 μM. In embodiments, the antibody has an EC_{50} of 30-36 μM. In embodiments, the antibody has an EC_{50} of 30-35 μM. In embodiments, the antibody has an EC_{50} of 30-34 μM. In embodiments, the antibody has an EC_{50} of 30-33 μM. In embodiments, the antibody has an EC_{50} of 30-32 μM. In embodiments, the antibody has an EC_{50} of 30-31 μM.

[0234] In embodiments, the antibody has an EC_{50} of about 30 μM, about 31 μM, about 32 μM, about 33 μM, about 34 μM, about 35 μM, about 36 μM, about 37 μM, about 38 μM, about 39 μM, or about 40 μM. In embodiments, the antibody has an EC_{50} of 30 μM, 31 μM, 32 μM, 33 μM, 34 μM, 35 μM, 36 μM, 37 μM, 38 μM, 39 μM, or 40 μM.

[0235] In embodiments, the antibody has an EC_{50} of about 35.75 μM. In embodiments, the antibody has an EC_{50} of 35.75 μM.

[0236] In embodiments, the antibody has an EC_{50} of about 0.2-8 μM. In embodiments, the antibody has an EC_{50} of about 0.4-8 μM. In embodiments, the antibody has an EC_{50} of about 0.6-8 μM. In embodiments, the antibody has an EC_{50} of about 0.8-8 μM. In embodiments, the antibody has an EC_{50} of about 1-8 μM. In embodiments, the antibody has an EC_{50} of about 1.5-8 μM. In embodiments, the antibody has an EC_{50} of about 2-8 μM. In embodiments, the antibody has an EC_{50} of about 2.5-8 μM. In embodiments, the antibody has an EC_{50} of about 3-8 μM. In embodiments, the antibody has an EC_{50} of about 3.5-8 μM. In embodiments, the antibody has an EC_{50} of about 4-8 μM. In embodiments, the antibody has an EC_{50} of about 4.5-8 μM. In embodiments, the antibody has an EC_{50} of about 5-8 μM. In embodiments, the antibody has an EC_{50} of about 5.5-8 μM. In embodiments, the antibody has an EC_{50} of about 6-8 μM. In embodiments, the antibody has an EC_{50} of about 6.5-8 μM. In embodiments, the antibody has an EC_{50} of about 7-8 μM. In embodiments, the antibody has an EC_{50} of about 7.5-8 μM.

[0237] In embodiments, the antibody has an EC_{50} from 0.2-8 μM. In embodiments, the antibody has an EC_{50} of 0.4-8 μM. In embodiments, the antibody has an EC_{50} of 0.6-8 μM. In embodiments, the antibody has an EC_{50} of 0.8-8 μM. In embodiments, the antibody has an EC_{50} of 1-8 μM. In embodiments, the antibody has an EC_{50} of 1.5-8 μM. In embodiments, the antibody has an EC_{50} of 2-8 μM. In embodiments, the antibody has an EC_{50} of 2.5-8 μM. In embodiments, the antibody has an EC_{50} of 3-8 μM. In embodiments, the antibody has an EC_{50} of 3.5-8 μM. In embodiments, the antibody has an EC_{50} of 4-8 μM. In embodiments, the antibody has an EC_{50} of 4.5-8 μM. In embodiments, the antibody has an EC_{50} of 5-8 μM. In embodiments, the antibody has an EC_{50} of 5.5-8 μM. In embodiments, the antibody has an EC_{50} of 6-8 μM. In embodiments, the antibody has an EC_{50} of 6.5-8 μM. In embodiments, the antibody has an EC_{50} of 7-8 μM. In embodiments, the antibody has an EC_{50} of 7.5-8 μM.

[0238] In embodiments, the antibody has an EC_{50} of about 0.2-7.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-7 μM. In embodiments, the antibody has an EC_{50} of about 0.2-6.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-6 μM. In embodiments, the antibody has an EC_{50} of about 0.2-5.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-4.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-4 μM. In embodiments, the antibody has an EC_{50} of about 0.2-3.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-3 μM. In embodiments, the

antibody has an EC_{50} of about 0.2-2.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-2 μM. In embodiments, the antibody has an EC_{50} of about 0.2-1.5 μM. In embodiments, the antibody has an EC_{50} of about 0.2-1 μM. In embodiments, the antibody has an EC_{50} of about 0.2-0.8 μM. In embodiments, the antibody has an EC_{50} of about 0.2-0.6 μM. In embodiments, the antibody has an EC_{50} of about 0.2-0.4 μM.

[0239] In embodiments, the antibody has an EC_{50} of 0.2-7.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-7 μM. In embodiments, the antibody has an EC_{50} of 0.2-6.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-6 μM. In embodiments, the antibody has an EC_{50} of 0.2-5.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-5 μM. In embodiments, the antibody has an EC_{50} of 0.2-4.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-4 μM. In embodiments, the antibody has an EC_{50} of 0.2-3.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-3 μM. In embodiments, the antibody has an EC_{50} of 0.2-2.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-2 μM. In embodiments, the antibody has an EC_{50} of 0.2-1.5 μM. In embodiments, the antibody has an EC_{50} of 0.2-1 μM. In embodiments, the antibody has an EC_{50} of 0.2-0.8 μM. In embodiments, the antibody has an EC_{50} of 0.2-0.6 μM. In embodiments, the antibody has an EC_{50} of 0.2-0.4 μM.

[0240] In embodiments, the antibody has an EC_{50} of about 8 μM, about 7.5 μM, about 7 μM, about 6.5 μM, about 6 μM, about 5.5 μM, about 5 μM, about 4.5 μM, about 4 μM, about 3.5 μM, about 3 μM, about 2.5 μM, about 2 μM, about 1.5 μM, about 1 μM, about 0.8 μM, about 0.6 μM, about 0.4 μM, or about 0.2 μM. In embodiments, the antibody has an EC_{50} of 8 μM, 7.5 μM, 7 μM, 6.5 μM, 6 μM, 5.5 μM, 5 μM, 4.5 μM, 4 μM, 3.5 μM, 3 μM, 2.5 μM, 2 μM, 1.5 μM, 1 μM, 0.8 μM, 0.6 μM, 0.4 μM, or 0.2 μM.

[0241] In embodiments, the antibody has an EC_{50} of about 3.07 μM. In embodiments, the antibody has an EC_{50} of 3.07 μM.

[0242] In embodiments, the the antibody has an EC_{50} of about 2.11 μM. In embodiments, the antibody has an EC_{50} of 2.11 μM.

[0243] In embodiments, the antibody has an EC_{50} of about 0.85 μM. In embodiments, the antibody has an EC_{50} of 0.85 μM.

[0244] In embodiments, the the antibody has an EC_{50} of about 1.4 μM. In embodiments, the antibody has an EC_{50} of 1.4 μM.

[0245] In embodiments, the antibody has an EC_{50} of about 6.63 μM. In embodiments, the antibody has an EC_{50} of 6.63 μM.

[0246] In embodiments, the antibody has an EC_{50} of one of Table 1.

[0247] Table 1 shows EC_{50} values of exemplary anti-IL1RAP antibodies provided herein.

ID	EC_{50} (mg/ml)
1A1	~ 289884
1A4	3.575
1A5	~ 140188
1A6	24.98
1A11	~ 271.3
1A12	~ 2695
1B8	0.3072
1E12	0.2111
2E12	0.0854
D1A4	0.1404
D1F6	0.6298
1D5	0.005291

[0248] In embodiments, the antibody is bound to an IL1RAP. In embodiments, the IL1RAP is a human IL1RAP. In embodiments, the IL1RAP forms part of a cell. In embodiments, the IL1RAP is expressed on the surface of the cell. In embodiments, the cell is a cancer cell. In embodiments, the cancer cell is a leukemia stem cell (LSC). In embodiments, the cancer cell is an acute myeloid leukemia (AML) cell. In embodiments, the cancer cell is a chronic myeloid leukemia (CML) cell. In embodiments, the cancer cell is a lung cancer cell. In embodiments, the cancer cell is a non-small cell lung cancer (NSCLC) cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is a melanoma cell. In embodiments, the cancer cell is a breast cancer cell. In embodiments, the cancer cell is a colon cancer cell.

RECOMBINANT PROTEIN COMPOSITIONS

[0249] As described above, the light chain variable (VL) domain and the heavy chain variable (VH) domain provided herein including embodiments thereof, may each independently form part of an antibody, an antibody variant, a fragment of an antibody, a fragment of an antibody variant, or a recombinant protein (e.g., a chimeric antigen receptor, bispecific antibody). Provided herein are, *inter alia*, recombinant proteins (e.g., a chimeric antigen receptor, a bispecific antibody),

which include the light chain variable (VL) domain and/or the heavy chain variable (VH) domain as provided herein and are therefore capable of binding IL1RAP and recruiting effector cells to IL1RAP-expressing cells (e.g., LSCs) thereby eliminating the IL1RAP-expressing cells. In embodiments, the recombinant protein is a chimeric antigen receptor (CAR). In embodiments, the recombinant protein is a bispecific antibody.

CHIMERIC ANTIGEN RECEPTOR PROTEINS

[0250] Provided herein are, *inter alia*, recombinant proteins, wherein the recombinant protein is a chimeric antigen receptor. The antibody region of the recombinant protein may include any of the light chain and heavy chain variable domains provided herein including embodiments thereof. The light chain variable (VL) domain and/or the heavy chain variable (VH) domain as provided herein may form part of a chimeric antigen receptor. Thus, in an aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6; and (ii) a transmembrane domain.

[0251] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12; and (ii) a transmembrane domain.

[0252] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24; and (ii) a transmembrane domain.

[0253] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set

forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30; and (ii) a transmembrane domain.

[0254] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36; and (ii) a transmembrane domain.

[0255] The recombinant proteins provided herein may be chimeric antigen receptors including an antibody region wherein the antibody region is a single domain antibody. Thus, in an aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain.

[0256] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and (ii) a transmembrane domain.

[0257] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45; and (ii) a transmembrane domain.

[0258] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (ii) a transmembrane domain.

[0259] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51; and (ii) a transmembrane domain.

[0260] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a

CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54; and (ii) a transmembrane domain.

[0261] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57; and (ii) a transmembrane domain.

[0262] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60; and (ii) a transmembrane domain.

[0263] An "antibody region" as provided herein refers to a monovalent or multivalent protein moiety that forms part of the recombinant protein (e.g., CAR) provided herein including embodiments thereof. A person of ordinary skill in the art will therefore immediately recognize that the antibody region is a protein moiety capable of binding an antigen (epitope). Thus, the antibody region provided herein may include a domain of an antibody (e.g., a light chain variable (VL) domain, a heavy chain variable (VH) domain) or a fragment of an antibody (e.g., Fab). In embodiments, the antibody region is a protein conjugate. A "protein conjugate" as provided herein refers to a construct consisting of more than one polypeptide, wherein the polypeptides are bound together covalently or non-covalently. In embodiments, the protein conjugate includes a Fab moiety (a monovalent Fab) covalently attached to an scFv moiety (a monovalent scFv). In embodiments, the protein conjugate includes a plurality (at least two) Fab moieties. In embodiments, the polypeptides of a protein conjugate are encoded by one nucleic acid molecule. In embodiments, the polypeptides of a protein conjugate are encoded by different nucleic acid molecules. In embodiments, the polypeptides are connected through a linker. In embodiments, the polypeptides are connected through a chemical linker. In embodiments, the antibody region is an scFv. The antibody region may include a light chain variable (VL) domain and/or a heavy chain variable (VH) domain. Thus, in embodiments, the antibody region includes a single domain antibody. In embodiments, the antibody region includes a light chain variable (VL) domain. In embodiments, the antibody region includes a heavy chain variable (VH) domain. In embodiments, the antibody region is a single domain antibody. In embodiments, the single domain antibody includes a heavy chain variable (VH) domain. In embodiments, the single domain antibody includes a light chain variable (VL) domain. In embodiments, the single

domain antibody is a heavy chain variable (VH) domain. In embodiments, the single domain antibody is a light chain variable (VL) domain.

[0264] In an aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and (ii) a transmembrane domain.

[0265] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42; and (ii) a transmembrane domain.

[0266] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45; and (ii) a transmembrane domain.

[0267] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48; and (ii) a transmembrane domain.

[0268] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51; and (ii) a transmembrane domain.

[0269] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54; and (ii) a transmembrane domain.

[0270] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57; and (ii) a transmembrane domain.

[0271] In another aspect is provided a recombinant protein including: (i) an antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60; and (ii) a transmembrane domain.

[0272] A "transmembrane domain" as provided herein refers to a polypeptide forming part of a biological membrane. The transmembrane domain provided herein is capable of spanning a biological membrane (e.g., a cellular membrane) from one side of the membrane through to the other side of the membrane. In embodiments, the transmembrane domain spans from the intracellular side to the extracellular side of a cellular membrane. Transmembrane domains may include non-polar, hydrophobic residues, which anchor the proteins provided herein including embodiments thereof in a biological membrane (e.g., cellular membrane of a T cell). Any transmembrane domain capable of anchoring the proteins provided herein including embodiments thereof are contemplated. Non-limiting examples of transmembrane domains include the transmembrane domains of CD28, CD8, CD4 or CD3-zeta. In embodiments, the transmembrane domain is a CD4 transmembrane domain.

[0273] In embodiments, the transmembrane domain is a CD28 transmembrane domain. The term "CD28 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD28, or variants or homologs thereof that maintain CD28 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD28 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28 transmembrane domain polypeptide. In embodiments, CD28 is the protein as identified by the NCBI sequence reference GI:340545506, homolog or functional fragment thereof.

[0274] In embodiments, the transmembrane domain is a CD8 transmembrane domain. The term "CD8 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD8, or variants or homologs thereof that maintain CD8 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD8 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100,

150 or 200 continuous amino acid portion) compared to a naturally occurring CD8 transmembrane domain polypeptide. In embodiments, CD8 is the protein as identified by the NCBI sequence reference GI:225007534, homolog or functional fragment thereof.

[0275] In embodiments, the transmembrane domain is a CD4 transmembrane domain. The term "CD4 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD4, or variants or homologs thereof that maintain CD4 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD4 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD4 transmembrane domain polypeptide. In embodiments, CD4 is the protein as identified by the NCBI sequence reference GI:303522473, homolog or functional fragment thereof.

[0276] In embodiments, the transmembrane domain is a CD3-zeta (also known as CD247) transmembrane domain. The term " CD3-zeta transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD3-zeta, or variants or homologs thereof that maintain CD3-zeta transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD3-zeta transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3-zeta transmembrane domain polypeptide. In embodiments, CD3-zeta is the protein as identified by the NCBI sequence reference GI:166362721, homolog or functional fragment thereof.

[0277] The recombinant proteins (e.g., chimeric antigen receptors) provided herein may include any of the IL1RAP antibodies or fragments thereof described herein. Thus, the recombinant proteins (e.g., chimeric antigen receptors) may include any of the CDRs, FRs, heavy chain variable domains, or light chain variable domains provided herein. For example, the heavy chain variable domain may include the sequence of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, or SEQ ID NO:71. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, or SEQ ID NO:71. For example, the light chain variable domain

may include the sequence of SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, or SEQ ID NO:80. In embodiments, light chain variable domain is the sequence of SEQ ID NO: 62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, or SEQ ID NO:80.

[0278] Thus, the heavy chain variable domain may include, for example, a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83, and a FR H4 as set forth in SEQ ID NO:84. Further, the light chain variable domain may include, for example, a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87, and a FR L4 as set forth in SEQ ID NO:88.

[0279] The light chain variable domain may include, for example, a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131, and a FR L4 as set forth in SEQ ID NO:132.

[0280] The recombinant proteins provided herein include any of the antibodies provided herein. Thus, the recombinant proteins may bind IL1RAP with a dissociation constant (K_D) of 2.9 M, 35.75 μM, 1.40 M, 249.8 μM, 2.71 mM, 26.95 mM, 3.07 μM, 2.11 μM, 0.85 μM, 1.40 μM or 6.63 μM.

[0281] In embodiments, the recombinant protein is bound to an IL1RAP. In embodiments, the IL1RAP is a human IL1RAP. In embodiments, the IL1RAP forms part of a cell. In embodiments, the IL1RAP is expressed on the surface of the cell. In embodiments, the cell is a cancer cell. In embodiments, the cancer cell is a leukemia stem cell (LSC). In embodiments, the cancer cell is an acute myeloid leukemia (AML) cell. In embodiments, the cancer cell is a chronic myeloid leukemia (CML) cell. In embodiments, the cancer cell is a lung cancer cell. In embodiments, the cancer cell is a non-small cell lung cancer (NSCLC) cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is a melanoma cell. In embodiments, the cancer cell is a breast cancer cell. In embodiments, the cancer cell is a colon cancer cell.

[0282] In embodiments, the antibody region includes an Fc domain. In embodiments, the Fc domain is an IgG4 Fc domain. In embodiments, the antibody region includes an Fc hinge domain. In embodiments, the antibody region includes an IgG4 Fc hinge domain. In embodiments, the antibody region includes a spacer region. In embodiments, the spacer region

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

[0283] In embodiments, the recombinant protein as provided herein, including embodiments thereof, further includes an intracellular co-stimulatory signaling domain. An "intracellular co-stimulatory signaling domain" as provided herein includes amino acid sequences capable of providing co-stimulatory signaling in response to binding of an antigen to the antibody region provided herein including embodiments thereof. In embodiments, the signaling of the co-stimulatory signaling domain results in production of cytokines and proliferation of the T cell expressing the same. In embodiments, the intracellular co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain, a 4-1BB intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling domain, or an OX-40 intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is a 4-1BB intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is a ICOS intracellular co-stimulatory signaling domain. In embodiments, the intracellular co-stimulatory signaling domain is an OX-40 intracellular co-stimulatory signaling domain.

[0284] In embodiments, the recombinant protein as provided herein including embodiments thereof, further includes an intracellular T-cell signaling domain. An "intracellular T-cell signaling domain" as provided herein includes amino acid sequences capable of providing primary signaling in response to binding of an antigen to the antibody region provided herein including embodiments thereof. In embodiments, the signaling of the intracellular T-cell signaling domain results in activation of the T cell expressing the same. In embodiments, the signaling of the intracellular T-cell signaling domain results in proliferation (cell division) of the

T cell expressing the same. In embodiments, the signaling of the intracellular T-cell signaling domain results expression by said T cell of proteins known in the art to characteristic of activated T cell (e.g., CTLA-4, PD-1, CD28, CD69). In embodiments, the intracellular T-cell signaling domain includes the signaling domain of the zeta chain of the human CD3 complex. In embodiments, the intracellular T-cell signaling domain is a CD3 ζ intracellular T-cell signaling domain.

[0285] The term "CTLA-4" as referred to herein includes any of the recombinant or naturally-occurring forms of the cytotoxic T-lymphocyte-associated protein 4 protein, also known as CD152 (cluster of differentiation 152), or variants or homologs thereof that maintain CTLA-4 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CTLA-4). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CTLA-4 protein. In embodiments, the CTLA-4 protein is substantially identical to the protein identified by the UniProt reference number P16410 or a variant or homolog having substantial identity thereto.

[0286] The term "PD-1" as referred to herein includes any of the recombinant or naturally-occurring forms of the Programmed cell death protein 1 protein, also known as CD279 (cluster of differentiation 279), or variants or homologs thereof that maintain PD-1 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to PD-1). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring PD-1 protein. In embodiments, the PD-1 protein is substantially identical to the protein identified by the UniProt reference number Q15116 or a variant or homolog having substantial identity thereto.

[0287] The term "CD28" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 28 protein, or variants or homologs thereof that maintain CD28 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD28). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28 protein. In embodiments, the CD28 protein is substantially identical

to the protein identified by the UniProt reference number P10747 or a variant or homolog having substantial identity thereto.

[0288] The term "CD69" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 69 protein, or variants or homologs thereof that maintain CD69 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD69). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD69 protein. In embodiments, the CD69 protein is substantially identical to the protein identified by the UniProt reference number Q07108 or a variant or homolog having substantial identity thereto.

[0289] The term "4-1BB" as referred to herein includes any of the recombinant or naturally-occurring forms of the 4-1BB protein, also known as tumor necrosis factor receptor superfamily member 9 (TNFRSF9), Cluster of Differentiation 137 (CD137) and induced by lymphocyte activation (ILA), or variants or homologs thereof that maintain 4-1BB activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to 4-1BB). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring EGFR protein. In embodiments, the 4-1BB protein is substantially identical to the protein identified by the UniProt reference number Q07011 or a variant or homolog having substantial identity thereto.

[0290] In embodiments, the recombinant protein as provided herein including embodiments thereof, further includes a self-cleaving peptidyl sequence. In embodiments, the self-cleaving peptidyl linker sequence is a T2A sequence or a 2A sequence. In embodiments, the self-cleaving peptidyl linker sequence is a T2A sequence. In embodiments, the self-cleaving peptidyl linker sequence is a 2A sequence.

[0291] In embodiments, the recombinant protein as provided herein including embodiments thereof, further includes a detectable domain. A “detectable domain” as provided herein is peptide moiety detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, a detectable domain as provided herein may be a protein or other entity which can be made detectable, e.g., by incorporating a radiolabel or

being reactive to an antibody specifically. Any appropriate method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego. In embodiments, the detectable domain is a truncated EGFR (EGFRt) domain. The term "EGFRt" refers to a truncated epidermal growth factor receptor protein lacking intracellular signaling capabilities. As used herein, EGFRt is an inert cell surface molecule which functions as a detectable domain allowing identification of transduced T cells. In embodiments, the recombinant protein forms part of a cell. In embodiments, the recombinant protein forms part of a T cell.

[0292] The term "EGFR" as referred to herein includes any of the recombinant or naturally-occurring forms of the epidermal growth factor receptor protein, also known as ErbB-1 and HER1, or variants or homologs thereof that maintain EGFR activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to EGFR). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring EGFR protein. In embodiments, the EGFR protein is substantially identical to the protein identified by the UniProt reference number P00533 or a variant or homolog having substantial identity thereto.

BISPECIFIC ANTIBODIES

[0293] The recombinant proteins provided herein may, *inter alia*, be chimeric antigen receptors. Thus, the second antibody region may include any of the light chain and/or heavy chain variable domains provided herein including embodiments thereof. The light chain variable (VL) domain and/or the heavy chain variable (VH) domain as provided herein may form part of a bispecific antibody. Thus, in another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2, and a CDR H3 as set forth in SEQ ID NO:3; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5 and a CDR L3 as set forth in SEQ ID NO:6.

[0294] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8, and a CDR H3 as set forth in SEQ ID NO:9; and (b) a light chain variable

domain including a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11 and a CDR L3 as set forth in SEQ ID NO:12.

[0295] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20, and a CDR H3 as set forth in SEQ ID NO:21; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23 and a CDR L3 as set forth in SEQ ID NO:24.

[0296] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID NO:27; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30.

[0297] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a heavy chain variable domain a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID NO:33; and (b) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36.

[0298] The term “effector cell ligand” as provided herein refers to a cell surface molecule expressed on an effector cell of the immune system (e.g., a cytotoxic T cell, a helper T cell, a B cell, a natural killer cell). Upon binding of the first antibody region to the effector cell ligand expressed on the effector cell, the effector cell is activated and able to exert its function (e.g., selective killing or eradication of malignant, infected or otherwise unhealthy cells). In embodiments, the effector cell ligand is a CD3 protein. In embodiments, the effector cell ligand is a CD16 protein. In embodiments, the effector cell ligand is a CD32 protein. In embodiments, the effector cell ligand is a NKp46 protein. The first antibody region as provided herein may be an antibody, an antibody variant, a fragment of an antibody or a fragment of an antibody variant.

[0299] A "CD3 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 3 (CD3) proteins or variants or homologs thereof that comprise the CD3 complex that mediates signal transduction and maintains CD3

complex activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD3 complex). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3 proteins in the CD3 complex.

[0300] A "CD16 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 16 (CD16) protein, also known as low affinity immunoglobulin gamma Fc region receptor III-A, or variants or homologs thereof that maintain CD16 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD16). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD16 protein. In embodiments, the CD16 protein is substantially identical to the protein identified by the UniProt reference number P08637 or a variant or homolog having substantial identity thereto.

[0301] A "CD32 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the Cluster of Differentiation 32 (CD32) protein, also known as low affinity immunoglobulin gamma Fc region receptor II-A, or variants or homologs thereof that maintain CD32 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD32). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD32 protein. In embodiments, the CD32 protein is substantially identical to the protein identified by the UniProt reference number P12318 or a variant or homolog having substantial identity thereto.

[0302] A "NKp46 protein" as referred to herein includes any of the recombinant or naturally-occurring forms of the NKp46 protein, also known as natural cytotoxicity triggering receptor 1, or variants or homologs thereof that maintain NKp46 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to NKp46). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring NKp46 protein. In

embodiments, the NKp46 protein is substantially identical to the protein identified by the UniProt reference number O76036 or a variant or homolog having substantial identity thereto.

[0303] The recombinant proteins (e.g., bispecific antibody) provided herein may include any of the IL1RAP antibodies or fragments thereof described herein. Thus, the recombinant protein (e.g., bispecific antibody) may include any of the CDRs, FRs, heavy chain variable domains, or light chain variable domains provided herein. For example, the heavy chain variable domain may include the sequence of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, or SEQ ID NO:71. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, or SEQ ID NO:71. For example, the light chain variable domain may include the sequence of SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, or SEQ ID NO:80. In embodiments, light chain variable domain is the sequence of SEQ ID NO: 62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, or SEQ ID NO:80.

[0304] The heavy chain variable domain of the recombinant protein (e.g., bispecific antibody) provided herein may include any of the CDRs or FRs provided herein. Thus, the heavy chain variable domain may include, for example, a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83, and a FR H4 as set forth in SEQ ID NO:84. The light chain variable domain of the recombinant protein (e.g., bispecific antibody) provided herein may include any of the CDRs or FRs provided herein. For example, the light chain variable domain may include, for example, a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87, and a FR L4 as set forth in SEQ ID NO:88. The light chain variable domain may include, for example, a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131, and a FR L4 as set forth in SEQ ID NO:132.

[0305] In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:61. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:62. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:63. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:64. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:67. In

embodiments, the light chain variable domain is the sequence of SEQ ID NO:68. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:69. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:70. In embodiments, the heavy chain variable domain is the sequence of SEQ ID NO:71. In embodiments, the light chain variable domain is the sequence of SEQ ID NO:72.

[0306] In embodiments, the heavy chain variable domain includes a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84. In embodiments, the light chain variable domain includes a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

[0307] In embodiments, the recombinant protein (bispecific antibody) includes a tryptophan at a position corresponding to Kabat position 366. In embodiments, the recombinant protein (bispecific antibody) includes a serine at a position corresponding to Kabat position 366. In embodiments, the recombinant protein (bispecific antibody) includes an alanine at a position corresponding to Kabat position 368. In embodiments, the recombinant protein (bispecific antibody) includes a valine at a position corresponding to Kabat position 407. In embodiments, the recombinant protein (bispecific antibody) includes an alanine at a position corresponding to Kabat position 234. In embodiments, the recombinant protein (bispecific antibody) includes an alanine at a position corresponding to Kabat position 235.

[0308] In embodiments, the first antibody region is a first Fab' fragment or the second antibody region is a second Fab' fragment. In embodiments, the first antibody region is a single chain variable fragment (scFv) or the second antibody region is a second single chain variable fragment (scFv).

[0309] The recombinant proteins provided herein may be bispecific antibodies including a second antibody region wherein the second antibody region is a single domain antibody. The second antibody region may include a light chain variable (VL) domain or a heavy chain variable (VH) domain. In embodiments, the second antibody region includes a single domain antibody. In embodiments, the second antibody region includes a light chain variable (VL) domain. In embodiments, the second antibody region includes a heavy chain variable (VH) domain. In embodiments, the second antibody region is a single domain antibody. In embodiments, the single domain antibody includes a heavy chain variable (VH) domain. In embodiments, the single domain antibody includes a light chain variable (VL) domain. In embodiments, the single

domain antibody is a heavy chain variable (VH) domain. In embodiments, the single domain antibody is a light chain variable (VL) domain.

[0310] Thus, in another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39.

[0311] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42.

[0312] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44 and a CDR L3 as set forth in SEQ ID NO:45.

[0313] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48.

[0314] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50 and a CDR L3 as set forth in SEQ ID NO:51.

[0315] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53 and a CDR L3 as set forth in SEQ ID NO:54.

[0316] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56 and a CDR L3 as set forth in SEQ ID NO:57.

[0317] In another aspect is provided a recombinant protein including: (i) a first antibody region capable of binding an effector cell ligand; and (ii) a second antibody region, including: (a) a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59 and a CDR L3 as set forth in SEQ ID NO:60.

[0318] In embodiments, the second antibody region is bound to an IL1RAP. In embodiments, the IL1RAP is a human IL1RAP. In embodiments, the IL1RAP forms part of a cell. In embodiments, the IL1RAP is expressed on the surface of the cell.

[0319] In embodiments, the cell is a cancer cell. In embodiments, the cancer cell is a leukemia stem cell (LSC). In embodiments, the cancer cell is an acute myeloid leukemia (AML) cell.

NUCLEIC ACID COMPOSITIONS

[0320] The compositions provided herein include nuceic acid molecules encoding the anti-IL1RAP antibodies and recombinant proteins provided herein including embodiments thereof. Thus, in an aspect, an isolated nucleic acid encoding an antibody as provided herein including embodiments thereof is provided.

[0321] In another aspect, an isolated nucleic acid encoding a recombinant protein as provided herein, including embodiments thereof, is provided.

PHARMACEUTICAL COMPOSITIONS

[0322] The compositions provided herein include pharmaceutical compositions including the anti IL1RAP antibodies and recombinant proteins provided herein including embodiments thereof. Thus, in an aspect is provided a pharmaceutical composition including a therapeutically effective amount of an antibody as provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

[0323] In another aspect is provided a pharmaceutical composition including a therapeutically effective amount of a recombinant protein as provided herein, including embodiments thereof, and a pharmaceutically acceptable excipient.

METHODS OF TREATMENT

[0324] The compositions (e.g., the anti IL1RAP antibodies and recombinant proteins) provided herein, including embodiments thereof, are contemplated as providing effective treatments for diseases such as cancer (e.g., leukemia [e.g., AML]). Thus, in an aspect is provided a method of treating cancer in a subject in need thereof, the method including administering to a subject a

therapeutically effective amount of an antibody as provided herein including embodiments thereof, thereby treating cancer in the subject.

[0325] In another aspect is provided a method of treating cancer in a subject in need thereof, the method including administering to a subject a therapeutically effective amount of a recombinant protein as described herein, including embodiments thereof, thereby treating cancer in the subject. In embodiments, the cancer is leukemia. In embodiments, the cancer is acute myeloid leukemia. In embodiments, the cancer is chronic myeloid leukemia (CML). In embodiments, the cancer is lung cancer. In embodiments, the cancer is non-small cell lung cancer (NSCLC). In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is melanoma. In embodiments, the cancer is breast cancer. In embodiments, the cancer is colon cancer. In embodiments, the method further includes administering to the subject a second therapeutic agent.

[0326] In embodiments, the antibody is administered at an amount from about 0.01nM to about 10nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 10nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 10nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 10nM. In embodiments, the antibody is administered at an amount from about 1nM to about 10nM. In embodiments, the antibody is administered at an amount from about 2nM to about 10nM. In embodiments, the antibody is administered at an amount from about 4nM to about 10nM. In embodiments, the antibody is administered at an amount from about 6nM to about 10nM. In embodiments, the antibody is administered at an amount from about 4nM to about 10nM. In embodiments, the antibody is administered at an amount from about 8nM to about 10nM. In embodiments, the antibody is administered at an amount of about 0.01 nM, 0.05 nM, 0.1 nM, 0.5 nM, 1 nM, 2 nM, 2 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM or 10 nM.

[0327] In embodiments, the antibody is administered at an amount from 0.01nM to 10nM. In embodiments, the antibody is administered at an amount from 0.05nM to 10nM. In embodiments, the antibody is administered at an amount from 0.1nM to 10nM. In embodiments, the antibody is administered at an amount from 0.5nM to 10nM. In embodiments, the antibody is administered at an amount from 1nM to 10nM. In embodiments, the antibody is administered at an amount from 2nM to 10nM. In embodiments, the antibody is administered at an amount from 4nM to 10nM. In embodiments, the antibody is administered at an amount from 6nM to 10nM. In embodiments, the antibody is administered at an amount from 4nM to 10nM. In

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

[0328] In embodiments, the antibody is administered at an amount from about 0.01nM to about 8nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 8nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 8nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 8nM. In embodiments, the antibody is administered at an amount from about 1nM to about 8nM. In embodiments, the antibody is administered at an amount from about 2nM to about 8nM. In embodiments, the antibody is administered at an amount from about 4nM to about 8nM. In embodiments, the antibody is administered at an amount from about 6nM to about 8nM. In embodiments, the antibody is administered at an amount from about 4nM to about 8nM.

[0329] In embodiments, the antibody is administered at an amount from 0.01nM to 8nM. In embodiments, the antibody is administered at an amount from 0.05nM to 8nM. In embodiments, the antibody is administered at an amount from 0.1nM to 8nM. In embodiments, the antibody is administered at an amount from 0.5nM to 8nM. In embodiments, the antibody is administered at an amount from 1nM to 8nM. In embodiments, the antibody is administered at an amount from 2nM to 8nM. In embodiments, the antibody is administered at an amount from 4nM to 8nM. In embodiments, the antibody is administered at an amount from 6nM to 8nM. In embodiments, the antibody is administered at an amount from 4nM to 8nM.

[0330] In embodiments, the antibody is administered at an amount from about 0.01nM to about 6nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 6nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 6nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 8nM. In embodiments, the antibody is administered at an amount from about 1nM to about 6nM. In embodiments, the antibody is administered at an amount from about 2nM to about 6nM. In embodiments, the antibody is administered at an amount from about 4nM to about 6nM.

[0331] In embodiments, the antibody is administered at an amount from 0.01nM to 6nM. In embodiments, the antibody is administered at an amount from 0.05nM to 6nM. In embodiments, the antibody is administered at an amount from 0.1nM to 6nM. In embodiments, the antibody is

administered at an amount from 0.5nM to 6nM. In embodiments, the antibody is administered at an amount from 1nM to 6nM. In embodiments, the antibody is administered at an amount from 2nM to 6nM. In embodiments, the antibody is administered at an amount from 4nM to 6nM.

[0332] In embodiments, the antibody is administered at an amount from about 0.01nM to about 4nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 4nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 4nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 4nM. In embodiments, the antibody is administered at an amount from about 1nM to about 4nM. In embodiments, the antibody is administered at an amount from about 2nM to about 4nM.

[0333] In embodiments, the antibody is administered at an amount from 0.01nM to 4nM. In embodiments, the antibody is administered at an amount from 0.05nM to 4nM. In embodiments, the antibody is administered at an amount from 0.1nM to 4nM. In embodiments, the antibody is administered at an amount from 0.5nM to 4nM. In embodiments, the antibody is administered at an amount from 1nM to 4nM. In embodiments, the antibody is administered at an amount from 2nM to 4nM.

[0334] In embodiments, the antibody is administered at an amount from about 0.01nM to about 2nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 2nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 2nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 2nM. In embodiments, the antibody is administered at an amount from about 1nM to about 2nM.

[0335] In embodiments, the antibody is administered at an amount from 0.01nM to 2nM. In embodiments, the antibody is administered at an amount from 0.05nM to 2nM. In embodiments, the antibody is administered at an amount from 0.1nM to 2nM. In embodiments, the antibody is administered at an amount from 0.5nM to 2nM. In embodiments, the antibody is administered at an amount from 1nM to 2nM.

[0336] In embodiments, the antibody is administered at an amount from about 0.01nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.05nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.1nM to about 1nM. In embodiments, the antibody is administered at an amount from about 0.5nM to about 1nM.

[0337] In embodiments, the antibody is administered at an amount from 0.01nM to 1nM. In embodiments, the antibody is administered at an amount from 0.05nM to 1nM. In embodiments, the antibody is administered at an amount from 0.1nM to 1nM. In embodiments, the antibody is administered at an amount from 0.5nM to 1nM.

[0338] In embodiments, the antibody is administered at an amount of about 3.15nM. In embodiments, the antibody is administered at an amount of 3.15nM. In embodiments, the antibody is administered at an amount of about 1.05nM. In embodiments, the antibody is administered at an amount of 1.05nM.

[0339] It is understood that the recombinant protein (i.e., the bispecific antibody or the chimeric antigen receptor) provided herein including embodiments thereof may be administered at any of the concentrations described herein for the administration of the antibody (e.g., 0.01nM-10nM).

[0340] In embodiments, the antibody is administered at an amount from about 10 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 20 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 30 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 40 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 50 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 60 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 70 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 80 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 90 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 100 μg to about 500 μg.

[0341] In embodiments, the antibody is administered at an amount from about 110 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 120 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 130 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 140 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 150 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 160 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 170 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 180 μg to about

500 μg. In embodiments, the antibody is administered at an amount from about 190 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 200 μg to about 500 μg.

[0342] In embodiments, the antibody is administered at an amount from about 210 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 220 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 230 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 240 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 250 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 260 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 270 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 280 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 290 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 300 μg to about 500 μg.

[0343] In embodiments, the antibody is administered at an amount from about 310 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 320 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 330 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 340 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 350 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 360 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 370 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 380 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 390 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 400 μg to about 500 μg.

[0344] In embodiments, the antibody is administered at an amount from about 410 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 420 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 430 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 440 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 450 μg to about

500 μg. In embodiments, the antibody is administered at an amount from about 460 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 470 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 480 μg to about 500 μg. In embodiments, the antibody is administered at an amount from about 490 μg to about 500 μg.

[0345] In embodiments, the antibody is administered at an amount from about 10 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 20 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 30 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 40 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 50 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 60 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 70 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 80 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 90 μg to about 400 μg. In embodiments, the antibody is administered at an amount from about 100 μg to about 400 μg.

[0346] In embodiments, the antibody is administered at an amount from about 10 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 20 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 30 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 40 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 50 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 60 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 70 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 80 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 90 μg to about 300 μg. In embodiments, the antibody is administered at an amount from about 100 μg to about 300 μg.

[0347] In embodiments, the antibody is administered at an amount from about 10 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 20 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 30 μg to about

200 μg. In embodiments, the antibody is administered at an amount from about 40 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 50 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 60 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 70 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 80 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 90 μg to about 200 μg. In embodiments, the antibody is administered at an amount from about 100 μg to about 200 μg.

[0348] In embodiments, the antibody is administered at an amount from about 10 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 20 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 30 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 40 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 50 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 60 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 70 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 80 μg to about 100 μg. In embodiments, the antibody is administered at an amount from about 90 μg to about 100 μg.

[0349] In embodiments, the antibody is administered at an amount of about 10 μg, 20 μg, 30 μg, 40 μg, 50 μg, 60 μg, 70 μg, 80 μg, 90 μg, 100 μg, 110 μg, 120 μg, 130 μg, 140 μg, 150 μg, 160 μg, 170 μg, 180 μg, 190 μg, 200 μg, 210 μg, 220 μg, 230 μg, 240 μg, 250 μg, 260 μg, 270 μg, 280 μg, 290 μg, 300 μg, 310 μg, 320 μg, 330 μg, 340 μg, 350 μg, 360 μg, 370 μg, 380 μg, 390 μg, 400 μg, 410 μg, 420 μg, 430 μg, 440 μg, 450 μg, 460 μg, 470 μg, 480 μg, 490 μg, or 500 μg.

[0350] In embodiments, the antibody is administered at an amount of 10 μg, 20 μg, 30 μg, 40 μg, 50 μg, 60 μg, 70 μg, 80 μg, 90 μg, 100 μg, 110 μg, 120 μg, 130 μg, 140 μg, 150 μg, 160 μg, 170 μg, 180 μg, 190 μg, 200 μg, 210 μg, 220 μg, 230 μg, 240 μg, 250 μg, 260 μg, 270 μg, 280 μg, 290 μg, 300 μg, 310 μg, 320 μg, 330 μg, 340 μg, 350 μg, 360 μg, 370 μg, 380 μg, 390 μg, 400 μg, 410 μg, 420 μg, 430 μg, 440 μg, 450 μg, 460 μg, 470 μg, 480 μg, 490 μg, or 500 μg.

[0351] It is understood that the recombinant protein (i.e., the bispecific antibody or the chimeric antigen receptor) provided herein including embodiments thereof may be administered at any of the concentrations described herein for the administration of the antibody (e.g., 10 μg - 500 μg).

[0352] In embodiments, the recombinant protein or antibody is administered at an amount of about 200μg. In embodiments, the recombinant protein or antibody is administered at an amount of 200μg.

METHODS OF INHIBITING CELL PROLIFERATION

[0353] The compositions provided herein, including embodiments thereof, are further contemplated for inhibiting cell proliferation. Thus, in an aspect is provided a method of inhibiting proliferation of a cell, the method including: (i) contacting a cell with an anti-IL1RAP antibody as provided herein including embodiments thereof, or a recombinant protein as provided herein including embodiments thereof, thereby forming a contacted cell; and (ii) allowing the anti-IL1RAP antibody, the recombinant protein as provided herein including embodiments thereof to bind an IL1RAP on the contacted cell, thereby inhibiting proliferation of the cell. In embodiments, the cell is a cancer cell. In embodiments, the cell is a leukemia stem cell (LSC). In embodiments, the cancer cell is an acute myeloid leukemia (AML) cell. In embodiments, the cancer cell is a chronic myeloid leukemia (CML) cell. In embodiments, the cancer cell is a lung cancer cell. In embodiments, the cancer cell is a non-small cell lung cancer (NSCLC) cell. In embodiments, the cancer cell is a pancreatic cancer cell. In embodiments, the cancer cell is a melanoma cell. In embodiments, the cancer cell is a breast cancer cell. In embodiments, the cancer cell is a colon cancer cell.

[0354] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

EXAMPLE 1

[0355] Applicants showed that interleukin-1 receptor accessory protein (IL1RAP) is exclusively expressed on human AML blasts, including leukemia stem cell (LSC)-enriched

subpopulations, but not on normal hematopoietic cells including hematopoietic stem cells (HSCs), thereby providing a better target for AML than current immunotherapeutic targets used in clinical trials (i.e. CD33 and CD123), which are also expressed on normal HSCs. Therefore, Applicants designed an anti-IL1RAP/CD3 T cell-dependent bispecific antibody to target leukemic cells and LSCs while sparing normal HSCs. In vitro functional analyses demonstrated the IL1RAP/CD3 bispecific antibody in combination with T cells not only depleted AML cell lines, but also effectively eliminated leukemic cells including LSCs from different subtypes of AML patient samples. In vivo treatment with IL1RAP/CD3 bispecific antibody plus T cells significantly reduced leukemic burden and prolonged survival in NSG-SGM3 mice transplanted with AML MV4-11 cells, and also generated prolonged survival in primary and secondary recipient NSG-SGM3 mice transplanted with human AML blasts, as compared with treatment with IgG or T cells only. Altogether, these results determined IL1RAP/CD3 bispecific antibody plus T cells as a novel and effective immunotherapeutic approach in the treatment of AML.

EXAMPLE 2: GENERATION AND SELECTION OF THE ANTIBODY

[0356] A human phage display library was constructed using purified peripheral blood mononuclear cells (PBMCs) from ten healthy donors, as described previously. Twelve unique clones were identified as IL1RAP-binding clones. The gene sequences of single-chain fragment variables (scFv) of these clones were ligated individually into a scFv-FC expression vector (TEGX-SCblue, Antibody Design). Antibodies were expressed in transient expi293 cells, and purified by protein A affinity chromatography. The IL1RAP EC50 (Table 2) of these antibodies was determined by ELISA and antibody-dependent T cell-mediated cytotoxicity (ADCC). The antibody with the highest binding affinity (i.e., lowest EC_{50}) was selected for constructing bispecific antibody.

[0357] Table 2. Half maximal effective concentration (EC_{50}) studies of exemplary IL1RAP antibodies and fragments thereof provided herein.

IL1RAP Antibody Clone ID	EC_{50}
1A1	2.89884 M
1A4	35.75 uM
1A5	1.40188 M
1A6	249.8 uM
1A11	2.71 mM
1A12	26.95 mM

IL1RAP Antibody Clone ID	EC_{50}
1B8	3.072 uM
1E12	2.111 uM
2E12	0.854 uM
D1A4	1.404 uM
D1F6	6.6298 uM
1D5	52.91 pM

EXAMPLE 3: T CELL DEPENDENT CELLULAR CYTOTOXICITY (TDCC) LONG TERM KILL ASSAY

[0358] To determine T cell mediated killing of AML cell lines and AML primary cells, different concentrations of anti-IL1RAP antibodies combined with purified T cells from healthy donors or AML patient samples were incubated with $1x10^4$ target cells per well at various effector-to-target (E:T) ratios. 48 hours after incubation, the cells were stained with antibodies, $CD34^+CD45^{dim}$ or $CD33^+CD45^{dim}CD14^-$ cells were designated as leukemia cells, $CD45^+CD4^+$ or $CD45^+CD8^+$ as T cells, and $CD25^+$ or $CD69^+$ as activated T cells. Numbers of leukemia cells and T cells were counted and cytotoxicity was calculated as: cytotoxicity (%) = 100 x (1 – treated target cells/control target cells).

[0359] Table 3. TDCC studies using recombinant proteins (IgG antibodies) provided herein.

ID	cell lysis%-1	cell lysis%-2	cell lysis%-3	cell lysis%-average
H14	37.92	45.03	45.97	42.97
1A1	24.52	16.4	20.49	20.47
1A4	24.63	22.95	22.75	23.44
1A5	24	26.14	25.89	25.34
1A6	28.61	22.12	26.82	25.85
1A11	25.08	21.44	25.58	24.03
1A12	16.49	12.47	13.8	14.25
1B8	34.57	30.17	34.42	33.05
1E12	39.63	36.3	39.72	38.55
2E12	27.2	28.7	23.71	26.54
D1A4	29.78	26.37	24.54	26.90
D1F6	23.23	27.02	31.72	27.32
1D5	48.9	42.56	48.27	46.58
Control	16.7	14.04	17.57	16.10
1C7	N/A	N/A	N/A	N/A

ID	cell lysis%-1	cell lysis%-2	cell lysis%-3	cell lysis%-average
1A7	N/A	N/A	N/A	N/A

EXAMPLE 4: CDR SEQUENCES OF THE HEAVY CHAIN VARIABLE DOMAINS AND LIGHT CHAIN VARIABLE DOMAINS FOR ANTI-IL1RAP ANTIBODY CLONES

[0360] Table 4. CDR sequences of the heavy chain variable domains and light chain variable domains of anti-IL1RAP antibodies provided herein.

SEQ ID NO.	Sequence	CDR	IL1RAP Antibody Clone ID
1	GFPFNMYG	CDR H1	D1A4
2	ISAYNGRT	CDR H2	D1A4
3	ARSGKQQLGSAQPLDS	CDR H3	D1A4
4	SSNIGSNT	CDR L1	D1A4
5	SNN	CDR L2	D1A4
6	AAWDDSLNGL	CDR L3	D1A4
7	GYRFTDYW	CDR H1	1C7
8	IYLGDSET	CDR H2	1C7
9	ARGFAYGDWYFDL	CDR H3	1C7
10	QGIAGW	CDR L1	1C7
11	AAS	CDR L2	1C7
12	QQSSSTPHT	CDR L3	1C7
13	GYSFSSHW	CDR H1	ID5
14	IYPGDSDT	CDR H2	ID5
15	ARGELPGEAYYFD	CDR H3	ID5
16	QSLLHSNGYKY	CDR L1	ID5
17	LGS	CDR L2	ID5
18	MQALQTPLT	CDR L3	ID5
19	GFTFSRYW	CDR H1	2E12
20	IHTDGSSI	CDR H2	2E12
21	ARDIGGGYSYGSVDY	CDR H3	2E12
22	NIGSKS	CDR L1	2E12
23	GGG	CDR L2	2E12
24	QVWDGSTDHYI	CDR L3	2E12
25	DYTFTSYG	CDR H1	1A7
26	ISAYNGNT	CDR H2	1A7
27	ARVHPRHIIGAGYFDY	CDR H3	1A7
28	SSDVGVYDY	CDR L1	1A7
29	DVS	CDR L2	1A7
30	CAYTFVFGT	CDR L3	1A7

SEQ ID NO.	Sequence	CDR	IL1RAP Antibody Clone ID
31	GYTFTSYY	CDR H1	1B8
32	INPSGGST	CDR H2	1B8
33	AIFAPPDYGDYVDAFDI	CDR H3	1B8
34	QSLLHSNGYNY	CDR L1	1B8
35	LGS	CDR L2	1B8
36	MQALQTPRGTKVE	CDR L3	1B8
37	SGDIGFYNY	CDR L1	1A12
38	EVN	CDR L2	1A12
39	VSYGISDTVL	CDR L3	1A12
40	SGDIGFYNY	CDR L1	1A5
41	EVN	CDR L2	1A5
42	VSYGISDTVL	CDR L3	1A5
43	ISNIGSNA	CDR L1	1A6
44	SDN	CDR L2	1A6
45	AAWDDSLNGNV	CDR L3	1A6
46	SSNIGINA	CDR L1	1A1
47	SND	CDR L2	1A1
48	AAWDDSLNANV	CDR L3	1A1
49	SSNIGSNP	CDR L1	1A4
50	NTG	CDR L2	1A4
51	AAWDDRLNGNV	CDR L3	1A4
52	QSVNNF	CDR L1	1A11
53	AVS	CDR L2	1A11
54	QQSSSAPNT	CDR L3	1A11
55	SGSVGEYY	CDR L1	1E12
56	EDY	CDR L2	1E12
57	QSYDGSNFV	CDR L3	1E12
58	GSNIGINP	CDR L1	D1F6
59	SDD	CDR L2	D1F6
60	AAWDDSLNGPGNV	CDR L3	D1F6

EXAMPLE 5: SEQUENCES OF THE HEAVY CHAIN VARIABLE DOMAINS AND LIGHT CHAIN VARIABLE DOMAINS FOR ANTI-IL1RAP ANTIBODY CLONES

[0361] Table 5. Sequences of heavy variable chain domains and light chain variable domains of IL1RAP antibodies provided herein.

SEQ ID NO.	Sequence	Fragment	Clone
61	PGPLVQSGAEVKKPGASVKVSCTTSGFPFNMYGFNWVRQAPGQ GLEWMGWISAYNGRTNYAQKFQGRVTMTTDTSTSTSYVELESL TSDDTAVYYCARSGKQQLGSAQPLDSWGQGTLIIVSS	VH	D1A4
62	NFMLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGT APKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEAD YYCAAWDDSLNGLFGGGTKLTVL	VL	D1A4
63	QVQLVQSGAEVKKPGESLKISCKASGYRFTDYWIGWVRQMPGK GLEWMGIIYLGDSETIYSPSFQGQVTISADKSISTAFLQLTSL KASDSAIYSCARGFAYGDWYFDLWGRGTLVIVS	VH	1C7
64	NIQMTQSPSSVSASVGDRVTITCRASQGIAGWLAWYQQKPGKR PNLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQSSSTPHTFGQGTKLEIK	VL	1C7
65	QVQLVQSGAEVKKPGESLKISCKGSGYSFSSHWIGWVRQMPGK GLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSL KASDTAMYYCARGELPGEAYYFDNWGQGTLVTVSS	VH	1D5
66	EIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYKYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQALQTPLTFGGGTKVEIK	VL	1D5
67	PGAAAGVGGGLVQPGGSLRLSCEASGFTFSRYWMHWVRQAPGK GLVWVSRIHTDGSSISYADSVKGRFTISRDNAKNTLYLQMNSL RAEDTAVYYCARDIGGGYSYGSVDYWGQGTLVTVSS	VH	2E12
68	QPVLTQSPSVSVAPGKTTRITCGGDNIGSKSVHWFQQKPGQAP VLVVFGGGDRPSGIPERFSGSNSGNTATLIISGVEGGDEADYY CQVWDGSTDHYIFGAGTMVTVL	VL	2E12
69	QVKLVESGPEVKKPGASVKVSCKASDYTFTSYGISWVRLAPGQ GLEWMGWISAYNGNTNYPQKLQGRVTVTTDTSTSTAYMELRSL TSDDTAVYYCARVHPRHIIGAGYFDYWGQGTMVTVSS	VH	1A7
70	LPVLTQPRSVAGSPGQSVTISCTGSSSDVGVYDYVSWYQQHPG KVPRLMIYDVSKRPPGVPDRFSGSRSGNTASLTISGLQTEDEA DYYCAYTFVFGTGTNVSVL	VL	1A7

SEQ ID NO.	Sequence	Fragment	Clone
71	PSFVVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVPMTRDTSTSTVYLELNSL RSEDTAVYYCAIFAPPDYGDYVDAFDIWGQGTLIIVSS	VH	1B8
72	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQALQTPRGTKVEIK	VL	1B8
73	QSALNQPPSASGSPGQAVTISCTGSSGDIGFYNYVSWYQQHPG KAPKLLIFEVNQRPSGVPDRFSGSRSGSTASLTVSGLQADDEA DYYCVSYGISDTVLFGGGTRLTVL	VL	1A12
74	QSALTQPPSASGSPGQAVTISCTGSSGDIGFYNYVSWYQQHPG KAPKLLIFEVNQRPSGVPDRFSGSKSGTTASLTVSGLQADDEA HYYCVSYGISDTVLFGGGTKLTVL	VL	1A5
75	QSVLTQPPSASGTPGQRVTFSCSGSISNIGSNAVNWYQQLPGT APSLLIYSDNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEAD YYCAAWDDSLNGNVFGTGTKVTVL	VL	1A6
76	QSVLTQPPSVSGAPGQRVTISCSGSSSNIGINAVNWYQQVPGT APKLLMYSNDQRPSGVPARFSGSKSGTSASLAISGLQSEDEAD YYCAAWDDSLNANVFGTGTKVTVL	VL	1A1
77	QSVLTQSPSASGTPGQRVTISCSGSSSNIGSNPVNWYQQLPGT VPTLLIFNTGQRPSGVPDRFSGSRSGTSASLAISGLQSEDEAD YYCAAWDDRLNGNVFGTGTKVTVL	VL	1A4
78	DIVMTQSPSSLSASVGDRVTITCRASQSVNNFLNWYQHRPGKA PKLLIYAVSSLQSGVPSRFSGSGFGTDFTLTISSLQPEDFATY YCQQSSSAPNTFGQGTKLEIK	VL	1A11
79	NFMLTQPHSVSESPGKTVTISCTRSSGSVGEYYVQWYQHRPGS IPTFVIYEDYKRPSGVPVRFSGSVDSASNSATLIISGLIPEDE ADYYCQSYDGSNFVFGTGTRVTVL	VL	1E12
80	QAVLTQPPSASGTPGQRVTISCSGSGSNIGINPVNWYQQLPGT APKLLIYSDDQRPSGVPDRFSGSKSGTSASLAISGLQSEDEAD YYCAAWDDSLNGPGNVFGTGTKVTVL	VL	D1F6

EXAMPLE 6: FRAMEWORK SEQUENCES OF HEAVY CHAIN VARIABLE DOMAINS AND LIGHT CHAIN VARIABLE DOMAINS FOR ANTI-IL1RAP ANTIBODY CLONES

[0362] Table 6. The framework sequences of heavy chain variable domains and light chain variable domains of IL1RAP antibodies provided herein

SEQ ID NO.	Sequence	FR	Clone
81	PGPLVQSGAEVKKPGASVKVSCTTS	FR H1	D1A4
82	FNWVRQAPGQGLEWMGW	FR H2	D1A4
83	NYAQKFQGRVTMTTDTSTSTSYVELESLTSDDTAVYYC	FR H3	D1A4
84	WGQGTLIIVSS	FR H4	D1A4
85	NFMLTQPPSASGTPGQRVTISCSGS	FR L1	D1A4
86	VNWYQQLPGTAPKLLIY	FR L2	D1A4
87	QRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC	FR L3	D1A4
88	FGGGTKLTVL	FR L4	D1A4
89	QVQLVQSGAEVKKPGESLKISCKAS	FR H1	1C7
90	IGWVRQMPGKGLEWMGI	FR H2	1C7
91	IYSPSFQGQVTISADKSISTAFLQLTSLKASDSAIYSC	FR H3	1C7
92	WGRGTLVIVS	FR H4	1C7
93	NIQMTQSPSSVSASVGDRVTITCRAS	FR L1	1C7
94	LAWYQQKPGKRPNLLIY	FR L2	1C7
95	TLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	FR L3	1C7
96	FGQGTKLEIK	FR L4	1C7
97	QVQLVQSGAEVKKPGESLKISCKGS	FR H1	1D5
98	IGWVRQMPGKGLEWMGI	FR H2	1D5
99	RYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC	FR H3	1D5
100	NWGQGTLVTVSS	FR H4	1D5
101	EIVMTQSPLSLPVTPGEPASISCRSS	FR L1	1D5
102	LDWYLQKPGQSPQLLIY	FR L2	1D5
103	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	FR L3	1D5
104	FGGGTKVEIK	FR L4	1D5
105	PGAAAGVGGGLVQPGGSLRLSCEAS	FR H1	2E12

SEQ ID NO.	Sequence	FR	Clone
106	MHWVRQAPGKGLVWVSR	FR H2	2E12
107	SYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYC	FR H3	2E12
108	WGQGTLVTVSS	FR H4	2E12
109	QPVLTQSPSVSVAPGKTTRITCGGD	FR L1	2E12
110	VHWFQQKPGQAPVLVVF	FR L2	2E12
111	DRPSGIPERFSGSNSGNTATLIISGVEGGDEADYYC	FR L3	2E12
112	FGAGTMVTVL	FR L4	2E12
113	QVKLVESGPEVKKPGASVKVSCKAS	FR H1	1A7
114	ISWVRLAPGQGLEWMGW	FR H2	1A7
115	NYPQKLQGRVTVTTDTSTSTAYMELRSLTSDDTAVYYC	FR H3	1A7
116	WGQGTMVTVSS	FR H4	1A7
117	LPVLTQPRSVAGSPGQSVTISCTGS	FR L1	1A7
118	VSWYQQHPGKVPRLMIY	FR L2	1A7
119	KRPPGVPDRFSGSRSGNTASLTISGLQTEDEADYY	FR L3	1A7
120	GTNVSVL	FR L4	1A7
121	PSFVVQSGAEVKKPGASVKVSCKAS	FR H1	1B8
122	MHWVRQAPGQGLEWMGI	FR H2	1B8
123	SYAQKFQGRVPMTRDTSTSTVYLELNSLRSEDTAVYYC	FR H3	1B8
124	WGQGTLIIVSS	FR H4	1B8
125	DVVMTQSPLSLPVTPGEPASISCRSS	FR L1	1B8
126	LDWYLQKPGQSPQLLIY	FR L2	1B8
127	NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	FR L3	1B8
128	IK	FR L4	1B8
129	QSALNQPPSASGSPGQAVTISCTGS	FR L1	1A12
130	VSWYQQHPGKAPKLLIF	FR L2	1A12
131	QRPSGVPDRFSGSRSGSTASLTVSGLQADDEADYYC	FR L3	1A12
132	FGGGTRLTVL	FR L4	1A12
133	QSALTQPPSASGSPGQAVTISCTGS	FR L1	1A5
134	VSWYQQHPGKAPKLLIF	FR L2	1A5

SEQ ID NO.	Sequence	FR	Clone
135	QRPSGVPDRFSGSKSGTTASLTVSGLQADDEAHYYC	FR L3	1A5
136	FGGGTKLTVL	FR L4	1A5
137	QSVLTQPPSASGTPGQRVTFSCSGS	FR L1	1A6
138	VNWYQQLPGTAPSLLIY	FR L2	1A6
139	QRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC	FR L3	1A6
140	FGTGTKVTVL	FR L4	1A6
141	QSVLTQPPSVSGAPGQRVTISCSGS	FR L1	1A1
142	VNWYQQVPGTAPKLLMY	FR L2	1A1
143	QRPSGVPARFSGSKSGTSASLAISGLQSEDEADYYC	FR L3	1A1
144	FGTGTKVTVL	FR L4	1A1
145	QSVLTQSPSASGTPGQRVTISCSGS	FR L1	1A4
146	VNWYQQLPGTVPTLLIF	FR L2	1A4
147	QRPSGVPDRFSGSRSGTSASLAISGLQSEDEADYYC	FR L3	1A4
148	FGTGTKVTVL	FR L4	1A4
149	DIVMTQSPSSLSASVGDRVTITCRAS	FR L1	1A11
150	LNWYQHRPGKAPKLLIY	FR L2	1A11
151	SLQSGVPSRFSGSGFGTDFTLTISSLQPEDFATYYC	FR L3	1A11
152	FGQGTKLEIK	FR L4	1A11
153	NFMLTQPHSVSESPGKTVTISCTRS	FR L1	1E12
154	VQWYQHRPGSIPTFVIY	FR L2	1E12
155	KRPSGVPVRFSGSVDSASNSATLIISGLIPEDEADYYC	FR L3	1E12
156	FGTGTRVTVL	FR L4	1E12
157	QAVLTQPPSASGTPGQRVTISCSGS	FR L1	D1F6
158	VNWYQQLPGTAPKLLIY	FR L2	D1F6
159	QRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC	FR L3	D1F6
160	FGTGTKVTVL	FR L4	D1F6

EXAMPLE 7: NUCLEIC ACID SEQUENCES ENCODING HEAVY CHAIN VARIABLE DOMAINS AND LIGHT CHAIN VARIABLE DOMAINS FOR ANTI-IL1RAP ANTIBODY CLONES

[0363] Table 7. Nucleic acid sequences encoding heavy chain variable domains and light chain variable domains of IL1RAP antibodies provided herein.

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
D1A4	VH	161	CCAGGTCCGCTGGTGCAGTCTGGAGCTGAGGTG AAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGC ACAACCTCTGGATTCCCCTTTAACATGTATGGT TTCAACTGGGTGCGACAGGCCCCTGGACAAGGT CTTGAGTGGATGGGATGGATCAGCGCTTACAAT GGTCGCACAAATTATGCACAGAAGTTCCAGGGC AGAGTCACCATGACCACAGACACATCCACGAGC ACATCTTATGTGGAACTGGAGAGCCTCACATCT GACGACACGGCCGTTTATTACTGTGCGAGGAGC GGAAAGCAGCAGCTGGGTTCCGCGCAACCTCTT GACTCGTGGGGCCAGGGAACCCTGATCATCGTC TCTTCAG
D1A4	VL	162	AATTTTATGCTGACTCAGCCACCCTCAGCGTC TGGGACCCCCGGGCAGAGGGTCACCATCTCTT GTTCTGGAAGCAGCTCCAACATCGGAAGTAAT ACTGTAAACTGGTACCAGCAGCTCCCAGGAAC GGCCCCCAAACTCCTCATCTATAGTAATAATC AGCGGCCCTCAGGGGTCCCTGACCGATTCTCT GGCTCCAAGTCTGGCACCTCAGCCTCCCTGGC CATCAGTGGGCTCCAGTCTGAGGATGAGGCTG ATTATTACTGTGCAGCATGGGATGACAGCCTG AATGGCCTATTCGGCGGAGGGACCAAGCTGAC CGTCCTA
1C7	VH	163	CAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGT GAAAAAGCCCGGGGAGTCTCTGAAGATCTCCT GTAAGGCTTCTGGATATCGCTTTACCGACTAT TGGATCGGCTGGGTGCGCCAGATGCCCGGGAA AGGCCTGGAGTGGATGGGGATCATCTATCTTG GTGACTCTGAAACCATATACAGTCCGTCCTTC CAAGGCCAGGTCACCATCTCAGCCGACAAGTC CATCAGCACCGCCTTCCTGCAGTTGACCAGCC TGAAGGCCTCGGACAGCGCCATTTATTCCTGT GCGAGAGGATTCGCTTATGGGGACTGGTACTT CGATCTCTGGGGCCGTGGCACCCTGGTCATCG TCTC

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
1C7	VL	164	AACATCCAGATGACCCAGTCTCCATCTTCTGT GTCTGCATCTGTAGGAGACAGAGTCACCATCA CTTGTCGGGCGAGTCAGGGTATTGCCGGCTGG TTAGCCTGGTATCAGCAGAAACCTGGGAAACG CCCTAACCTCCTGATCTATGCTGCATCCACTT TGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCAT CAGCAGTCTGCAACCTGAAGATTTTGCAACTT ACTACTGTCAACAGAGTTCCAGTACCCCTCAC ACTTTTGGCCAGGGGACCAAGCTGGAGATCAA AC
1D5	VH	165	ATACAGCTTTAGCAGCCACTGGATCGGCTGGG TGCGCCAGATGCCCGGGAAAGGCCTGGAGTGG ATGGGGATCATCTATCCTGGTGACTCTGATAC CAGATACAGTCCGTCCTTCCAAGGCCAGGTCA CCATCTCAGCCGACAAGTCCATCAGCACCGCC TACCTGCAGTGGAGTAGCCTGAAGGCCTCGGA CACCGCCATGTATTATTGTGCGAGAGGGGAGT TACCGGGAGAGGCGTACTACTTTGACAACTGG GGCCAGGGAACCCTGGTCACCGTCTCCTCAG
1D5	VL	166	GAAATTGTAATGACACAGTCTCCACTCTCCCT GCCCGTCACCCCTGGAGAGCCGGCCTCCATCT CCTGCAGGTCTAGTCAGAGCCTCCTGCATAGT AATGGATACAAGTATTTGGATTGGTATCTGCA GAAGCCAGGGCAGTCTCCACAGCTCCTGATCT ACTTGGGCTCTAATCGGGCCTCCGGGGTCCCT GACAGGTTCAGTGGCAGTGGATCAGGCACAGA TTTTACACTGAAAATCAGCAGAGTGGAGGCTG AGGATGTTGGGGTTTATTACTGCATGCAAGCT CTACAAACTCCTCTCACTTTCGGCGGAGGGAC CAAGGTGGAGATCAAA
2E12	VH	167	CCAGGTGCAGCTGCAGGAGTCGGGGGAGGCTT AGTTCAGCCTGGGGGGTCCCTGAGACTCTCCT GTGAAGCCTCTGGATTCACCTTCAGTAGGTAC TGGATGCACTGGGTCCGCCAAGCTCCAGGGAA GGGGCTGGTGTGGGTCTCACGTATTCATACTG ATGGGAGTAGCATAAGTTATGCGGACTCCGTG AAGGGCCGATTCACCATCTCCAGAGACAACGC CAAGAACACGCTGTATCTGCAAATGAACAGTC TGAGAGCCGAGGACACGGCTGTGTATTACTGT GCAAGAGATATAGGGGGTGGATACAGCTATGG TTCGGTTGACTACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCAG

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
2E12	VL	168	CAGCCTGTGCTGACTCAATCACCCTCTGTGTC AGTGGCCCCAGGAAAGACGACCAGGATTACCT GTGGGGGAGACAACATTGGAAGTAAAAGTGTG CACTGGTTCCAGCAGAAGCCAGGCCAGGCCCC TGTCCTGGTCGTCTTTGGTGGTGGCGACCGGC CCTCAGGGATCCCTGAGCGATTCTCTGGCTCC AACTCTGGGAATACGGCCACCCTAATCATCAG TGGGGTCGAAGGCGGGGATGAGGCCGACTATT ACTGTCAGGTTTGGGATGGTAGTACTGATCAT TATATCTTCGGAGCTGGGACCATGGTCACCGT CCTA
1A7	VH	169	CAGGTGAAGCTGGTGGAGTCTGGACCTGAGGT GAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCT GCAAGGCTTCTGATTACACCTTTACCAGTTAT GGTATCAGCTGGGTGCGGCTGGCCCCTGGACA AGGGCTTGAGTGGATGGGATGGATCAGCGCTT ACAATGGTAACACAAACTATCCACAGAAGCTC CAGGGCAGAGTCACCGTGACCACAGACACATC CACGAGCACAGCCTACATGGAGCTGAGGAGCC TGACATCTGACGACACGGCCGTGTATTACTGT GCGAGAGTCCATCCCCGCCACATAATCGGGGC GGGGTACTTTGACTACTGGGGCCAGGGGACAA TGGTCACCGTCTCCTCAG
1A7	VL	170	CTGCCTGTGCTGACTCAGCCTCGCTCAGTGGC CGGGTCTCCTGGACAGTCAGTCACCATCTCCT GCACTGGGTCCAGCAGTGATGTTGGTGTTTAT GACTATGTCTCCTGGTACCAACAACACCCCGG CAAAGTCCCCCGACTCATGATTTATGATGTCA GTAAGCGGCCCCCAGGGGTCCCGGATCGCTTC TCTGGCTCCAGGTCTGGAAACACGGCCTCCCT GACCATCTCTGGCCTCCAGACTGAGGATGAGG CTGATTATTaCtgcGCCTACACCTTTGTCTTC GGAACTGGGACCAATGTCTCCGTCCTA
1B8	VH	171	CCCAGTTTCGTGGTGCAGTCTGGGGCTGAGGT GAAGAAGCCTGGGGCCTCAGTGAAGGTTTCCT GCAAGGCATCTGGATACACCTTCACCAGCTAC TATATGCACTGGGTGCGACAGGCCCCTGGACA AGGGCTTGAGTGGATGGGAATAATCAACCCTA GTGGTGGTAGCACAAGCTACGCACAGAAGTTC CAGGGCAGAGTCCCCATGACCAGGGACACGTC CACGAGCACAGTCTACCTGGAGCTGAACAGCC TGAGATCTGAGGACACGGCCGTGTATTACTGT GCTATTTTTGCCCCACCGGACTACGGTGACTA CGTTGATGCTTTTGATATCTGGGGCCAAGGGA CATTGATCATCGTCTCTTCA

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
1B8	VL	172	GATGTTGTGATGACACAGTCTCCACTCTCCCT GCCCGTCACCCCTGGAGAGCCGGCCTCCATCT CCTGCAGGTCTAGTCAGAGCCTCCTGCATAGT AATGGATACAACTATTTGGATTGGTACCTGCA GAAGCCAGGGCAGTCTCCACAGCTCCTGATCT ATTTGGGTTCTAATCGGGCCTCCGGGGTCCCT GACAGGTTCAGTGGCAGTGGATCAGGCACAGA TTTTACACTGAAAATCAGCAGAGTGGAGGCTG AGGATGTTGGGGTTTATTACTGCATGCAAGCT CTACAAACTCCTCGAGGGACCAAGGTGGAGAT CAAA
1A12	VL	173	CAGTCTGCCCTGAATCAGCCTCCCTCCGCGTC CGGGTCTCCTGGACAGGCAGTCACCATCTCCT GCACTGGCTCCAGCGGCGACATTGGGTTTTAT AATTATGTCTCGTGGTACCAGCAGCACCCAGG CAAGGCCCCCAAACTCCTGATCTTTGAGGTCA ATCAGCGACCCTCAGGGGTCCCTGATCGCTTC TCAGGGTCCAGGTCTGGCAGCACGGCCTCCCT GACCGTCTCGGGGCTCCAGGCTGACGATGAGG CTGACTATTACTGCGTCTCATATGGAATTTCC GACACTGTTCTTTTCGGCGGAGGCACCAGGTT GACCGTCCTAG
1A5	VL	174	CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTC CGGGTCTCCTGGACAGGCAGTCACCATCTCCT GCACTGGCTCCAGCGGCGACATTGGGTTTTAT AATTATGTCTCCTGGTACCAGCAACACCCAGG CAAAGCCCCCAAACTCCTCATCTTTGAGGTCA ATCAGCGACCCTCAGGGGTCCCTGATCGCTTC TCTGGCTCCAAGTCTGGCACCACGGCCTCCCT CACCGTCTCGGGACTCCAGGCTGACGATGAGG CTCACTATTACTGCGTCTCATATGGAATCTCC GACACTGTTCTTTTCGGCGGAGGCACCAAGTT GACCGTCCTAG
1A6	VL	175	CAGTCTGTGCTGACTCAGCCACCCTCAGCGTC TGGGACCCCCGGGCAGAGGGTCACCTTCTCTT GTTCTGGAAGCATCTCCAACATCGGGAGTAAT GCTGTAAACTGGTACCAGCAGCTCCCAGGAAC GGCCCCCAGTCTCCTCATCTATAGTGATAATC AGCGGCCCTCAGGGGTCCCTGACCGATTCTCT GGCTCCAAGTCTGGCACCTCAGCCTCCCTGGC CATCAGTGGGCTCCAGTCTGAGGATGAGGCTG ATTATTACTGTGCAGCATGGGATGACAGCCTG AATGGTAATGTCTTCGGAACTGGGACCAAGGT CACCGTCCTAG

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
1A1	VL	176	CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTC TGGGGCCCCAGGGCAGAGGGTCACCATCTCTT GTTCTGGAAGCAGCTCCAACATCGGAATTAAT GCTGTAAACTGGTACCAGCAGGTCCCAGGAAC GGCCCCCAAACTCCTCATGTATAGTAATGATC AGCGGCCCTCAGGGGTCCCTGCCCGATTTTCT GGCTCCAAGTCCGGCACCTCAGCCTCCCTGGC CATCAGTGGGCTCCAGTCTGAGGATGAGGCTG ATTATTACTGTGCAGCATGGGATGACAGCCTG AATGCCAATGTCTTCGGAACCGGGACCAAGGT CACCGTCCTAG
1A4	VL	177	CAGTCTGTGCTGACTCAGTCACCCTCAGCGTC TGGGACCCCCGGGCAGAGGGTCACCATCTCTT GCTCAGGAAGCAGCTCCAACATCGGAAGTAAT CCTGTAAACTGGTACCAACAGCTCCCAGGAAC GGTCCCCACACTCCTCATCTTTAATACTGGTC AGCGGCCCTCAGGGGTCCCTGACCGATTCTCT GGCTCCAGGTCTGGCACCTCAGCCTCCCTGGC CATCAGTGGGCTCCAGTCTGAGGATGAGGCTG ACTATTACTGTGCAGCATGGGATGACCGCCTG AATGGTAATGTCTTCGGAACTGGGACCAAGGT CACCGTCCTAG
D1A11	VL	178	GACATCGTGATGACCCAGTCTCCATCCTCCCT GTCTGCATCTGTAGGAGACAGAGTGACCATCA CTTGCCGGGCAAGCCAGAGCGTTAACAATTTT TTAAATTGGTATCAACACAGACCAGGGAAAGC CCCTAAGCTCCTGATCTATGCTGTATCCAGTT TGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATTTGGGACAGATTTCACTCTCACCAT CAGCAGTCTGCAACCTGAAGATTTTGCAACTT ATTATTGTCAACAGAGTTCCAGTGCCCCTAAC ACTTTTGGCCAGGGGACCAAGCTGGAGATCAA A
1E12	VL	179	AATTTTATGCTGACTCAGCCACACTCTGTGTC GGAGTCTCCGGGGAAGACGGTGACCATCTCCT GCACCCGCAGCAGTGGCAGCGTTGGCGAATAT TATGTGCAGTGGTACCAACACCGCCCGGGCAG TATTCCCACCTTTGTCATCTATGAGGACTACA AAAGACCCTCTGGGGTCCCTGTTCGGTTTTCT GGCTCTGTCGACAGCGCCTCCAACTCCGCCAC CCTCATCATCTCTGGGCTGATACCTGAGGACG AGGCTGACTACTACTGTCAGTCTTATGATGGC TCCAACTTTGTCTTCGGAACTGGGACCAGGGT CACCGTCCTA

IL1RAP Antibody Clone ID	Fragment	SEQ ID NO.	Sequence
D1F6	VL	180	CAGGCTGTGCTGACTCAGCCACCCTCAGCGTC TGGGACCCCCGGGCAGAGGGTCACCATCTCTT GTTCTGGAAGCGGCTCCAACATCGGAATTAAT CCTGTAAACTGGTACCAGCAGCTCCCAGGAAC GGCCCCCAAACTCCTCATCTATAGTGATGATC AGCGGCCCTCAGGGGTCCCTGACCGATTCTCT GGCTCCAAGTCTGGCACCTCAGCCTCCCTGGC CATTAGTGGGCTCCAGTCTGAGGATGAGGCTG ATTATTACTGTGCAGCATGGGATGACAGCCTG AATGGTCCGGGGAATGTCTTCGGAACTGGGAC CAAGGTCACCGTCCTA

EMBODIMENTS

[0364] Embodiment 1. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

[0365] Embodiment 2. The antibody of embodiment 1, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:61.

[0366] Embodiment 3. The antibody of embodiment 1 or 2, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

[0367] Embodiment 4. The antibody of any one of embodiments 1-3, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

[0368] Embodiment 5. The antibody of any one of embodiments 1 to 4, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

[0369] Embodiment 6. An isolated nucleic acid encoding an antibody of any one of embodiments 1 to 5.

[0370] Embodiment 7. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 1 to 5 and a pharmaceutically acceptable excipient.

[0371] Embodiment 8. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 1 to 5, thereby treating cancer in said subject.

[0372] Embodiment 9. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6; and

(ii) a transmembrane domain.

[0373] Embodiment 10. The recombinant protein of embodiment 9, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 61.

[0374] Embodiment 11. The recombinant protein of embodiment 9 or 10, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

[0375] Embodiment 12. The recombinant protein of any one of embodiments 9 to 11, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

[0376] Embodiment 13. The recombinant protein of any one of embodiments 9 to 12, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

[0377] Embodiment 14. The recombinant protein of any one of embodiments 9 to 13, further comprising an intracellular co-stimulatory signaling domain.

[0378] Embodiment 15. The recombinant protein of any one of embodiments 9 to 14, further comprising an intracellular T-cell signaling domain.

[0379] Embodiment 16. The recombinant protein of any one of embodiments 9 to 15, further comprising a self-cleaving peptidyl sequence.

[0380] Embodiment 17. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 9 to 16.

[0381] Embodiment 18. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 9 to 16 and a pharmaceutically acceptable excipient.

[0382] Embodiment 19. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 9 to 16, thereby treating cancer in said subject.

[0383] Embodiment 20. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and (b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

[0384] Embodiment 21. The recombinant protein of embodiment 20, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:61.

[0385] Embodiment 22. The recombinant protein of embodiment 20 or 21, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

[0386] Embodiment 23. The recombinant protein of any one of embodiments 20 to 22, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

[0387] Embodiment 24. The recombinant protein of any one of embodiments 20 to 23, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

[0388] Embodiment 25. The recombinant protein of any one of embodiments 20 to 24, wherein said effector cell ligand is a CD3 protein.

[0389] Embodiment 26. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 20 to 25 and a pharmaceutically acceptable excipient.

[0390] Embodiment 27. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 20 to 25, thereby treating cancer in said subject.

[0391] Embodiment 28. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

[0392] Embodiment 29. The antibody of embodiment 28, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:63.

[0393] Embodiment 30. The antibody of embodiment 28 or 29, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

[0394] Embodiment 31. The antibody of any one of embodiments 28 to 30, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

[0395] Embodiment 32. The antibody of any one of embodiments 28 to 31, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

[0396] Embodiment 33. An isolated nucleic acid encoding an antibody of any one of embodiments 28 to 32.

[0397] Embodiment 34. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 28 to 32 and a pharmaceutically acceptable excipient.

[0398] Embodiment 35. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of claims 28-32, thereby treating cancer in said subject.

[0399] Embodiment 36. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12; and

(ii) a transmembrane domain.

[0400] Embodiment 37. The recombinant protein of embodiment 36, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 63.

[0401] Embodiment 38. The recombinant protein of embodiment 36 or 37, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

[0402] Embodiment 39. The recombinant protein of any one of embodiments 36 to 38, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

[0403] Embodiment 40. The recombinant protein of any one of embodiments 36 to 39, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

[0404] Embodiment 41. The recombinant protein of any one of embodiments 36 to 40, further comprising an intracellular co-stimulatory signaling domain.

[0405] Embodiment 42. The recombinant protein of any one of embodiments 36 to 41, further comprising an intracellular T-cell signaling domain.

[0406] Embodiment 43. The recombinant protein of any one of embodiments 36 to 42, further comprising a self-cleaving peptidyl sequence.

[0407] Embodiment 44. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 36 to 43.

[0408] Embodiment 45. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 36 to 43 and a pharmaceutically acceptable excipient.

[0409] Embodiment 46. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 36 to 43, thereby treating cancer in said subject.

[0410] Embodiment 47. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

[0411] Embodiment 48. The recombinant protein of embodiment 47, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:63.

[0412] Embodiment 49. The recombinant protein of embodiment 47 or 48, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

[0413] Embodiment 50. The recombinant protein of any one of embodiments 47 to 49, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

[0414] Embodiment 51. The recombinant protein of any one of embodiments 47 to 50, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

[0415] Embodiment 52. The recombinant protein of any one of embodiments 47 to 51, wherein said effector cell ligand is a CD3 protein.

[0416] Embodiment 53. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 47 to 52 and a pharmaceutically acceptable excipient.

[0417] Embodiment 54. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 47 to 52, thereby treating cancer in said subject.

[0418] Embodiment 55. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

[0419] Embodiment 56. The antibody of embodiment 55, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:67.

[0420] Embodiment 57. The antibody of embodiment 55 or 56, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

[0421] Embodiment 58. The antibody of any one of embodiments 55 to 57, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

[0422] Embodiment 59. The antibody of any one of embodiments 55 to 58, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

[0423] Embodiment 60. An isolated nucleic acid encoding an antibody of any one of embodiments 55 to 59.

[0424] Embodiment 61. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 55 to 59 and a pharmaceutically acceptable excipient.

[0425] Embodiment 62. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 55 to 59, thereby treating cancer in said subject.

[0426] Embodiment 63. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24; and

(ii) a transmembrane domain.

[0427] Embodiment 64. The recombinant protein of embodiment 63, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 67.

[0428] Embodiment 65. The recombinant protein of embodiment 63 or 64, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

[0429] Embodiment 66. The recombinant protein of any one of embodiments 63 to 65, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

[0430] Embodiment 67. The recombinant protein of any one of embodiments 63 to 66, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

[0431] Embodiment 68. The recombinant protein of any one of embodiments 63 to 67, further comprising an intracellular co-stimulatory signaling domain.

[0432] Embodiment 69. The recombinant protein of any one of embodiments 63 to 68, further comprising an intracellular T-cell signaling domain.

[0433] Embodiment 70. The recombinant protein of any one of embodiments 63 to 69, further comprising a self-cleaving peptidyl sequence.

[0434] Embodiment 71. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 63 to 70.

[0435] Embodiment 72. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 63 to 70 and a pharmaceutically acceptable excipient.

[0436] Embodiment 73. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 63 to 70, thereby treating cancer in said subject.

[0437] Embodiment 74. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

[0438] Embodiment 75. The recombinant protein of embodiment 74, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:67.

[0439] Embodiment 76. The recombinant protein of embodiment 74 or 75, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

[0440] Embodiment 77. The recombinant protein of any one of embodiments 74 to 76, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

[0441] Embodiment 78. The recombinant protein of any one of embodiments 74 to 77, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

[0442] Embodiment 79. The recombinant protein of any one of embodiments 74 to 78, wherein said effector cell ligand is a CD3 protein.

[0443] Embodiment 80. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 74 to 79 and a pharmaceutically acceptable excipient.

[0444] Embodiment 81. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 74 to 79, thereby treating cancer in said subject.

[0445] Embodiment 82. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0446] Embodiment 83. The antibody of embodiment 82, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:69.

[0447] Embodiment 84. The antibody of embodiment 82 or 83, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

[0448] Embodiment 85. The antibody of any one of embodiments 82 to 84, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

[0449] Embodiment 86. The antibody of any one of embodiments 82 to 85, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

[0450] Embodiment 87. An isolated nucleic acid encoding an antibody of any one of embodiments 82 to 86.

[0451] Embodiment 88. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 82 to 86 and a pharmaceutically acceptable excipient.

[0452] Embodiment 89. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 82 to 86, thereby treating cancer in said subject.

[0453] Embodiment 90. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30; and

(ii) a transmembrane domain.

[0454] Embodiment 91. The recombinant protein of embodiment 90, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 69.

[0455] Embodiment 92. The recombinant protein of embodiment 90 or 91, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

[0456] Embodiment 93. The recombinant protein of any one of embodiments 90 to 92, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

[0457] Embodiment 94. The recombinant protein of any one of embodiments 90 to 93, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

[0458] Embodiment 95. The recombinant protein of any one of embodiments 90 to 94, further comprising an intracellular co-stimulatory signaling domain.

[0459] Embodiment 96. The recombinant protein of any one of embodiments 90 to 95, further comprising an intracellular T-cell signaling domain.

[0460] Embodiment 97. The recombinant protein of any one of embodiments 90 to 96, further comprising a self-cleaving peptidyl sequence.

[0461] Embodiment 98. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 90 to 97.

[0462] Embodiment 99. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 90 to 97 and a pharmaceutically acceptable excipient.

[0463] Embodiment 100. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 90 to 97, thereby treating cancer in said subject.

[0464] Embodiment 101. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

[0465] Embodiment 102. The recombinant protein of embodiment 101, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:69.

[0466] Embodiment 103. The recombinant protein of embodiment 101 or 102, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

[0467] Embodiment 104. The recombinant protein of any one of embodiments 101 to 103, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

[0468] Embodiment 105. The recombinant protein of any one of embodiments 101 to 204, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a

FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

[0469] Embodiment 106. The recombinant protein of any one of embodiments 101 to 105, wherein said effector cell ligand is a CD3 protein.

[0470] Embodiment 107. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 101 to 106 and a pharmaceutically acceptable excipient.

[0471] Embodiment 108. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 101 to 106, thereby treating cancer in said subject.

[0472] Embodiment 109. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0473] Embodiment 110. The antibody of embodiment 109, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:71.

[0474] Embodiment 111. The antibody of embodiment 109 or 110, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

[0475] Embodiment 112. The antibody of any one of embodiments 109 to 111, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

[0476] Embodiment 113. The antibody of any one of embodiments 109 to 111, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set

forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

[0477] Embodiment 114. An isolated nucleic acid encoding an antibody of any one of embodiments 109 to 113.

[0478] Embodiment 115. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 109 to 113 and a pharmaceutically acceptable excipient.

[0479] Embodiment 116. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 109 to 113, thereby treating cancer in said subject.

[0480] Embodiment 117. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36; and

(ii) a transmembrane domain.

[0481] Embodiment 118. The recombinant protein of embodiment 117, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 71.

[0482] Embodiment 119. The recombinant protein of embodiment 117 or 118, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

[0483] Embodiment 120. The recombinant protein of any one of embodiments 117 to 119, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

[0484] Embodiment 121. The recombinant protein of any one of embodiments 117 to 120, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a

FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

[0485] Embodiment 122. The recombinant protein of any one of embodiments 117 to 121, further comprising an intracellular co-stimulatory signaling domain.

[0486] Embodiment 123. The recombinant protein of any one of embodiments 117 to 122 further comprising an intracellular T-cell signaling domain.

[0487] Embodiment 124. The recombinant protein of any one of embodiments 117 to 123, further comprising a self-cleaving peptidyl sequence.

[0488] Embodiment 125. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 117 to 124.

[0489] Embodiment 126. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 117 to 124 and a pharmaceutically acceptable excipient.

[0490] Embodiment 127. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 117 to 124, thereby treating cancer in said subject.

[0491] Embodiment 128. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

[0492] Embodiment 129. The recombinant protein of embodiment 128, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:71.

[0493] Embodiment 130. The recombinant protein of embodiment 128 or 129, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

[0494] Embodiment 131. The recombinant protein of any one of embodiments 128 to 130, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

[0495] Embodiment 132. The recombinant protein of any one of embodiments 128 to 131, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

[0496] Embodiment 133. The recombinant protein of any one of embodiments 128 to 132, wherein said effector cell ligand is a CD3 protein.

[0497] Embodiment 134. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 128 to 133 and a pharmaceutically acceptable excipient.

[0498] Embodiment 135. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 128 to 133, thereby treating cancer in said subject.

[0499] Embodiment 136. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39

[0500] Embodiment 137. The antibody of embodiment 136, wherein said light chain variable domain comprises the sequence of SEQ ID NO: 73.

[0501] Embodiment 138. The antibody of embodiment 136 or 137, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

[0502] Embodiment 139. An isolated nucleic acid encoding an antibody of any one of embodiments 136 to 138.

[0503] Embodiment 140. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 136 to 138 and a pharmaceutically acceptable excipient.

[0504] Embodiment 141. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 136 to 138, thereby treating cancer in said subject.

[0505] Embodiment 142. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and

(ii) a transmembrane domain.

[0506] Embodiment 143. The recombinant protein of embodiment 142, wherein said light chain variable domain comprises the sequence of SEQ ID NO: 73.

[0507] Embodiment 144. The recombinant protein of embodiment 142 or 143, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

[0508] Embodiment 145. The recombinant protein of any one of embodiments 142 to 144, further comprising an intracellular co-stimulatory signaling domain.

[0509] Embodiment 146. The recombinant protein of any one of claims embodiments 142 to 145, further comprising an intracellular T-cell signaling domain.

[0510] Embodiment 147. The recombinant protein of any one of embodiments 142 to 146, further comprising a self-cleaving peptidyl sequence.

[0511] Embodiment 148. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 142 to 147.

[0512] Embodiment 149. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 142 to 147 and a pharmaceutically acceptable excipient.

[0513] Embodiment 150. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 142 to 147, thereby treating cancer in said subject.

[0514] Embodiment 151. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39.

[0515] Embodiment 152. The recombinant protein of embodiment 151, wherein said light chain variable domain comprises the sequence of SEQ ID NO:73.

[0516] Embodiment 153. The recombinant protein of embodiment 151 or 152, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

[0517] Embodiment 154. The recombinant protein of any one of embodiments 151 to 153, wherein said effector cell ligand is a CD3 protein.

[0518] Embodiment 155. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 151 to 154 and a pharmaceutically acceptable excipient.

[0519] Embodiment 156. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 151 to 154, thereby treating cancer in said subject.

[0520] Embodiment 157. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0521] Embodiment 158. The antibody of embodiment 157, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

[0522] Embodiment 159. The antibody of embodiment 157 or 158, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

[0523] Embodiment 160. An isolated nucleic acid encoding an antibody of any one of embodiments 157 to 159.

[0524] Embodiment 161. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 157 to 159 and a pharmaceutically acceptable excipient.

[0525] Embodiment 162. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 157 to 159, thereby treating cancer in said subject.

[0526] Embodiment 163. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42; and

(ii) a transmembrane domain.

[0527] Embodiment 164. The recombinant protein of embodiment 163, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

[0528] Embodiment 165. The recombinant protein of embodiment 163 or 164, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

[0529] Embodiment 166. The recombinant protein of any one of embodiments 163 to 165, further comprising an intracellular co-stimulatory signaling domain.

[0530] Embodiment 167. The recombinant protein of any one of embodiments 163 to 166, further comprising an intracellular T-cell signaling domain.

[0531] Embodiment 168. The recombinant protein of any one of embodiments 163 to 167, further comprising a self-cleaving peptidyl sequence.

[0532] Embodiment 169. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 163 to 168.

[0533] Embodiment 170. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 163 to 168 and a pharmaceutically acceptable excipient.

[0534] Embodiment 171. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 163 to 168, thereby treating cancer in said subject.

[0535] Embodiment 172. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

[0536] Embodiment 173. The recombinant protein of embodiment 172, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

[0537] Embodiment 174. The recombinant protein of embodiment 172 or 173, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

[0538] Embodiment 175. The recombinant protein of any one of embodiments 172 to 174, wherein said effector cell ligand is a CD3 protein.

[0539] Embodiment 176. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 172 to 175 and a pharmaceutically acceptable excipient.

[0540] Embodiment 177. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a

recombinant protein of any one of embodiments 172 to 175, thereby treating cancer in said subject.

[0541] Embodiment 178. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45

[0542] Embodiment 179. The antibody of embodiment 178, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

[0543] Embodiment 180. The antibody of embodiment 178 or 179, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

[0544] Embodiment 181. An isolated nucleic acid encoding an antibody of any one of embodiments 178 to 180.

[0545] Embodiment 182. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 178 to 180 and a pharmaceutically acceptable excipient.

[0546] Embodiment 183. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 178 to 180, thereby treating cancer in said subject.

[0547] Embodiment 184. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45; and

(ii) a transmembrane domain.

[0548] Embodiment 185. The recombinant protein of embodiment 184, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

[0549] Embodiment 186. The recombinant protein of embodiment 184 or 185, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set

forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

[0550] Embodiment 187. The recombinant protein of any one of embodiments 184 to 186, further comprising an intracellular co-stimulatory signaling domain.

[0551] Embodiment 188. The recombinant protein of any one of embodiments 184 to 187, further comprising an intracellular T-cell signaling domain.

[0552] Embodiment 189. The recombinant protein of any one of embodiments 184 to 188, further comprising a self-cleaving peptidyl sequence.

[0553] Embodiment 190. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 184 to 189.

[0554] Embodiment 191. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 184 to 189 and a pharmaceutically acceptable excipient.

[0555] Embodiment 192. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 184 to 189, thereby treating cancer in said subject.

[0556] Embodiment 193. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45.

[0557] Embodiment 194. The recombinant protein of embodiment 193, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

[0558] Embodiment 195. The recombinant protein of embodiment 193 or 194, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

[0559] Embodiment 196. The recombinant protein of any one of embodiments 193 to 195, wherein said effector cell ligand is a CD3 protein.

[0560] Embodiment 197. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 193 to 196 and a pharmaceutically acceptable excipient.

[0561] Embodiment 198. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 193 to 196, thereby treating cancer in said subject.

[0562] Embodiment 199. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

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

[0563] Embodiment 200. The antibody of embodiment 199, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

[0564] Embodiment 201. The antibody of embodiment 199 or 200, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

[0565] Embodiment 202. An isolated nucleic acid encoding an antibody of any one of claims 199-201.

[0566] Embodiment 203. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 199 to 201 and a pharmaceutically acceptable excipient.

[0567] Embodiment 204. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 199 to 201, thereby treating cancer in said subject.

[0568] Embodiment 205. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48; and

(ii) a transmembrane domain.

[0569] Embodiment 206. The recombinant protein of embodiment 205, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

[0570] Embodiment 207. The recombinant protein of embodiment 205 or 206, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

[0571] Embodiment 208. The recombinant protein of any one of embodiments 205 to 207, further comprising an intracellular co-stimulatory signaling domain.

[0572] Embodiment 209. The recombinant protein of any one of embodiments 205 to 208, further comprising an intracellular T-cell signaling domain.

[0573] Embodiment 210. The recombinant protein of any one of embodiments 205 to 209, further comprising a self-cleaving peptidyl sequence.

[0574] Embodiment 211. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 205 to 210.

[0575] Embodiment 212. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 205 to 210 and a pharmaceutically acceptable excipient.

[0576] Embodiment 213. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 205 to 210, thereby treating cancer in said subject.

[0577] Embodiment 214. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

[0578] Embodiment 215. The recombinant protein of embodiment 214, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

[0579] Embodiment 216. The recombinant protein of embodiment 214 or 215, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

[0580] Embodiment 217. The recombinant protein of any one of embodiments 214 to 216, wherein said effector cell ligand is a CD3 protein.

[0581] Embodiment 218. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 214 to 217 and a pharmaceutically acceptable excipient.

[0582] Embodiment 219. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 214 to 217, thereby treating cancer in said subject.

[0583] Embodiment 220. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

[0584] Embodiment 221. The antibody of embodiment 220, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77.

[0585] Embodiment 222. The antibody of any one of embodiment 220 or 221, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

[0586] Embodiment 223. An isolated nucleic acid encoding an antibody of any one of embodiments 220 to 222.

[0587] Embodiment 224. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 220 to 222 and a pharmaceutically acceptable excipient.

[0588] Embodiment 225. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 220 to 222, thereby treating cancer in said subject.

[0589] Embodiment 226. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51; and

(ii) a transmembrane domain.

[0590] Embodiment 227. The recombinant protein of embodiment 226, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77.

[0591] Embodiment 228. The recombinant protein of embodiment 226 or 227, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

[0592] Embodiment 229. The recombinant protein of any one of embodiments 226 to 228, further comprising an intracellular co-stimulatory signaling domain.

[0593] Embodiment 230. The recombinant protein of any one of embodiments 226 to 229, further comprising an intracellular T-cell signaling domain.

[0594] Embodiment 231. The recombinant protein of any one of embodiments 226 to 230, further comprising a self-cleaving peptidyl sequence.

[0595] Embodiment 232. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 226 to 231.

[0596] Embodiment 233. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 226 to 231 and a pharmaceutically acceptable excipient.

[0597] Embodiment 234. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 226 to 231, thereby treating cancer in said subject.

[0598] Embodiment 235. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

[0599] Embodiment 236. The recombinant protein of embodiment 235, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77.

[0600] Embodiment 237. The recombinant protein of embodiment 235 or 236, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

[0601] Embodiment 238. The recombinant protein of any one of embodiments 235 to 237, wherein said effector cell ligand is a CD3 protein.

[0602] Embodiment 239. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 235 to 238 and a pharmaceutically acceptable excipient.

[0603] Embodiment 240. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 235 to 238, thereby treating cancer in said subject.

[0604] Embodiment 241. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

[0605] Embodiment 242. The antibody of embodiment 241, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

[0606] Embodiment 243. The antibody of embodiment 241 or 242, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

[0607] Embodiment 244. An isolated nucleic acid encoding an antibody of any one of embodiments 241 to 243.

[0608] Embodiment 245. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 241 to 243 and a pharmaceutically acceptable excipient.

[0609] Embodiment 246. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 241 to 243, thereby treating cancer in said subject.

[0610] Embodiment 247. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54; and

(ii) a transmembrane domain.

[0611] Embodiment 248. The recombinant protein of embodiment 247, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

[0612] Embodiment 249. The recombinant protein of embodiment 247 or 248, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

[0613] Embodiment 250. The recombinant protein of any one of embodiments 247 to 249, further comprising an intracellular co-stimulatory signaling domain.

[0614] Embodiment 251. The recombinant protein of any one of embodiments 247 to 250, further comprising an intracellular T-cell signaling domain.

[0615] Embodiment 252. The recombinant protein of any one of embodiments 247 to 251, further comprising a self-cleaving peptidyl sequence.

[0616] Embodiment 253. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 247 to 252.

[0617] Embodiment 254. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 247 to 252 and a pharmaceutically acceptable excipient.

[0618] Embodiment 255. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 247 to 252, thereby treating cancer in said subject.

[0619] Embodiment 256. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

[0620] Embodiment 257. The recombinant protein of embodiment 256, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

[0621] Embodiment 258. The recombinant protein of embodiment 256 or 257, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

[0622] Embodiment 259. The recombinant protein of any one of embodiments 256 to 258, wherein said effector cell ligand is a CD3 protein.

[0623] Embodiment 260. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 256 to 259 and a pharmaceutically acceptable excipient.

[0624] Embodiment 261. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 256 to to 259, thereby treating cancer in said subject.

[0625] Embodiment 262. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

[0626] Embodiment 263. The antibody of embodiment 262, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

[0627] Embodiment 264. The antibody of embodiment 262 or 263, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

[0628] Embodiment 265. An isolated nucleic acid encoding an antibody of any one of embodiments 262 to 264.

[0629] Embodiment 266. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 262 to 264 and a pharmaceutically acceptable excipient.

[0630] Embodiment 267. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 262 to 264, thereby treating cancer in said subject.

[0631] Embodiment 268. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57; and

(ii) a transmembrane domain

[0632] Embodiment 269. The recombinant protein of embodiment 268, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

[0633] Embodiment 270. The recombinant protein of embodiment 268 or 269, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

[0634] Embodiment 271. The recombinant protein of any one of embodiments 268 to 270, further comprising an intracellular co-stimulatory signaling domain.

[0635] Embodiment 272. The recombinant protein of any one of embodiments 268 to 271, further comprising an intracellular T-cell signaling domain.

[0636] Embodiment 273. The recombinant protein of any one of embodiments 268 to 272, further comprising a self-cleaving peptidyl sequence.

[0637] Embodiment 274. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 268 to 273.

[0638] Embodiment 275. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 268 to 273 and a pharmaceutically acceptable excipient.

[0639] Embodiment 276. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 268 to 273, thereby treating cancer in said subject.

[0640] Embodiment 277. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

[0641] Embodiment 278. The recombinant protein of embodiment 277, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

[0642] Embodiment 279. The recombinant protein of embodiment 277 or 278, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

[0643] Embodiment 280. The recombinant protein of any one of embodiments 277 to 279, wherein said effector cell ligand is a CD3 protein.

[0644] Embodiment 281. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 277 to 280 and a pharmaceutically acceptable excipient.

[0645] Embodiment 282. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 277 to 280, thereby treating cancer in said subject.

[0646] Embodiment 283. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

[0647] Embodiment 284. The antibody of embodiment 283, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

[0648] Embodiment 285. The antibody of embodiment 283 or 284, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

[0649] Embodiment 286. An isolated nucleic acid encoding an antibody of any one of embodiments 283 to 285.

[0650] Embodiment 287. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of any one of embodiments 283 to 285 and a pharmaceutically acceptable excipient.

[0651] Embodiment 288. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of an antibody of any one of embodiments 283 to 285, thereby treating cancer in said subject.

[0652] Embodiment 289. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60; and

(ii) a transmembrane domain.

[0653] Embodiment 290. The recombinant protein of embodiment 289, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

[0654] Embodiment 291. The recombinant protein of embodiment 289 or 290, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

[0655] Embodiment 292. The recombinant protein of any one of embodiments 289 to 291, further comprising an intracellular co-stimulatory signaling domain.

[0656] Embodiment 293. The recombinant protein of any one of embodiments 289 to 292, further comprising an intracellular T-cell signaling domain.

[0657] Embodiment 294. The recombinant protein of any one of embodiments 289 to 293, further comprising a self-cleaving peptidyl sequence.

[0658] Embodiment 295. An isolated nucleic acid encoding a recombinant protein of any one of embodiments 289 to 294.

[0659] Embodiment 296. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 289 to 294 and a pharmaceutically acceptable excipient.

[0660] Embodiment 297. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of a recombinant protein of any one of embodiments 289 to 294, thereby treating cancer in said subject.

[0661] Embodiment 298. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

[0662] Embodiment 299. The recombinant protein of embodiment 298, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

[0663] Embodiment 300. The recombinant protein of embodiment 298 or 299, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

[0664] Embodiment 301. The recombinant protein of any one of embodiments 298 to 300, wherein said effector cell ligand is a CD3 protein.

[0665] Embodiment 302. A pharmaceutical composition comprising a therapeutically effective amount of a recombinant protein of any one of embodiments 298 to 301 and a pharmaceutically acceptable excipient.

WHAT IS CLAIMED IS:

1. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

2. The antibody of claim 1, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:61.

3. The antibody of claim 1, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

4. The antibody of claim 1, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

5. The antibody of claim 1, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

6. An isolated nucleic acid encoding the antibody of claim 1.

7. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 1 and a pharmaceutically acceptable excipient.

8. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 1, thereby treating cancer in said subject.

9. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6; and

(ii) a transmembrane domain.

10. The recombinant protein of claim 9, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 61.

11. The recombinant protein of claim 9, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

12. The recombinant protein of claim 9, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

13. The recombinant protein of claim 9, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

14. The recombinant protein of claim 9, further comprising an intracellular co-stimulatory signaling domain.

15. The recombinant protein of claim 9, further comprising an intracellular T-cell signaling domain.

16. The recombinant protein of claim 9, further comprising a self-cleaving peptidyl sequence.

17. An isolated nucleic acid encoding the recombinant protein of claim 9.

18. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 9 and a pharmaceutically acceptable excipient.

19. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 9, thereby treating cancer in said subject.

20. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 as set forth in SEQ ID NO:3; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 as set forth in SEQ ID NO:5, and a CDR L3 as set forth in SEQ ID NO:6.

21. The recombinant protein of claim 20, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:61.

22. The recombinant protein of claim 20, wherein said light chain variable domain comprises the sequence of SEQ ID NO:62.

23. The recombinant protein of claim 20, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:81, a FR H2 as set forth in SEQ ID NO:82, a FR H3 as set forth in SEQ ID NO:83 and a FR H4 as set forth in SEQ ID NO:84.

24. The recombinant protein of claim 20, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:85, a FR L2 as set forth in SEQ ID NO:86, a FR L3 as set forth in SEQ ID NO:87 and a FR L4 as set forth in SEQ ID NO:88.

25. The recombinant protein of claim 20, wherein said effector cell ligand is a CD3 protein.

26. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 20 and a pharmaceutically acceptable excipient.

27. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 20, thereby treating cancer in said subject.

28. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

29. The antibody of claim 28, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:63.

30. The antibody of claim 28, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

31. The antibody of claim 28, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

32. The antibody of claim 28 wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

33. An isolated nucleic acid encoding the antibody of claim 28.

34. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 28 and a pharmaceutically acceptable excipient.

35. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 28, thereby treating cancer in said subject.

36. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12; and

(ii) a transmembrane domain.

37. The recombinant protein of claim 36, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 63.

38. The recombinant protein of claim 36, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

39. The recombinant protein of claim 36, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

40. The recombinant protein of claim 36, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

41. The recombinant protein of claim 36, further comprising an intracellular co-stimulatory signaling domain.

42. The recombinant protein of claim 36, further comprising an intracellular T-cell signaling domain.

43. The recombinant protein of claim 36, further comprising a self-cleaving peptidyl sequence.

44. An isolated nucleic acid encoding the recombinant protein of claim 36.

45. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 36 and a pharmaceutically acceptable excipient.

46. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 36, thereby treating cancer in said subject.

47. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:7, a CDR H2 as set forth in SEQ ID NO:8 and a CDR H3 as set forth in SEQ ID NO:9; and (b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:10, a CDR L2 as set forth in SEQ ID NO:11, and a CDR L3 as set forth in SEQ ID NO:12.

48. The recombinant protein of claim 47, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:63.

49. The recombinant protein of claim 47, wherein said light chain variable domain comprises the sequence of SEQ ID NO:64.

50. The recombinant protein of claim 47, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:89, a FR H2 as set forth in SEQ ID NO:90, a FR H3 as set forth in SEQ ID NO:91 and a FR H4 as set forth in SEQ ID NO:92.

51. The recombinant protein of claim 47, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:93, a FR L2 as set forth in SEQ ID NO:94, a FR L3 as set forth in SEQ ID NO:95 and a FR L4 as set forth in SEQ ID NO:96.

52. The recombinant protein of claim 47, wherein said effector cell ligand is a CD3 protein.

53. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 47 and a pharmaceutically acceptable excipient.

54. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 47, thereby treating cancer in said subject.

55. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

56. The antibody of claim 55, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:67.

57. The antibody of claim 55, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

58. The antibody of claim 55, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

59. The antibody of claim 55, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

60. An isolated nucleic acid encoding the antibody of claim 55.

61. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 55 and a pharmaceutically acceptable excipient.

62. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 55, thereby treating cancer in said subject.

63. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24; and

(ii) a transmembrane domain.

64. The recombinant protein of claim 63, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 67.

65. The recombinant protein of claim 63, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

66. The recombinant protein of claim 63, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

67. The recombinant protein of claim 63, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

68. The recombinant protein of claim 63, further comprising an intracellular co-stimulatory signaling domain.

69. The recombinant protein of claim 63, further comprising an intracellular T-cell signaling domain.

70. The recombinant protein of claim 63, further comprising a self-cleaving peptidyl sequence.

71. An isolated nucleic acid encoding the recombinant protein of claim 63.

72. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 63 and a pharmaceutically acceptable excipient.

73. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 63, thereby treating cancer in said subject.

74. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:19, a CDR H2 as set forth in SEQ ID NO:20 and a CDR H3 as set forth in SEQ ID NO:21; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:22, a CDR L2 as set forth in SEQ ID NO:23, and a CDR L3 as set forth in SEQ ID NO:24.

75. The recombinant protein of claim 74, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:67.

76. The recombinant protein of claim 74, wherein said light chain variable domain comprises the sequence of SEQ ID NO:68.

77. The recombinant protein of claim 74, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:105, a FR H2 as set forth in SEQ ID NO:106, a FR H3 as set forth in SEQ ID NO:107 and a FR H4 as set forth in SEQ ID NO:108.

78. The recombinant protein of claim 74, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:109, a FR L2 as set forth in SEQ ID NO:110, a FR L3 as set forth in SEQ ID NO:111 and a FR L4 as set forth in SEQ ID NO:112.

79. The recombinant protein of claim 74, wherein said effector cell ligand is a CD3 protein.

80. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 74 and a pharmaceutically acceptable excipient.

81. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 74, thereby treating cancer in said subject.

82. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

83. The antibody of claim 82, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:69.

84. The antibody of claim 82, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

85. The antibody of claim 82, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

86. The antibody of claim 90, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

87. An isolated nucleic acid encoding the antibody of claim 82.

88. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 82 and a pharmaceutically acceptable excipient.

89. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 82, thereby treating cancer in said subject.

90. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30; and

(ii) a transmembrane domain.

91. The recombinant protein of claim 90, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 69.

92. The recombinant protein of claim 90, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

93. The recombinant protein of claim 90, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

94. The recombinant protein of claim 90, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

95. The recombinant protein of claim 90, further comprising an intracellular co-stimulatory signaling domain.

96. The recombinant protein of claim 90, further comprising an intracellular T-cell signaling domain.

97. The recombinant protein of claim 90, further comprising a self-cleaving peptidyl sequence.

98. An isolated nucleic acid encoding the recombinant protein of claim 90.

99. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 90 and a pharmaceutically acceptable excipient.

100. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 90, thereby treating cancer in said subject.

101. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

102. The recombinant protein of claim 101, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:69.

103. The recombinant protein of claim 101, wherein said light chain variable domain comprises the sequence of SEQ ID NO:70.

104. The recombinant protein of claim 101, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:113, a FR H2 as set forth in SEQ ID NO:114, a FR H3 as set forth in SEQ ID NO:115 and a FR H4 as set forth in SEQ ID NO:116.

105. The recombinant protein of claim 101, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:117, a FR L2 as set forth in SEQ ID NO:118, a FR L3 as set forth in SEQ ID NO:119 and a FR L4 as set forth in SEQ ID NO:120.

106. The recombinant protein of claim 101, wherein said effector cell ligand is a CD3 protein

107. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 101 and a pharmaceutically acceptable excipient.

108. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 101, thereby treating cancer in said subject.

109. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

110. The antibody of claim 109, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:71.

111. The antibody of claim 109, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

112. The antibody of claim 109, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

113. The antibody of claim 109, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

114. An isolated nucleic acid encoding the antibody of claim 109.

115. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 109 and a pharmaceutically acceptable excipient.

116. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 109, thereby treating cancer in said subject.

117. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36; and

(ii) a transmembrane domain.

118. The recombinant protein of claim 117, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO: 71.

119. The recombinant protein of claim 117, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

120. The recombinant protein of claim 117, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

121. The recombinant protein of claim 117, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

122. The recombinant protein of claim 117, further comprising an intracellular co-stimulatory signaling domain.

123. The recombinant protein of claim 117 further comprising an intracellular T-cell signaling domain.

124. The recombinant protein of claim 117, further comprising a self-cleaving peptidyl sequence.

125. An isolated nucleic acid encoding the recombinant protein of any one of claim 117.

126. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 117 and a pharmaceutically acceptable excipient.

127. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 117, thereby treating cancer in said subject.

128. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a heavy chain variable domain comprising a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and

(b) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

129. The recombinant protein of claim 128, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:71.

130. The recombinant protein of claim 128, wherein said light chain variable domain comprises the sequence of SEQ ID NO:72.

131. The recombinant protein of claim 128, wherein said heavy chain variable domain comprises a FR H1 as set forth in SEQ ID NO:121, a FR H2 as set forth in SEQ ID NO:122, a FR H3 as set forth in SEQ ID NO:123 and a FR H4 as set forth in SEQ ID NO:124.

132. The recombinant protein of claim 128, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:125, a FR L2 as set forth in SEQ ID NO:126, a FR L3 as set forth in SEQ ID NO:127 and a FR L4 as set forth in SEQ ID NO:128.

133. The recombinant protein of claim 128, wherein said effector cell ligand is a CD3 protein.

134. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 128 and a pharmaceutically acceptable excipient.

135. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of any one of claims 128-133, thereby treating cancer in said subject.

136. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39.

137. The antibody of claim 136, wherein said light chain variable domain comprises the sequence of SEQ ID NO: 73.

138. The antibody of claim 136, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

139. An isolated nucleic acid encoding the antibody of claim 136.

140. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 136 and a pharmaceutically acceptable excipient.

141. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 136, thereby treating cancer in said subject.

142. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39; and

(ii) a transmembrane domain.

143. The recombinant protein of claim 142, wherein said light chain variable domain comprises the sequence of SEQ ID NO: 73.

144. The recombinant protein of claim 142, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

145. The recombinant protein of claim 142, further comprising an intracellular co-stimulatory signaling domain.

146. The recombinant protein of claim 142, further comprising an intracellular T-cell signaling domain.

147. The recombinant protein of claim 142, further comprising a self-cleaving peptidyl sequence.

148. An isolated nucleic acid encoding the recombinant protein of claim 142.

149. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 142 and a pharmaceutically acceptable excipient.

150. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 142, thereby treating cancer in said subject.

151. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:37, a CDR L2 as set forth in SEQ ID NO:38 and a CDR L3 as set forth in SEQ ID NO:39.

152. The recombinant protein of claim 151, wherein said light chain variable domain comprises the sequence of SEQ ID NO:73.

153. The recombinant protein of claim 151, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:129, a FR L2 as set forth in SEQ ID NO:130, a FR L3 as set forth in SEQ ID NO:131 and a FR L4 as set forth in SEQ ID NO:132.

154. The recombinant protein of claim 151, wherein said effector cell ligand is a CD3 protein.

155. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 151 and a pharmaceutically acceptable excipient.

156. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 151, thereby treating cancer in said subject.

157. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

158. The antibody of claim 157, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

159. The antibody of claim 157, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

160. An isolated nucleic acid encoding the antibody of claim 157.

161. A pharmaceutical composition comprising a therapeutically effective amount of the antibody claim 157 and a pharmaceutically acceptable excipient.

162. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 157, thereby treating cancer in said subject.

163. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42; and

(ii) a transmembrane domain.

164. The recombinant protein of claim 163, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

165. The recombinant protein of claim 163, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

166. The recombinant protein of claim 163, further comprising an intracellular co-stimulatory signaling domain.

167. The recombinant protein of claim 163, further comprising an intracellular T-cell signaling domain.

168. The recombinant protein of claim 163, further comprising a self-cleaving peptidyl sequence.

169. An isolated nucleic acid encoding the recombinant protein of claim 163.

170. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 163 and a pharmaceutically acceptable excipient.

171. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 163, thereby treating cancer in said subject.

172. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

173. The recombinant protein of claim 172, wherein said light chain variable domain comprises the sequence of SEQ ID NO:74.

174. The recombinant protein of claim 172, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:133, a FR L2 as set forth in SEQ ID NO:134, a FR L3 as set forth in SEQ ID NO:135 and a FR L4 as set forth in SEQ ID NO:136.

175. The recombinant protein of claim 172, wherein said effector cell ligand is a CD3 protein.

176. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 172 and a pharmaceutically acceptable excipient.

177. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 172, thereby treating cancer in said subject.

178. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45.

179. The antibody of claim 178, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

180. The antibody of claim 178, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

181. An isolated nucleic acid encoding the antibody of claim 178.

182. A pharmaceutical composition comprising the therapeutically effective amount of the antibody of claim 178 and a pharmaceutically acceptable excipient.

183. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 178, thereby treating cancer in said subject.

184. A recombinant protein comprising:

(i) an antibody region comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45; and

(ii) a transmembrane domain.

185. The recombinant protein of claim 184, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

186. The recombinant protein of claim 184, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

187. The recombinant protein of claim 184, further comprising an intracellular co-stimulatory signaling domain.

188. The recombinant protein of claim 184, further comprising an intracellular T-cell signaling domain.

189. The recombinant protein of claim 184, further comprising a self-cleaving peptidyl sequence.

190. An isolated nucleic acid encoding the recombinant protein of claim 184.

191. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 184 and a pharmaceutically acceptable excipient.

192. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 184, thereby treating cancer in said subject.

193. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:43, a CDR L2 as set forth in SEQ ID NO:44, and a CDR L3 as set forth in SEQ ID NO:45.

194. The recombinant protein of claim 193, wherein said light chain variable domain comprises the sequence of SEQ ID NO:75.

195. The recombinant protein of any one of claim 193, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:137, a FR L2 as set forth in SEQ ID NO:138, a FR L3 as set forth in SEQ ID NO:139 and a FR L4 as set forth in SEQ ID NO:140.

196. The recombinant protein of claim 193, wherein said effector cell ligand is a CD3 protein.

197. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 193 and a pharmaceutically acceptable excipient.

198. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 193, thereby treating cancer in said subject.

199. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

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

200. The antibody of claim 199, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

201. The antibody of claim 199, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

202. An isolated nucleic acid encoding the antibody of claim 199.

203. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 199 and a pharmaceutically acceptable excipient.

204. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 199, thereby treating cancer in said subject.

205. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48; and

(ii) a transmembrane domain.

206. The recombinant protein of claim 205, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

207. The recombinant protein of claim 205, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

208. The recombinant protein of claim 205, further comprising an intracellular co-stimulatory signaling domain.

209. The recombinant protein of claim 205, further comprising an intracellular T-cell signaling domain.

210. The recombinant protein of claim 205, further comprising a self-cleaving peptidyl sequence.

211. An isolated nucleic acid encoding the recombinant protein of claim 205.

212. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 205 and a pharmaceutically acceptable excipient.

213. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 205, thereby treating cancer in said subject.

214. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

215. The recombinant protein of claim 214, wherein said light chain variable domain comprises the sequence of SEQ ID NO:76.

216. The recombinant protein of claim 214, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:141, a FR L2 as set forth in SEQ ID NO:142, a FR L3 as set forth in SEQ ID NO:143 and a FR L4 as set forth in SEQ ID NO:144.

217. The recombinant protein of claim 214, wherein said effector cell ligand is a CD3 protein.

218. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 214 and a pharmaceutically acceptable excipient.

219. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 214, thereby treating cancer in said subject.

220. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

221. The antibody of claim 220, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77.

222. The antibody of claim 220, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

223. An isolated nucleic acid encoding the antibody of claim 220.

224. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 220 and a pharmaceutically acceptable excipient.

225. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 220, thereby treating cancer in said subject.

226. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51; and

(ii) a transmembrane domain.

227. The recombinant protein of claim 226, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77.

228. The recombinant protein of claim 226, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

229. The recombinant protein of claim 226, further comprising an intracellular co-stimulatory signaling domain.

230. The recombinant protein of claim 226, further comprising an intracellular T-cell signaling domain.

231. The recombinant protein of claim 226, further comprising a self-cleaving peptidyl sequence.

232. An isolated nucleic acid encoding the recombinant protein of claim 226.

233. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 226 and a pharmaceutically acceptable excipient.

234. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 226, thereby treating cancer in said subject.

235. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:49, a CDR L2 as set forth in SEQ ID NO:50, and a CDR L3 as set forth in SEQ ID NO:51.

236. The recombinant protein of claim 235, wherein said light chain variable domain comprises the sequence of SEQ ID NO:77 .

237. The recombinant protein of claim 235, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:145, a FR L2 as set forth in SEQ ID NO:146, a FR L3 as set forth in SEQ ID NO:147 and a FR L4 as set forth in SEQ ID NO:148.

238. The recombinant protein of claim 235, wherein said effector cell ligand is a CD3 protein.

239. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 235 and a pharmaceutically acceptable excipient.

240. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 235, thereby treating cancer in said subject.

241. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

242. The antibody of claim 241, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

243. The antibody of claim 241, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

244. An isolated nucleic acid encoding the antibody of claim 241.

245. A pharmaceutical composition comprising the therapeutically effective amount of the antibody of claim 241 and a pharmaceutically acceptable excipient.

246. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 241, thereby treating cancer in said subject.

247. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54; and

(ii) a transmembrane domain.

248. The recombinant protein of claim 247, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

249. The recombinant protein of claim 247, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

250. The recombinant protein of claim 247, further comprising an intracellular co-stimulatory signaling domain.

251. The recombinant protein of claim 247, further comprising an intracellular T-cell signaling domain.

252. The recombinant protein of claim 247, further comprising a self-cleaving peptidyl sequence.

253. An isolated nucleic acid encoding the recombinant protein of claim 247.

254. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 247 and a pharmaceutically acceptable excipient.

255. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 247, thereby treating cancer in said subject.

256. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:52, a CDR L2 as set forth in SEQ ID NO:53, and a CDR L3 as set forth in SEQ ID NO:54.

257. The recombinant protein of claim 256, wherein said light chain variable domain comprises the sequence of SEQ ID NO:78.

258. The recombinant protein of claim 256 or 257, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:149, a FR L2 as set forth in SEQ ID NO:150, a FR L3 as set forth in SEQ ID NO:151 and a FR L4 as set forth in SEQ ID NO:152.

259. The recombinant protein of claim 256, wherein said effector cell ligand is a CD3 protein.

260. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 256 and a pharmaceutically acceptable excipient.

261. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 256, thereby treating cancer in said subject.

262. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

263. The antibody of claim 262, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

264. The antibody of claim 262, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

265. An isolated nucleic acid encoding an antibody of claim 262.

266. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 262 and a pharmaceutically acceptable excipient.

267. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 262, thereby treating cancer in said subject.

268. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57; and

(ii) a transmembrane domain.

269. The recombinant protein of claim 268, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

270. The recombinant protein of claim 268, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

271. The recombinant protein of claim 268, further comprising an intracellular co-stimulatory signaling domain.

272. The recombinant protein of claim 268, further comprising an intracellular T-cell signaling domain.

273. The recombinant protein of claim 268, further comprising a self-cleaving peptidyl sequence.

274. An isolated nucleic acid encoding the recombinant protein of claim 268.

275. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 268 and a pharmaceutically acceptable excipient.

276. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 268, thereby treating cancer in said subject.

277. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

(a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:55, a CDR L2 as set forth in SEQ ID NO:56, and a CDR L3 as set forth in SEQ ID NO:57.

278. The recombinant protein of claim 277, wherein said light chain variable domain comprises the sequence of SEQ ID NO:79.

279. The recombinant protein of claim 277, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:153, a FR L2 as set forth in SEQ ID NO:154, a FR L3 as set forth in SEQ ID NO:155 and a FR L4 as set forth in SEQ ID NO:156.

280. The recombinant protein of claim 277, wherein said effector cell ligand is a CD3 protein.

281. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 277 and a pharmaceutically acceptable excipient.

282. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 277, thereby treating cancer in said subject.

283. An anti-interleukin-1 receptor accessory protein (IL1RAP) antibody comprising a light chain variable domain,

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

284. The antibody of claim 283, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

285. The antibody of claim 283, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

286. An isolated nucleic acid encoding the antibody of claim 283.

287. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 283 and a pharmaceutically acceptable excipient.

288. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the antibody of claim 283, thereby treating cancer in said subject.

289. A recombinant protein comprising:

(i) an antibody region comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60; and

(ii) a transmembrane domain.

290. The recombinant protein of claim 289, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

291. The recombinant protein of claim 289, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

292. The recombinant protein of claim 289, further comprising an intracellular co-stimulatory signaling domain.

293. The recombinant protein of claim 289, further comprising an intracellular T-cell signaling domain.

294. The recombinant protein of any one of claims 289-293, further comprising a self-cleaving peptidyl sequence.

295. An isolated nucleic acid encoding the recombinant protein of claim 289.

296. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 289 and a pharmaceutically acceptable excipient.

297. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 289, thereby treating cancer in said subject.

298. A recombinant protein comprising:

(i) a first antibody region capable of binding an effector cell ligand; and

(ii) a second antibody region, comprising:

a light chain variable domain comprising a CDR L1 as set forth in SEQ ID NO:58, a CDR L2 as set forth in SEQ ID NO:59, and a CDR L3 as set forth in SEQ ID NO:60.

299. The recombinant protein of claim 298, wherein said light chain variable domain comprises the sequence of SEQ ID NO:80.

300. The recombinant protein of claim 298, wherein said light chain variable domain comprises a FR L1 as set forth in SEQ ID NO:157, a FR L2 as set forth in SEQ ID NO:158, a FR L3 as set forth in SEQ ID NO:159 and a FR L4 as set forth in SEQ ID NO:160.

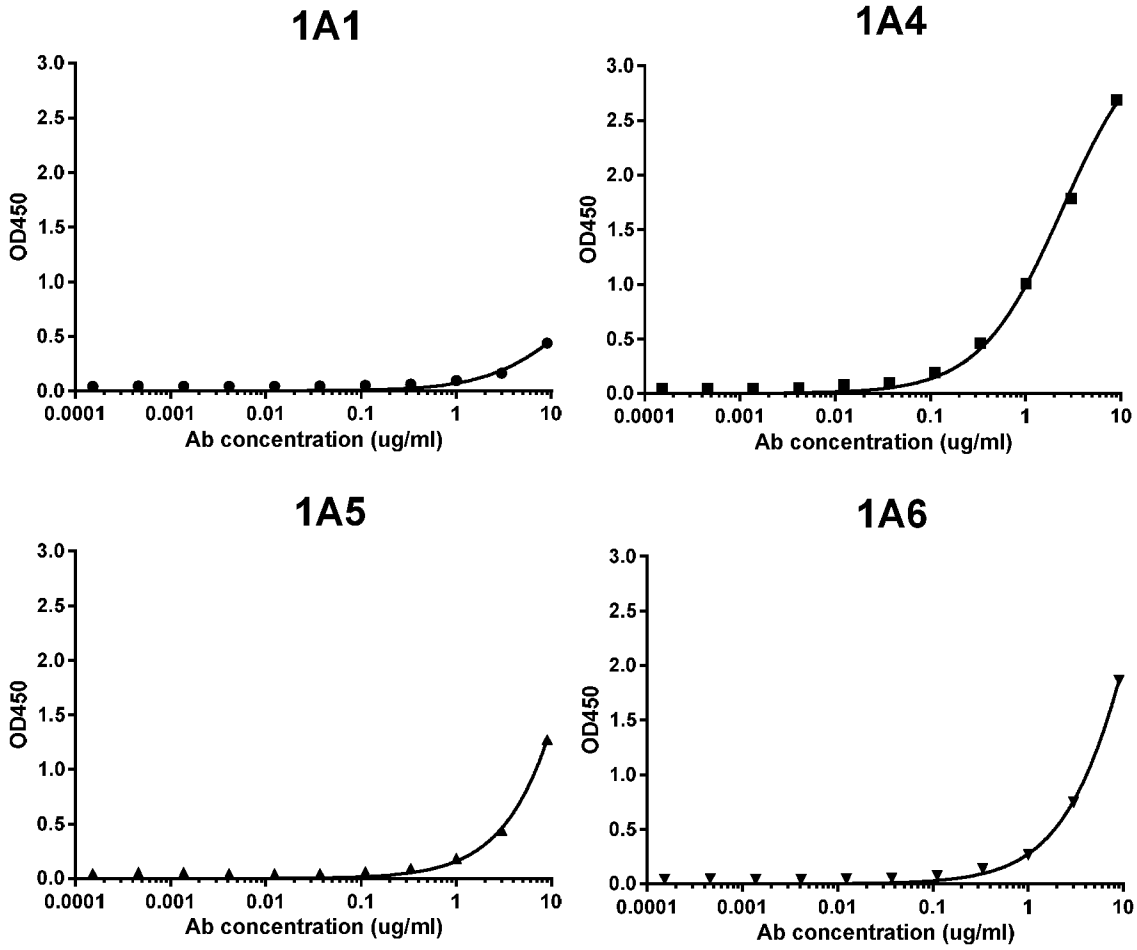
301. The recombinant protein of claim 298, wherein said effector cell ligand is a CD3 protein.

302. A pharmaceutical composition comprising a therapeutically effective amount of the recombinant protein of claim 298 and a pharmaceutically acceptable excipient.

303. A method of treating cancer in a subject in need thereof, said method comprising administering to a subject a therapeutically effective amount of the recombinant protein of claim 298, thereby treating cancer in said subject.

1

FIG. 1


1A1
1A4
1A5
1A6
OD450
Ab concentration (ug/ml)
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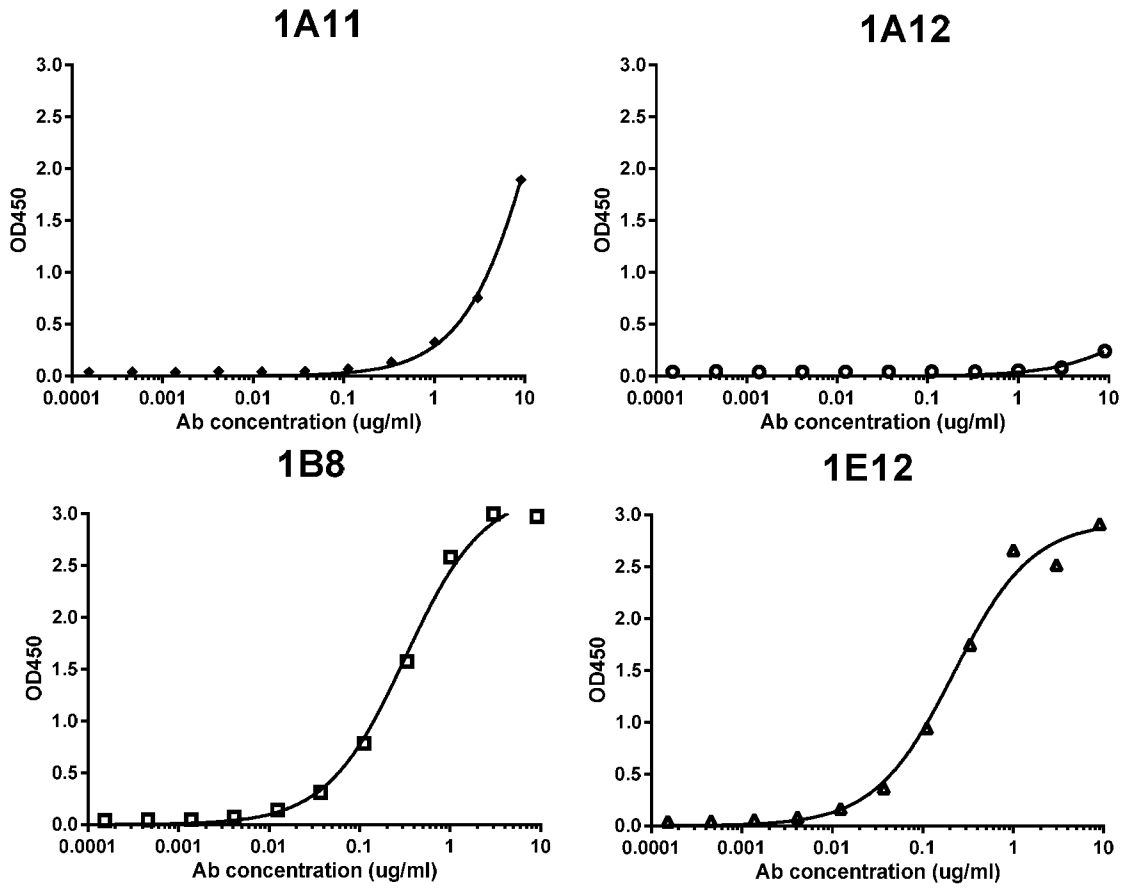
0.5
1.0
1.5
2.0
2.5
3.0
0.0001
0.001
0.01
0.1
1
10

FIG. 2


1A11
1A12
1B8
1E12
OD450
Ab concentration (ug/ml)
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0.5
1.0
1.5
2.0
2.5
3.0
0.0001
0.001
0.01
0.1
1
10

FIG. 3

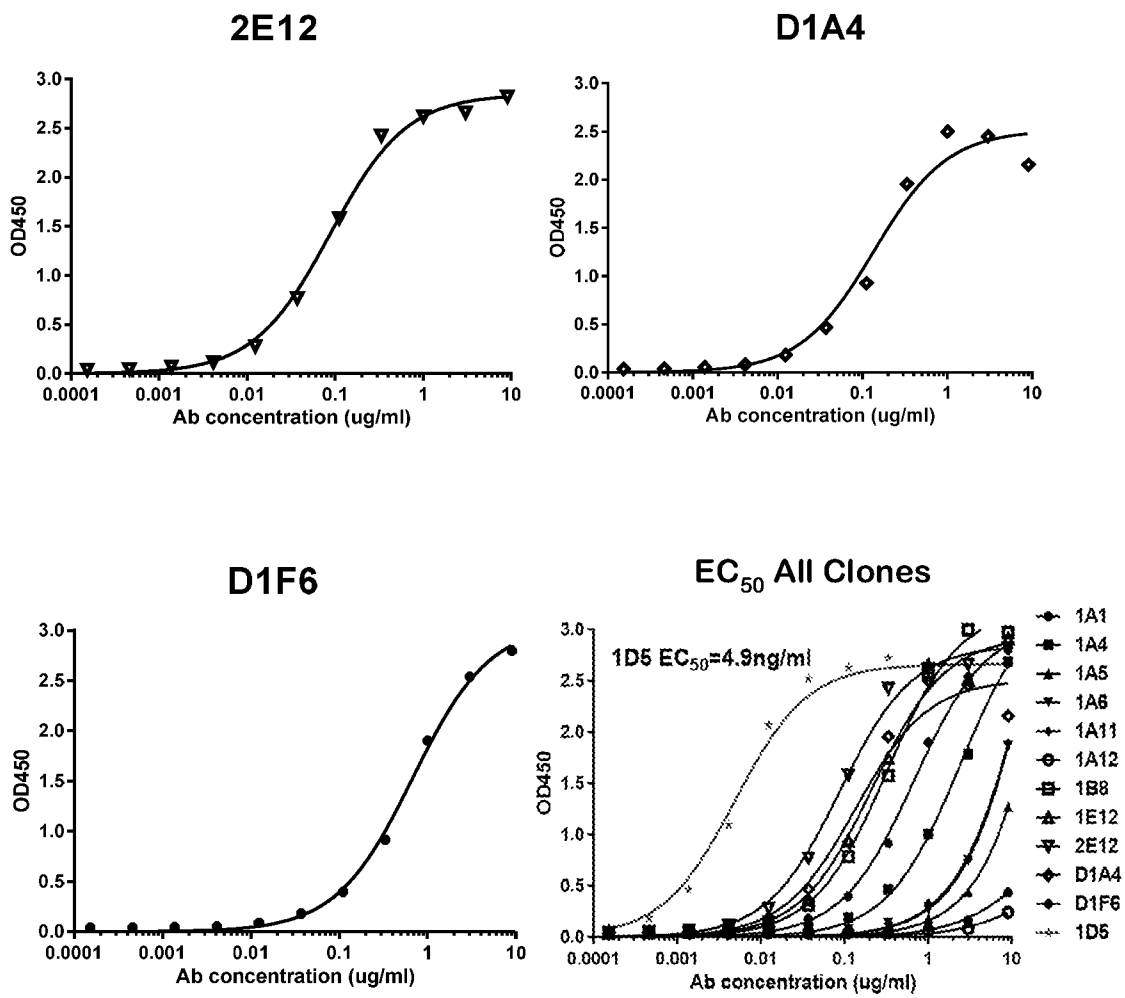
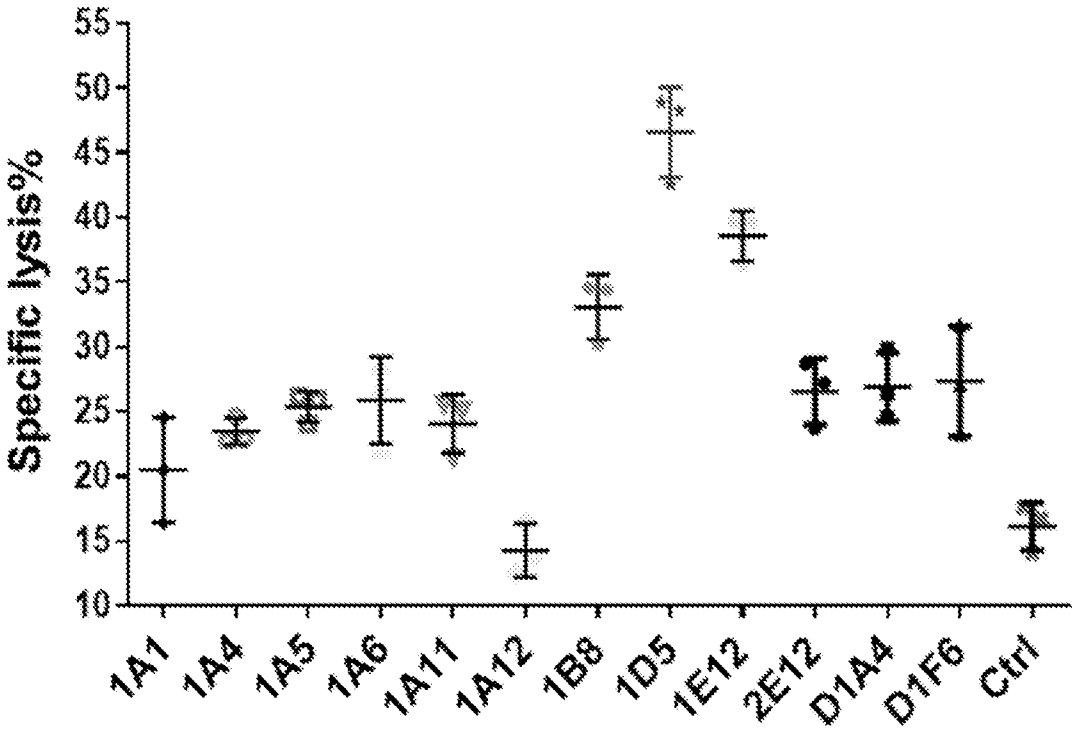

2E12
D1A4
D1F6
EC50 All Clones
OD450
Ab concentration (ug/ml)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0.0001
0.001
0.01
0.1
1
10
1D5 EC50=4.9ng/ml
1A1
1A4
1A5
1A6
1A11
1A12
1B8
1E12
2E12
D1A4
D1F6
1D5

FIG. 4


Specific lysis%
55
50
45
40
35
30
25
20
15
10
1A1
1A4
1A5
1A6
1A11
1A12
1B8
1D5
1E12
2E12
D1A4
D1F6
Ctrl