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(54) Title: IL-18 RECEPTOR ANTIGEN BINDING PROTEINS

(57) Abstract: Provided herein are IL-18 receptor antigen binding proteins and polynucleotides encoding the same. Expression vectors and host cells comprising the same for production of the antigen binding proteins are also provided. In addition, provided are compositions and methods for diagnosing and treating diseases mediated by IL-18 receptor.

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IL-18 RECEPTOR ANTIGEN BINDING PROTEINS

I. FIELD OF THE INVENTION

[0001] Provided herein are IL-18 receptor antigen binding proteins and polynucleotides encoding the same. Expression vectors and host cells comprising the same for production of the antigen binding proteins are also provided. In addition, provided are compositions and methods for diagnosing and treating diseases mediated by IL-18 receptor.

II. BACKGROUND

[0002] IL-18 is a proinflammatory cytokine that belongs to the IL-1 family of ligands. Okamura *et al.*, 1995, *Nature* 378:88-91. Also referred to as IFN-γ-inducing factor, IL-18 is a cytokine that plays an important role in the TH1 response, primarily by its ability to induce IFN-γ production in T cells and natural killer cells. IL-18 is related to the IL-1 family in both structure and function. In terms of structure, IL-18 and IL-1 β share significant primary amino acid sequences and are both folded as β-sheet polypeptides. In terms of function, IL-18 induces gene expression and synthesis of IL-1 , TNF, Fas ligand, and several cytokines.

[0003] The activity of IL-18 is transduced through a signal transducing pathway initiated by its forming of a IL-18 receptor (IL-18R) complex. The IL-18R includes a binding chain termed α-IL-18 receptor (α-IL-18R), a member of the IL-IR family previously identified as the IL-1 R-related protein (IL-1 Rrp), and a β-IL-18 receptor (β-IL-18R), also a member of the IL-1 R family and previously identified as AcPL; both chains are required for signaling. Born *et al.*, 1998, *J. Biol. Chem.* 273:29445-50. The IL-18/IL-18R complex recruits IL-1 R-activating kinase and TNF receptor-associated factor-6, which phosphorylates nuclear factor kappaB (NFkappaB)-inducing kinase with subsequent activation of NFkappaB. IL-18 participates in both innate and acquired immunity. Dinarello, 1999, *J. Allergy Clin. Immun.* 103:11-24.

[0004] Increased levels of IL-18 and/or involvement of IL-18 mediated signals in pathogenesis have been demonstrated in a variety of human disease states, including autoimmune diseases (WO2004/002519; WO2005/063290; WO2004/034988; Mallat *et al.*, 2002, *Circ. Res.* 91:441-448), hepatic diseases (Finitto *et al.*, 2004, *Liver* 53:392-400; Tsutsui *et al.*, 2000, *Immunological Reviews* 174:192-209; Ludwiczek *et al.*, 2002, *J. Clinical Immunology* 22:331-337), pancreatic diseases, and cardiovascular diseases (Gerdes *et al*, 2002, *J. Exp. Med.* 195:245-257; WO03/080104; WO02/060479; WO01/85201 ; Raeburn *et al.*, 2002, *Am. J. Physiol. Heart Circ. Physiol.* 283:H650-H657). Accordingly, it is desirable to generate new agents capable of modulating the IL-18/IL-18 receptor interaction.

III. SUMMARY

[0005] Provided herein are α- and β-IL-18 receptor (also referred to herein collectively as "IL-18 receptor" or "IL-18R") antigen binding proteins and polynucleotides that encode them. The IL-18 receptor antigen binding proteins inhibit, interfere with, or modulate at least one of the biological responses mediated by IL-18 and as such can be useful for ameliorating the effects of IL-18 mediated diseases or disorders. Also provided are expression systems, including cell lines, for the production of α- and β-IL-18 receptor antigen binding proteins and methods for diagnosing and treating diseases associated with aberrant IL-18 activity.

[0006] In one embodiment, antigen binding proteins bind the α- and β-IL-18 receptor, and comprise (a) a scaffold structure; and (b) at least one complementary determining region (CDR), selected from the CDRH regions of any of SEQ ID NOs:89-139 or the CDRL regions of any of SEQ ID NOs:140-190. In this embodiment, of particular use are antigen binding proteins with a CDRH3 or CDRL3 region of SEQ ID NO:91 , 94, 97, 100, 103, 106, 109, 112, 1 15, 118, 121 , 124, 127, 130, 133, 136, 139 or SEQ ID NO:142, 145, 148, 151 , 154, 157, 160, 163, 166, 169, 172, 175, 178, 181 , 184, 187, 190, respectively. Additional embodiments utilize antigen binding proteins with one CDR selected from the CDRH regions of any of SEQ ID NOs:89-139 and a CDRL region of any of SEQ ID NOs: 140-190 (e.g., the antigen binding protein has two CDR regions, one heavy and one light; again, in a specific embodiment the antigen binding proteins have both a CDRH3 and a CDRL3 region).

[0007] The antigen binding proteins can bind to an IL-18 receptor α- or β-chain having the amino acid sequence of SEQ ID NO:69 or SEQ ID NO:71 , respectively. In one embodiment there is provided an isolated antigen binding protein that binds to a three-dimensional structure formed by amino acid residues 250-253 and 267-271 of mature IL-18 receptor (SEQ ID NO:69).

[0008] Described herein are antigen binding proteins that comprise a heavy chain amino acid sequence that comprises at least one CDR selected from the group consisting of: (a) a CDRH 1 of any of SEQ ID NOs:89, 92, 95, 98, 101 , 104, 107, 110, 113, 1 16, 119, 122, 125, 128, 131 , 134, 137; (b) a CDRH2 of any of SEQ ID NOs:90, 93, 96, 99, 102, 105, 108, 111 , 114, 117, 120, 123, 126, 129, 132, 135, 138; and (c) a CDRH3 of any of SEQ ID NOs:91 , 94, 97, 100, 103, 106, 109, 112, 115, 118, 121 , 124, 127, 130, 133, 136, 139; and/or a light chain amino acid sequence that comprises at least one CDR selected from the group consisting of: (a) a CDRL1 of any of SEQ ID NOs: 140, 143, 146, 149, 152, 155, 158, 161 , 164, 167, 170, 173, 176, 179, 182, 185, 188; (b) a CDRL2 of any of SEQ ID NOs:141 , 144, 147, 150, 153, 156, 159, 162, 165, 168, 171 , 174, 177, 180, 183, 186, 189; and (c) a CDRL3 of any of SEQ ID NOs: 142, 145, 148, 151 , 154, 157, 160, 163, 166, 169, 172, 175, 178, 181 , 184, 187, 190.

[0009] In certain aspects, the antigen binding protein comprises a heavy chain amino acid sequence having a CDRHI , a CDRH2, and a CDRH3 of any of SEQ ID NOs:89-139, and/or a light chain amino acid sequence that comprises a CDRL1 , a CDRL2, and a CDRL3 of any of

SEQ ID NOs:140-190. Preferred antigen binding proteins comprise a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 1-17 and/or a light chain amino acid sequence selected from the group consisting of SEQ ID NOs: 18-34. Preferred CDRH3s include those set forth in any of SEQ ID NOs:91 , 94, 97, 100, 103, 106, 109, 112, 115, 118, 121 , 124, 127, 130, 133, 136, 139. Preferred CDRL3s include those set forth in any of SEQ ID NOs: 142, 145, 148, 151 , 154, 157, 160, 163, 166, 169, 172, 175, 178, 181 , 184, 187, 190.

[0010] In certain aspect, the present invention provides an isolated antigen binding protein that binds a human IL-18 receptor, wherein said antigen binding protein comprises: a heavy chain amino acid sequence that comprises: (a) a CDRH1 of SEQ ID NO: 104, (b) a CDRH2 of SEQ ID NO: 105 and (c) a CDRH3 of SEQ ID NO: 106; and a light chain amino acid sequence that comprises: (a) a CDRL1 of SEQ ID NO: 173, (b) a CDRL2 of SEQ ID NO: 174, and (c) a CDRL3 of SEQ ID NO: 175; or a heavy chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:6; and a light chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:19.

[0011] In certain aspects, the antigen binding protein comprises one or more IgG heavy or light chains, including those of the IgGI-, IgG2- IgG3- or IgG4-type. Preferred IgG heavy chains include, but are not limited to, those set forth in SEQ ID NO:73, 77, 81 , and 85. Preferred IgG light chains include, but are not limited to, those set forth in SEQ ID NO:75, 79, 83, and 87. In one embodiment there is provided an isolated antigen binding protein comprising an IgG heavy chain of SEQ ID NO: 73, or an IgG light chain of SEQ ID NO: 75.

[0012] As described herein, antigen binding proteins that bind to amino acid residues 250-253 and 267-271 of a three dimensional structure formed by mature α-IL-18 receptor (SEQ ID NO:69) are particularly useful in blocking the interaction of IL-18 with IL-18 receptor.

[0013] An antigen binding protein can be a monoclonal antibody, a human antibody, a recombinant antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or a fragment thereof. Antibody fragments include, but are not limited to, a minibody, a domain antibody, a F(ab) fragment, a F(ab') fragment, a $F(ab')_2$ fragment, a Fv fragment, a scFv fragment, a Fd fragment, a diabody, or a single chain antibody molecule.

[0014] In other aspects, provided herein are isolated nucleic acids encoding one or more IL-18 receptor antigen binding proteins. Such nucleic acids can be comprised within a vector and operably linked to a control sequence. Also, provided herein are host cells transformed with such isolated nucleic acids.

[0015] Additionally, provided herein are pharmaceutical compositions comprising an IL-18 receptor antigen binding protein and a pharmaceutically acceptable carrier. Such pharmaceutical compositions are useful in methods for preventing or treating a condition associated with IL-18 receptor in a patient, which comprise administering an effective amount

thereof to the patient. Diseases and conditions associated with IL-18 receptor include inflammatory and autoimmmune diseases (such as psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, Still's disease, ankylosing spondylitis, osteo arthritis, ulcerative arthritis, coleliac disease, psoriatic arthritis, chronic obstructive pulmonary disease, asthma, particularly chronic severe asthma, acute respiratory distress syndrome, sepsis, Alzheimer disease, lupus, allergic rhinitis, idiopathic thrombocytopenic purpura, transplantation, atopic dermatitis, type II diabetes, Crohn's disease, inflammatory bowel disease, multiple sclerosis, autoimmune hepatitis, HIV, atopic dermatitis, myasthenia gravis, sarcoidosis), a

hepatic disease (such as hepatitis), a pancreatic disease (such as chronic pancreatitis or acute pancreatitis), and a cardiovascular disease (such as acute heart attacks, atheromatous plaque rupture, post-ischemic heart failure, reperfusion injury, vascular inflammation, chronic heart failure, artherosclerosis, cardiovascular complications of rheumatoid arthritis, and atherogenesis).

[0016] Further provided herein are methods of inhibiting the binding of IL-18 to IL-18 receptor comprising contacting an IL-18 receptor with an IL-18 receptor antigen binding protein. Upon binding IL-18 receptor, the IL-18 receptor antigen binding protein will prevent or block binding of the receptor to IL-18.

IV. DESCRIPTION OF THE DRAWINGS

[0017] FIGURES 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J, 1K, 1L, 1M, 1N, 1O, 1P, and 1Q depict nucleic acid and amino acid sequences of VH and VL variable domains of α- and β-IL-18 receptor antigen binding proteins.

[0018] FIGURES 2A, 2B, 2C, 2D, and 2E show the CDR1, CDR2, and CDR3 regions of various heavy and light chain variable regions of antigen binding proteins. The amino acid sequences of the various heavy and light chain regions are identified in SEQ ID NOs:1-34. The sequences of the individual CDRs are identified in SEQ ID NOs:89-190.

[0019] FIGURES 3A and 3B depict an alignment of the amino acid sequences of heavy and light chain variable sequences of α- and β-IL-18 receptor antigen binding proteins. The CDR1, CDR2 and CDR3 regions are highlighted in grey.

[0020] FIGURE 4 depicts a chart showing various possible combinations of heavy chain variable regions and light chain variable region sequences. Shown are dimers of each one heavy and one light chain variable region. As naturally occurring antibodies typically are tetramers, an antibody may comprise a combination of two of the depicted dimers.

[0021] FIGURE 5 depicts the portions of the α-IL-18 receptor amino acid sequences that form the epitope for a specific antigen binding protein embodiment.

[0022] FIGURE 6 depicts the complete AM_H6 heavy chain nucleotide and amino acid sequences (SEQ ID NOs:74 and 73, respectively). The arrow indicates the cleavage site of the leader sequence.

[0023] FIGURE 7 depicts the complete AM_L12 light chain nucleotide and amino acid sequences (SEQ ID NOs:76 and 75, respectively). The arrow indicates the cleavage site of the leader sequence.

[0024] FIGURE 8 depicts the complete AM_H4 heavy chain nucleotide and amino acid sequences (SEQ ID NOs:78 and 77, respectively). The arrow indicates the cleavage site of the leader sequence.

[0025] FIGURE 9 depicts the complete AM_L14 light chain nucleotide and amino acid sequences (SEQ ID NOs:80 and 79, respectively). The arrow indicates the cleavage site of the leader sequence.

[0026] FIGURE 10 depicts the complete AM_H9 heavy chain nucleotide and amino acid sequences (SEQ ID NOs:82 and 81, respectively). The arrow indicates the cleavage site of the leader sequence.

[0027] FIGURE 11 depicts the complete AM_L9 light chain nucleotide and amino acid sequences (SEQ ID NOs:84 and 83, respectively). The arrow indicates the cleavage site of the leader sequence.

[0028] FIGURE 12 depicts the complete AM_H11 heavy chain nucleotide and amino acid sequences (SEQ ID NOs:86 and 85, respectively). The arrow indicates the cleavage site of the leader sequence.

[0029] FIGURE 13 depicts the complete AM_L7 light chain nucleotide and amino acid sequences (SEQ ID NOs:88 and 87, respectively). The arrow indicates the cleavage site of the leader sequence.

V. DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0030] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0031] Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, tissue culture and transformation, protein purification etc. Enzymatic reactions and purification techniques may be performed according to the manufacturer's specifications or as commonly accomplished in the art or as described herein. The following procedures and techniques may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the specification. *See*, *e.g.*, Sambrook *et al.*, 2001, *Molecular Cloning: A Laboratory Manual*, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., which is incorporated herein by reference for any purpose. Unless specific definitions are provided, the nomenclature used in connection with, and the the laboratory procedures and techniques of, analytical chemistry, organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, chemical analyses, pharmaceutical preparation, formulation, and delivery and treatment of patients.

A. General Overview

[0032] Provided herein are antigen binding proteins that bind an α- or β-IL-18 receptor; the amino acid sequence of the human α- and β-IL-18 receptor are depicted in SEQ ID NOs:69 and 71, respectively. The antigen binding proteins of the invention comprise a scaffold structure with one or more complementarity-determining region (CDRs) as depicted in FIGURES 2A-2E, 3A and 3B, namely the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 portion of SEQ ID NOs:1-34 (*see*, also SEQ ID NOs:89-292, depicting the amino acid sequences of the various CDRs). In certain

embodiments, the scaffold structure of the antigen binding proteins is based on antibodies (including, but not limited to, monoclonal antibodies, human antibodies, murine antibodies, chimeric antibodies, humanized antibodies, bispecific antibodies), antibody fragments (such as minibodies, domain antibodies, F(ab) fragments, F(ab') fragments, $F(ab)_2$ fragments, $F(ab')_2$ fragments, Fv fragments, scFv fragments, Fd fragments), synthetic antibodies (sometimes referred to herein as "antibody mimetics"), antibody fusions (sometimes referred to as "antibody conjugates"), including Fc fusions. The various structures are further described and defined hereinbelow.

[0033] α- and β-IL-18 receptor antigen binding proteins are useful in treating conditions associated with IL-18 activity, including TH1-driven autoimmune diseases (WO2004/002519; WO2005/063290; WO2004/034988; Mallat *et al.*, 2002, *Circ. Res.* 91:441-448), hepatic diseases (Finitto *et al.*, 2004, *Liver* 53:392-400; Tsutsui *et al.,* 2000, *Immunological Reviews* 174:192-209; Ludwiczek *et al.*, 2002, *J. Clinical Immunology* 22:331-337), pancreatic diseases (Yoshida *et al.*, 1998, *Anticancer Res.* 18:333-5), and cardiovascular diseases (Gerdes *et al*, 2002, *J. Exp. Med.* 195:245-257; WO03/080104; WO02/060479; WO01/85201; Raeburn *et al.*, *2002, Am. J. Physiol. Heart Circ. Physiol.* 283:H650-H657), as is further described below. Other uses for antigen binding proteins include, for example, diagnosis of IL-18 associated diseases or conditions and screening assays to determine the presence or absence of the α- or β-IL-18 receptor. Also provided are α- or β-IL-18 receptor antigen binding proteins, particularly antigen binding proteins that include at least one complementarity determining region (CDR) including heavy and/or light CDRs, as more fully described below, and combinations thereof.

[0034] The antigen binding proteins of the invention interfere with, block or modulate the interaction between IL-18 and the IL-18 receptor. In some embodiments, the antigen binding proteins interrupt the IL-18 pathway, thereby decreasing at least one biological activity of IL-18, including, but not limited to, induction of IFN-γ production, induction of killer cell formation, and enhancement of cytotoxicity of killer cells. As demonstrated in the Examples herein, antigen binding proteins that reduce IL-18 induced production of IFN-γ by KG cells include those comprising AM_H8 and AM_L11, AM_H9 and AM_L9, AM_H10 and AM_L8, AM_H11 and AM_L7, AM_H15 and AM_L3, AM_H13 and AM_L4, AM_H13 and AM_L5, AM_H16 and AM_L2, AM_H2 and AM_L16, AM_H2 and AM_L17, AM_H1 and AM_L16, AM_H1 and AM_L17, AM_H4 and AM_L14, AM_H4 and AM_L15, AM_H3 and AM_L14, AM_H3 and AM_L15, AM_H6 and AM_L12, AM_H6 and AM_L13, AM_H5 and AM_L12, and AM_H5 and AM_L13.

[0035] The antigen binding proteins of the invention thus may serve to identify conditions related to IL-18 or IL-18 receptor induced immune responses. In addition, the antigen binding proteins may be utilized to regulate and/or suppress IL-18 or IL-18 receptor mediated immune responses, as such having efficacy in the treatment and prevention of various diseases caused by excessive immune responses, *e.g.*, inflammatory diseases. Accordingly, the α- and β-IL-18 receptor antigen binding proteins of the present invention can be used for the diagnosis, prevention or treatment of diseases or conditions associated with the IL-18 and IL-18 receptor mediated signal transduction pathway.

B. IL-18 Receptor Antigen Binding Proteins

[0036] In one aspect, antigen binding proteins that bind an α- or β-IL-18 receptor are provided. By "antigen binding protein" as used herein is meant a protein that specifically binds a specified antigen. In specific embodiments, the antigen is a human α- or β-IL-18 receptor.

[0037] By "protein," as used herein, is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. In some embodiments, the two or more covalently attached amino acids are attached by a peptide bond. The protein may be made up of naturally occurring amino acids and peptide bonds, for example when the protein is made recombinantly using expression systems and host cells, as outlined below. Alternatively, the protein may include synthetic amino acids (*e.g.*, homophenylalanine, citrulline, ornithine, and norleucine), or peptidomimetic structures, *i.e.*, "peptide or protein analogs", such as peptoids (*see*, Simon *et al.*, 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:9367, incorporated by reference herein), which can be resistant to proteases or other physiological and/or storage conditions. Such synthetic amino acids may be incorporated in particular when the antigen binding protein is synthesized *in vitro* by conventional methods well known in the art. In addition, any combination of peptidomimetic, synthetic and naturally occurring residues/structures can be used. "Amino acid" also includes imino acid residues such as proline and hydroxyproline. The amino acid "R group" or "side chain" may be in either the (L)- or the (D)-configuration. In a specific embodiment, the amino acids are in the (L)- or (D)-configuration.

[0038] In certain aspects, the invention provides recombinant antigen binding proteins that bind an IL-18 receptor, in some embodiments a human IL-18 receptor. In this context, a "recombinant protein" is a protein made using recombinant techniques, *i.e.*, through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

[0039] In some embodiments, the antigen binding proteins are isolated proteins or substantially pure proteins. An "isolated" protein is unaccompanied by at least some of the material with which it is normally associated in its natural state, preferably constituting at least about 5%, more preferably at least about 50% by weight of the total protein in a given sample. A "substantially pure" protein comprises at least about 75% by weight of the total protein, with at least about 80% being preferred, and at least about 90% being particularly preferred. The definition includes the production of an antigen binding protein from one organism in a different organism or host cell. Alternatively, the protein may be made at a significantly higher concentration than is normally seen, through the use of an inducible promoter or high expression promoter, such that the protein is made at increased concentration levels.

[0040] The antigen binding proteins can specifically bind to an IL-18 receptor, preferably a human IL-18 receptor. "Specifically binds" as used herein means the equilibrium dissociation constant is at least 10^{-6} M, preferably 10^{-7} to 10^{-10} M, more preferably $<10^{-8}$ to $<10^{-10}$ M, even more preferably $<10^{-9}$

to $<10^{-10}$ M. In a specific embodiment, the antigen binding protein binds to a human IL-18 receptor having the amino acid sequence of SEQ ID NO:69 or 71. An epitope in the α- or β-IL-18 receptor to which preferred antigen binding proteins specifically bind is detailed below.

[0041] In embodiments where the antigen binding protein is used for therapeutic applications, an important characteristic of an IL-18 receptor antigen binding protein is whether it can inhibit, interfere with or modulate one or more biological activities of an IL-18 receptor. In this case, an antigen binding protein binds specifically and/or substantially inhibits binding of IL-18 to its receptor when an excess of antibody reduces the quantity of IL-18 bound to IL-18 receptor, or *vice versa*, by at least about 20%, 40%, 60%, 80%, 85%, or more (for example by measuring binding in an *in vitro* competitive binding assay). IL-18 receptor has many distinct biological effects, which can be measured in many different assays in different cell types. The ability of an IL-18 receptor antigen binding protein to inhibit, interfere with, or modulate the biological activity of IL-18 can be determined, for example, by measuring the inhibition of IFN-γ release in KG1 cells, as described in Example 4 or using a similar assay in which the ability of an antigen binding protein to inhibit IFN-γ release is measured.

[0042] Not every antigen binding protein that specifically binds to an antigen can block antigen binding to its normal ligand and thus inhibit or modulate the biological effects of the antigen. As is known in the art, such an effect can depend on what portion of the antigen the antigen binding protein binds to, and on both the absolute and the relative concentrations of the antigen and the antigen binding protein, in this case, an IL-18 receptor and the IL-18 receptor antigen binding protein. To be considered capable of inhibiting or modulating the biological activity of an IL-18 receptor as meant herein, an antigen binding protein may be able, for example, to inhibit the release of IFN-γ observed in the presence of IL-18, as measured in the KG1 cell assay of Example 4 or a similar assay, by at least about 20%, 40%, 60%, 80%, 85%, 90%, 95%, 99%, or more when the IL-18 concentration is within a range, for example, at about EC_{80} or EC_{90}, where the effects of an agent that inhibits its biological activity can be readily apparent. An EC_{80}, as meant herein, is the amount of IL-18 required for 80% of the maximal effect of IL-18 to be observed. If the IL-18 concentration is well above EC_{90}, effects of an inhibiting agent may be less apparent due to the excess of IL-18. The concentration of an antigen binding protein required to inhibit, interfere with or modulate the biological activity of IL-18 receptor can vary widely and may depend upon how tightly the antibody binds to IL-18 receptor. For example, one molecule or less of an antigen binding protein per molecule of IL-18 may be sufficient to inhibit, interfere with or modulate biological activity in the KG1 cell assay. In some embodiments, a ratio of IL-18 receptor/antibody of about 1,000:1 to about 1:1,000, including about 2:1, 1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:20, 1:40, 1:60, 1:100, 1:500, 1:1,000 or more may be required to inhibit, interfere with or modulate the biological activity of IL-18 receptor when the IL-18 concentration is from about EC_{50} to about EC_{90}. Ratios of IL-18 receptor antigen binding protein between these values are also possible.

[0043] As a general structure, the antigen binding proteins of the invention comprise (a) a scaffold, and (b) one or a plurality of CDRs, regions that are determinative to antigen binding specificity and affinity. A "complementary determining region" or "CDR," as used herein, refers to a binding protein region that constitutes the major surface contact points for antigen binding. One or more CDRs are embedded in the scaffold structure of the antigen binding protein. The scaffold structure of the antigen binding proteins may be the framework of an antibody, or fragment or variant thereof, or may be completely synthetic in nature. The various scaffold structures of antigen binding proteins are further described hereinbelow.

1. CDRs

[0044] An antigen binding protein may have six CDRs (as typically does each "arm" of a naturally occurring antibody), for example one heavy chain CDR1 ("CDRH1"), one heavy chain CDR2 ("CDRH2"), one heavy chain CDR3 ("CDRH3"), one light chain CDR1 ("CDRL1"), one light chain CDR2 ("CDRL2"), one light chain CDR3 ("CDRL3"). The term "naturally occurring" as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature. In naturally occurring antibodies, a CDRH1 typically comprises about five (5) to about seven (7) amino acids, CDRH2 typically comprises about sixteen (16) to about nineteen (19) amino acids, and CDRH3 typically comprises about three (3) to about twenty five (25) amino acids. CDRL1 typically comprises about ten (10) to about seventeen (17) amino acids, CDRL2 typically comprises about seven (7) amino acids, and CDRL3 typically comprises about seven (7) to about ten (10) amino acids. Preferred CDRs are depicted in Figures 2A-2E, 3A, and 3B.

[0045] The structure and properties of CDRs within a naturally occurring antibody are described further in this *Section* hereinbelow. Briefly, in a traditional antibody scaffold, the CDRs are embedded within a framework in the heavy and light chain variable region where they constitute the regions responsible for antigen binding and recognition. A variable region comprises at least three heavy or light chain CDRs, *see, supra* (Kabat *et al.*, 1991, *Sequences of Proteins of Immunological Interest*, Public Health Service N.I.H., Bethesda, MD; *see* also Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia *et al.*, 1989, *Nature* 342: 877-883), within a framework region (designated framework regions 1-4, FR1, FR2, FR3, and FR4, by Kabat *et al.*, 1991, *supra*; *see* also Chothia and Lesk, 1987, *supra*). *See, infra.* The CDRs provided by the present invention, however, may not only be used to define the antigen binding domain of a traditional antibody structure, but may be embedded in a variety of other scaffold structures, as described herein.

[0046] In certain embodiments, one or more CDRs of an antigen binding protein are each independently selected from the CDRH regions of any of SEQ ID NOs:89-139 and the CDRL regions of any of SEQ ID NOs:140-190. Thus, in one embodiment, the invention provides an antigen binding protein that binds an α- or β-IL-18 receptor, wherein said antigen binding protein comprises (a) a scaffold structure (as described below); and (b) at least one CDR selected from the CDRH regions of

any of SEQ ID NOs:89-139 and the CDRL regions of any of SEQ ID NOs:140-190. In this embodiment, of particular use are antigen binding proteins with a CDRH3 or CDRL3 region. Additional embodiments utilize antigen binding proteins with one CDR selected from the CDRH regions of any of SEQ ID NOs:89-139 and a CDRL region of any of SEQ ID NOs:140-190 (*e.g.*, the antigen binding protein has two CDR regions, one CDRH and one CDHL, a specific embodiment are antigen binding proteins with both a CDRH3 and a CDRL3 region).

[0047] As will be appreciated by those in the art, particularly useful embodiments may contain one, two, three, four, five or six of independently selected CDRs of SEQ ID NOs:89-190. However, as will be appreciated by those in the art, specific embodiments generally utilize combinations of CDRs that are non-repetitive, *e.g.*, antigen binding proteins are generally not made with two CDRH2 regions, etc.

[0048] In some embodiments, antigen binding proteins are generated that comprise a CDRH3 region and a CDRL3 region, particularly with the CDRH3 region being selected from a CDRH3 region of any of SEQ ID NOs:91, 94, 97, 100, 103, 106, 109, 112, 115, 118, 121, 124, 127, 130, 133, 136, 139 and the CDRL3 region being selected from a CDRL3 region of any of SEQ ID NOs:142, 145, 148, 151, 154, 157, 160, 163, 166, 169, 172, 175, 178, 181, 184, 187, 190. Particular combinations are depicted in FIGURE 4.

[0049] In additional embodiments, antigen binding proteins are utilized that comprise a CDRH1, a CDRH2, and a CDRH3 region independently selected from SEQ ID NOs:89-139. In more specific embodiments, of particular use may be antigen binding proteins of this type that have all three CDRH regions selected from the same variable region of any of SEQ ID NOs:1-17.

[0050] In further embodiments, antigen binding proteins are utilized that comprise a CDRL1, a CDRL2, and a CDRL3 region independently selected from SEQ ID NOs:140-190. In more specific embodiments, of particular use are antigen binding proteins of this type that have all three CDRL regions selected from the same variable region of any of SEQ ID NOs:18-34.

[0051] In an additional embodiment, the antigen binding protein comprises a CDRH1, CDRH2, and CDRH3 region independently selected from SEQ ID NOs:89-139, again, in one embodiment with all three regions selected from the same SEQ ID NO, and a CDRL1, CDRL2, and CDRL3 region independently selected from SEQ ID NOs:140-190, again, in one embodiment with all three regions selected from the same variable region of any of SEQ ID NOs:1-34.

[0052] In yet another aspect of the invention provides for an antigen binding protein that binds the α- or β IL-18 receptor where the isolated antigen binding protein comprises a heavy chain amino acid sequence that comprises a CDRH1, a CDRH2, or a CDRH3, each selected from any of SEQ ID NOs:89-139, or a fragment thereof, or a light chain amino acid sequence that comprises a CDRL1, a CDRL2, or a CDRL3, each selected from any of SEQ ID NOs:140-190, or a fragment thereof. A heavy or light chain variable region "fragment," as used herein includes at least one CDR and at least

a portion of a framework region of an antibody framework of SEQ ID NOs:1-34, said portion comprising at least one amino acid.

[0053] In yet another aspect, the invention provides for an antigen binding protein that binds an α- or β-IL-18 receptor where the isolated antigen binding protein comprises a heavy chain amino acid sequence that comprises a CDRH1, a CDRH2, and a CDRH3, each independently selected from any of SEQ ID NOs:89-139, or a light chain amino acid sequence that comprises a CDRL1, a CDRL2, and a CDRL3, each independently selected from any of SEQ ID NOs:140-190. In a specific embodiment, the CDRs are from the same contiguous heavy chain amino acid sequence of SEQ ID NOs:1-17 or from the same contiguous light chain amino acid sequence of SEQ ID NOs:18-34.

[0054] A further aspect of the invention provides for an isolated antigen binding protein that binds an α- or β-IL-18 receptor where the isolated antigen binding protein comprises a heavy chain amino acid sequence that comprises a CDRH1, a CDRH2, and a CDRH3, each independently selected from any of SEQ ID NOs:89-139, and a light chain amino acid sequence that comprises a CDRL1, a CDRL2, and a CDRL3, each independently selected from any of SEQ ID NOs:140-190. In a specific embodiment, the heavy chain CDRs are from the same contiguous heavy chain amino acid sequence of SEQ ID NO:1-17 and the light chain CDRs are from the same contiguous light chain amino acid sequence of SEQ ID NO:18-34.

[0055] An additional aspect of the invention provides for an isolated antigen binding protein that binds an α- or β-IL-18 receptor where the isolated antigen binding protein comprises a heavy chain amino acid sequence of any of SEQ ID NOs:1-17, or a light chain amino acid sequence of any of SEQ ID NOs:18-34.

[0056] A further aspect of the invention provides for an isolated antigen binding protein that binds an α- or β-IL-18 receptor where the isolated antigen binding protein comprises a heavy chain amino acid sequence of any of SEQ ID NOs:1-17, and a light chain amino acid sequence of any of SEQ ID NOs:18-34. It is noted that the any the heavy chain sequences of SEQ ID NOs:1-17 can be mixed and matched with any of the light chain sequences of SEQ ID NOs:18-34. The resulting possible combinations are depicted in FIGURE 4. Shown are dimers of a combination of each one heavy and one light chain variable region. As most antibodies are tetramers, an antigen binding protein of the invention may comprise any combination of any two of the depicted dimers thus including both hetero- and homo-tetramers, with homo-tetramers (*e.g.*, two identical dimers) being specific.

[0057] In again a further aspect the antigen binding protein of the invention comprises any of the sequences depicted in SEQ ID NOs:73-88.

[0058] TABLE 1 provides a brief description of the sequences as they relate to their sequence identification numbers. The CDRs within the variable regions of the invention are identified in FIGURES 2A-2E, 3A and 3B.

TABLE 1

Brief Description Of Sequence Listings

Brief Description	Sequence Identification Number
Amino acid sequence encoding the heavy chain variable region AM_H1	SEQ ID NO:1
Amino acid sequence encoding the heavy chain variable region AM_H2	SEQ ID NO:2
Amino acid sequence encoding the heavy chain variable region AM_H3	SEQ ID NO:3
Amino acid sequence encoding the heavy chain variable region AM_H4	SEQ ID NO:4
Amino acid sequence encoding the heavy chain variable region AM_H5	SEQ ID NO:5
Amino acid sequence encoding the heavy chain variable region AM_H6	SEQ ID NO:6
Amino acid sequence encoding the heavy chain variable region AM_H7	SEQ ID NO:7
Amino acid sequence encoding the heavy chain variable region AM_H8	SEQ ID NO:8
Amino acid sequence encoding the heavy chain variable region AM_H9	SEQ ID NO:9
Amino acid sequence encoding the heavy chain variable region AM_H10	SEQ ID NO:10
Amino acid sequence encoding the heavy chain variable region AM_H11	SEQ ID NO:11
Amino acid sequence encoding the heavy chain variable region AM_H12	SEQ ID NO:12
Amino acid sequence encoding the heavy chain variable region AM_H13	SEQ ID NO:13
Amino acid sequence encoding the heavy chain variable region AM_H14	SEQ ID NO:14
Amino acid sequence encoding the heavy chain variable region AM_H15	SEQ ID NO:15
Amino acid sequence encoding the heavy chain variable region AM_H16	SEQ ID NO:16
Amino acid sequence encoding the heavy chain variable region AM_H17	SEQ ID NO:17
Amino acid sequence encoding the light chain variable region AM_L1	SEQ ID NO:18
Amino acid sequence encoding the light chain variable region AM_L2	SEQ ID NO:19
Amino acid sequence encoding the light chain variable region AM_L3	SEQ ID NO:20
Amino acid sequence encoding the light chain variable region AM_L4	SEQ ID NO:21
Amino acid sequence encoding the light chain variable region AM_L5	SEQ ID NO:22
Amino acid sequence encoding the light chain variable region AM_L6	SEQ ID NO:23
Amino acid sequence encoding the light chain variable region AM_L7	SEQ ID NO:24
Amino acid sequence encoding the light chain variable region AM_L8	SEQ ID NO:25

Amino acid sequence encoding the light chain variable region AM_L9	SEQ ID NO:26
Amino acid sequence encoding the light chain variable region AM_L10	SEQ ID NO:27
Amino acid sequence encoding the light chain variable region AM_L11	SEQ ID NO:28
Amino acid sequence encoding the light chain variable region AM_L12	SEQ ID NO:29
Amino acid sequence encoding the light chain variable region AM_L13	SEQ ID NO:30
Amino acid sequence encoding the light chain variable region AM_L14	SEQ ID NO:31
Amino acid sequence encoding the light chain variable region AM_L15	SEQ ID NO:32
Amino acid sequence encoding the light chain variable region AM_L16	SEQ ID NO:33
Amino acid sequence encoding the light chain variable region AM_L17	SEQ ID NO:34
Nucleotide sequence encoding the heavy chain variable region AM_H1	SEQ ID NO:35
Nucleotide sequence encoding the heavy chain variable region AM_H2	SEQ ID NO:36
Nucleotide sequence encoding the heavy chain variable region AM_H3	SEQ ID NO:37
Nucleotide sequence encoding the heavy chain variable region AM_H4	SEQ ID NO:38
Nucleotide sequence encoding the heavy chain variable region AM_H5	SEQ ID NO:39
Nucleotide sequence encoding the heavy chain variable region AM_H6	SEQ ID NO:40
Nucleotide sequence encoding the heavy chain variable region AM_H7	SEQ ID NO:41
Nucleotide sequence encoding the heavy chain variable region AM_H8	SEQ ID NO:42
Nucleotide sequence encoding the heavy chain variable region AM_H9	SEQ ID NO:43
Nucleotide sequence encoding the heavy chain variable region AM_H10	SEQ ID NO:44
Nucleotide sequence encoding the heavy chain variable region AM_H11	SEQ ID NO:45
Nucleotide sequence encoding the heavy chain variable region AM_H12	SEQ ID NO:46
Nucleotide sequence encoding the heavy chain variable region AM_H13	SEQ ID NO:47
Nucleotide sequence encoding the heavy chain variable region AM_H14	SEQ ID NO:48
Nucleotide sequence encoding the heavy chain variable region AM_H15	SEQ ID NO:49
Nucleotide sequence encoding the heavy chain variable region AM_H16	SEQ ID NO:50
Nucleotide sequence encoding the heavy chain variable region AM_H17	SEQ ID NO:51
Nucleotide sequence encoding the light chain variable region AM_L1	SEQ ID NO:52
Nucleotide sequence encoding the light chain variable region AM_L2	SEQ ID NO:53

Nucleotide sequence encoding the light chain variable region AM_L3	SEQ ID NO:54
Nucleotide sequence encoding the light chain variable region AM_L4	SEQ ID NO:55
Nucleotide sequence encoding the light chain variable region AM_L5	SEQ ID NO:56
Nucleotide sequence encoding the light chain variable region AM_L6	SEQ ID NO:57
Nucleotide sequence encoding the light chain variable region AM_L7	SEQ ID NO:58
Nucleotide sequence encoding the light chain variable region AM_L8	SEQ ID NO:59
Nucleotide sequence encoding the light chain variable region AM_L9	SEQ ID NO:60
Nucleotide sequence encoding the light chain variable region AM_L10	SEQ ID NO:61
Nucleotide sequence encoding the light chain variable region AM_L11	SEQ ID NO:62
Nucleotide sequence encoding the light chain variable region AM_L12	SEQ ID NO:63
Nucleotide sequence encoding the light chain variable region AM_L13	SEQ ID NO:64
Nucleotide sequence encoding the light chain variable region AM_L14	SEQ ID NO:65
Nucleotide sequence encoding the light chain variable region AM_L15	SEQ ID NO:66
Nucleotide sequence encoding the light chain variable region AM_L16	SEQ ID NO:67
Nucleotide sequence encoding the light chain variable region AM_L17	SEQ ID NO:68
Amino acid sequence of human α-IL-18 receptor	SEQ ID NO:69
Nucleotide sequence of human α-IL-18 receptor	SEQ ID NO:70
Amino acid sequence of human β-IL-18 receptor	SEQ ID NO:71
Nucleotide sequence of human β-IL-18 receptor	SEQ ID NO:72
Amino acid sequence of complete heavy chain of AM_H6	SEQ ID NO:73
Nucleotide sequence of complete heavy chain of AM_H6	SEQ ID NO:74
Amino acid sequence of complete light chain of AM_L12	SEQ ID NO:75
Nucleotide sequence of complete light chain of AM_L12	SEQ ID NO:76
Amino acid sequence of complete heavy chain of AM_H4	SEQ ID NO:77
Nucleotide sequence of complete heavy chain of AM_H4	SEQ ID NO:78
Amino acid sequence of complete light chain of AM_L14	SEQ ID NO:79
Nucleotide sequence of complete light chain of AM_L14	SEQ ID NO:80
Amino acid sequence of complete heavy chain of AM_H9	SEQ ID NO:81

Nucleotide sequence of complete heavy chain of AM_H9	SEQ ID NO:82
Amino acid sequence of complete light chain of AM_L9	SEQ ID NO:83
Nucleotide sequence of complete light chain of AM_L9	SEQ ID NO:84
Amino acid sequence of complete heavy chain of AM_H11	SEQ ID NO:85
Nucleotide sequence of complete heavy chain of AM_H11	SEQ ID NO:86
Amino acid sequence of complete light chain of AM_L7	SEQ ID NO:87
Nucleotide sequence of complete light chain of AM_L7	SEQ ID NO:88
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H1	SEQ ID NO:89, 90, 91
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H2	SEQ ID NO:92, 93, 94
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H3	SEQ ID NO:95, 96, 97
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H4	SEQ ID NO:98, 99, 100
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H5	SEQ ID NO:101, 102, 103
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H6	SEQ ID NO:104, 105, 106
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H7	SEQ ID NO:107, 108, 109
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H8	SEQ ID NO:110, 111, 112
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H9	SEQ ID NO:113, 114, 115
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H10	SEQ ID NO:116, 117, 118
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H11	SEQ ID NO:119, 120, 121
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H12	SEQ ID NO:122, 123, 124
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H13	SEQ ID NO:125, 126, 127
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H14	SEQ ID NO:128, 129, 130

Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H15	SEQ ID NO:131, 132, 133
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H16	SEQ ID NO:134, 135, 136
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H17	SEQ ID NO:137, 138, 139
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L1	SEQ ID NO:140, 141, 142
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L2	SEQ ID NO:143, 144, 145
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L3	SEQ ID NO:146, 147, 148
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L4	SEQ ID NO:149, 150, 151
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L5	SEQ ID NO:152, 153, 154
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L6	SEQ ID NO:155, 156, 157
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L7	SEQ ID NO:158, 159, 160
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L8	SEQ ID NO:161, 162, 163
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L9	SEQ ID NO:164, 165, 166
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L10	SEQ ID NO:167, 168, 169
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L11	SEQ ID NO:170, 171, 172
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L12	SEQ ID NO:173, 174, 175
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L13	SEQ ID NO:176, 177, 178
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L14	SEQ ID NO:179, 180, 181
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L15	SEQ ID NO:182, 183, 184
Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L16	SEQ ID NO:185, 186, 187

Amino acid sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L17	SEQ ID NO:188, 189, 190
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H1	SEQ ID NO:191, 192, 193
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H2	SEQ ID NO:194, 195, 196
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H3	SEQ ID NO:197, 198, 199
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H4	SEQ ID NO:200, 201, 202
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H5	SEQ ID NO:203, 204, 205
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H6	SEQ ID NO:206, 207, 208
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H7	SEQ ID NO:209, 210, 211
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H8	SEQ ID NO:212, 213, 214
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H9	SEQ ID NO:215, 216, 217
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H10	SEQ ID NO:218, 219, 220
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H11	SEQ ID NO:221, 222, 223
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H12	SEQ ID NO:224, 225, 226
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H13	SEQ ID NO:227, 228, 229
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H14	SEQ ID NO:230, 231, 232
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H15	SEQ ID NO:233, 234, 235
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H16	SEQ ID NO:236, 237, 238
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of heavy chain variable region AM_H17	SEQ ID NO:239, 240, 241
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L1	SEQ ID NO:242, 243, 244

Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L2	SEQ ID NO:245, 246, 247
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L3	SEQ ID NO:248, 249, 250
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L4	SEQ ID NO:251, 252, 253
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L5	SEQ ID NO:254, 255, 256
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L6	SEQ ID NO:257, 258, 259
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L7	SEQ ID NO:260, 261, 262
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L8	SEQ ID NO:263, 264, 265
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L9	SEQ ID NO:266, 267, 268
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L10	SEQ ID NO:269, 270, 271
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L11	SEQ ID NO:272, 273, 274
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L12	SEQ ID NO:275, 276, 277
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L13	SEQ ID NO:278, 279, 280
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L14	SEQ ID NO:281, 282, 283
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L15	SEQ ID NO:284, 285, 286
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L16	SEQ ID NO:287, 288, 289
Nucleotide sequence encoding CDR1, CDR 2, CDR 3, respectively, of light chain variable region AM_L17	SEQ ID NO:290, 291, 292

2. Scaffolds

[0059] As noted herein, the antigen binding proteins can comprise a scaffold structure into which the CDR(s) are grafted. The scaffold structure may be based on antibodies (including, but not limited to, monoclonal antibodies, human antibodies, murine antibodies, chimeric antibodies, humanized antibodies, bispecific antibodies), antibody fragments (such as minibodies, domain antibodies, F(ab)

fragments, F(ab') fragments, $F(ab)_2$ fragments, $F(ab')_2$ fragments, Fv fragments, scFv fragments, Fd fragments), synthetic antibodies (sometimes referred to herein as "antibody mimetics"), antibody fusions (sometimes referred to as "antibody conjugates"), including Fc fusions. Some embodiments include the use of human scaffold components. The invention as such at least encompasses any of the below described scaffolds comprising one or several of the CDRs as identified in SEQ ID NOs:89-190, preferably of SEQ ID NOs:89-189, that can bind to and/or inhibit the biological activity of IL-18 receptor. In some embodiments, the scaffold comprises one or several heavy chain variable regions as identified in SEQ ID NOs:1-17, and or one or several light chain variable regions as identified in any of SEQ ID NOs:18-34. In some embodiments, the scaffold comprises an IgG chain as identified in any of SEQ ID NOs:77-88.

[0060] In one embodiment, the scaffold into which one or several CDRs are grafted is an antibody. As used herein, the term "antibody" refers to a multimeric protein having a traditional antibody structure, comprising at least two, more typically four polypeptide chains. An antibody binds specifically to an antigen and may be able to inhibit or modulate the biological activity of the antigen. In certain embodiments, antibodies are produced by recombinant DNA techniques. In additional embodiments, antibodies are produced by enzymatic or chemical cleavage of naturally occurring antibodies.

[0061] Traditional antibody structural units typically comprise a tetramer. Each tetramer is typically composed of two identical pairs of polypeptide chains, each pair having one "light" (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to IgG1, IgG2, IgG3, and IgG4. IgM has subclasses, including, but not limited to, IgM1 and IgM2.

[0062] Within light and heavy chains, the variable and constant regions are joined by a "J" region of about twelve (12) or more amino acids, with the heavy chain also including a "D" region of about ten (10) more amino acids. *See*, generally, Paul, W., ed., 1989, Fundamental Immunology Ch. 7, 2nd ed. Raven Press, N.Y. The variable regions of each light/heavy chain pair form the antibody binding site.

[0063] Some naturally occurring antibodies, for example found in camels and llamas, are dimers consisting of two heavy chain and include no light chains. Muldermans *et al.*, 2001, *J. Biotechnol.* 74:277-302; Desmyter *et al.*, 2001, *J. Biol. Chem.* 276:26285-26290. Crystallographic studies of a camel antibody have revealed that the CDR3 regions form a surface that interacts with the antigen and thus is critical for antigen binding like in the more typical tetrameric antibodies.

[0064] The variable regions of the heavy and light chains typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs are the hypervariable regions of an antibody (or antigen binding protein, as outlined herein), which are responsible for antigen recognition and binding. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest. Chothia *et al.*, 1987, *J. Mol. Biol.* 196:901-917; Chothia *et al.*, 1989, *Nature* 342:878-883.

[0065] CDRs constitute the major surface contact points for antigen binding. *See*, *e.g.*, Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917. Further, CDR3 of the light chain and, especially, CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. *See*, *e.g.,* Chothia and Lesk, 1987, *supra*; Desiderio *et al.*, 2001, *J. Mol. Biol.* 310:603-615; Xu and Davis, 2000, *Immunity* 13:37-45; Desmyter *et al.,* 2001, *J. Biol. Chem.* 276:26285-26290; and Muyldermans, 2001, *J. Biotechnol.* 74:277-302. In some antibodies, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. Desmyter *et al.*, 2001, *supra*. *In vitro* selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody. Muyldermans, 2001, *supra*; Desiderio *et al.*, 2001, *supra*.

[0066] Naturally occurring antibody chains typically include a signal sequence, which directs the antibody chain into the cellular pathway for protein secretion and which is not present in the mature antibody. A polynucleotide encoding an antibody chain may encode a naturally occurring signal sequence or a heterologous signal sequence as described below.

[0067] In one embodiment, the antigen binding protein is a monoclonal antibody, with from one (1) to six (6) of the depicted CDRs of any of SEQ ID NOs:89-190, as outlined herein. The antibodies of the invention may be of any type including IgM, IgG (including IgG1, IgG2, IgG3, IgG4), IgD, IgA, or IgE antibody. In specific embodiment, the antigen binding protein is an IgG type antibody. In an even more specific embodiment, the antigen binding protein is an IgG2 type antibody.

[0068] In some embodiments, for example when the antigen binding protein is an antibody with complete heavy and light chains, the CDRs are all from the same species, *e.g.*, human. In some embodiments, however, the scaffold components can be a mixture from different species. As such, if the antigen binding protein is an antibody, such antibody may be a chimeric antibody and/or a humanized antibody. In general, both “chimeric antibodies” refer to antibodies that combine regions from more than one species. For example, “chimeric antibodies” traditionally comprise variable region(s) from a mouse (or rat, in some cases) and the constant region(s) from a human.

[0069] For example in embodiments wherein the antigen binding protein contains less than six CDRs from the sequences outlined above, additional CDRs may be either from other species (*e.g.*, murine CDRs), or may be different human CDRs than those depicted in the sequences. For example, human CDRH3 and CDRL3 regions from the appropriate sequences identified herein may be used, with CDRH1, CDRH2, CDRL1 and CDRL2 being optionally selected from alternate species, or different human antibody sequences, or combinations thereof. For example, the CDRs of the invention can replace the CDR regions of commercially relevant chimeric or humanized antibodies.

[0070] Specific embodiments of the invention utilize scaffold components of the antigen binding proteins that are human components.

[0071] "Humanized antibodies" generally refer to non-human antibodies that have had the variable-domain framework regions swapped for sequences found in human antibodies. Generally, in a humanized antibody, the entire antibody, except the CDRs, is encoded by a polynucleotide of human origin or is identical to such an antibody except within its CDRs. The CDRs, some or all of which are encoded by nucleic acids originating in a non-human organism, are grafted into the beta-sheet framework of a human antibody variable region to create an antibody, the specificity of which is determined by the engrafted CDRs. The creation of such antibodies is described in, *e.g.*, WO 92/11018, Jones, 1986, *Nature* 321:522-525, Verhoeyen *et al.*, 1988, *Science* 239:1534-1536. Humanized antibodies can also be generated using mice with a genetically engineered immune system. Roque *et al.*, 2004, *Biotechnol. Prog.* 20:639-654. In the present invention, the identified CDRs are human, and thus both humanized and chimeric antibodies in this context include some non-human CDRs; for example, humanized antibodies may be generated that comprise the CDRH3 and CDRL3 regions, with one or more of the other CDR regions being of a different special origin.

[0072] In one embodiment, the IL-18 antigen binding protein is a multispecific antibody, and notably a bispecific antibody, also sometimes referred to as "diabodies". These are antibodies that bind to two (or more) different antigens. Diabodies can be manufactured in a variety of ways known in the art (Holliger and Winter, 1993, *Current Opinion Biotechnol.* 4:446-449), *e.g.*, prepared chemically or from hybrid hybridomas.

[0073] In one embodiment, the IL-18 antigen binding protein is a fully human antibody, *i.e.,* an antibody fully composed of human components. In this embodiment, as outlined above, specific structures comprise complete heavy and light chains depicted comprising the CDR regions depicted in FIGURES 2A-2E, 3A and 3B. Additional embodiments utilize one or more of the CDRs of the invention, with the other CDRs, framework regions, J and D regions, constant regions, etc., coming from other human antibodies. For example, the CDRs of the invention can replace the CDRs of any number of human antibodies, particularly commercially relevant antibodies.

[0074] In one embodiment, the IL-18 antigen binding protein is an antibody fragment, that is a fragment of any of the antibodies outlined herein that retain binding specificity to an α- or β-IL-18 receptor.

[0075] Specific antibody fragments include, but are not limited to, (i) the Fab fragment consisting of VL, VH, CL and CH1 domains, (ii) the Fab' fragment consisting of VL, VH, CL and CH1 domains plus the heavy chain hinge region; (ii) the Fd fragment consisting of the VH and CH1 domains, (iii) the Fv fragment consisting of the VL and VH domains of a single antibody; (iv) the dAb fragment (Ward *et al.*, 1989, *Nature* 341:544-546) which consists of a single variable, (v) isolated CDR regions, (vi) $F(ab')_2$ fragments, a bivalent fragment comprising two linked Fab' fragments (vii) single chain Fv molecules (scFv), wherein a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird *et al.*, 1988, *Science* 242:423-426, Huston *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:5879-5883), (viii) bispecific single chain Fv dimers (PCT/US92/09965) and (ix) "diabodies" or "triabodies", multivalent or multispecific fragments constructed by gene fusion (Tomlinson *et. al.*, 2000, *Methods Enzymol.* 326:461-479; WO94/13804; Holliger *et al.*, 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:6444-6448). The antibody fragments may be modified. For example, the molecules may be stabilized by the incorporation of disulphide bridges linking the VH and VL domains (Reiter *et al.*, 1996, *Nature Biotech.* 14:1239-1245). Again, as outlined herein, the non-CDR components of these fragments are preferably human sequences.

[0076] In one embodiment, the IL-18 antigen binding protein is a minibody. Minibodies are minimized antibody-like proteins comprising a scFv joined to a CH3 domain. Hu *et al.*, 1996, *Cancer Res.* 56:3055-3061.

[0077] In one embodiment, the IL-18 antigen binding protein is a domain antibody; *see* for example U.S. Patent No. 6,248,516. Domain antibodies (dAbs) are functional binding domains of antibodies, corresponding to the variable regions of either the heavy (VH) or light (VL) chains of human antibodies dABs have a molecular weight of approximately 13 kDa, or less than one-tenth the size of a full antibody. dABs are well expressed in a variety of hosts including bacterial, yeast, and mammalian cell systems. In addition, dAbs are highly stable and retain activity even after being subjected to harsh conditions, such as freeze-drying or heat denaturation. *See*, for example, US Patent 6,291,158; 6,582,915; 6,593,081; 6,172,197; US Serial No. 2004/0110941; European Patent 0368684; US Patent 6,696,245, WO04/058821, WO04/003019 and WO03/002609.

[0078] In one embodiment, the IL-18 antigen binding protein is an antibody fusion protein or an antibody fragment fusion, such as an Fc fusion (sometimes collectively referred to herein as an "antibody conjugate"). The conjugate partner can be proteinaceous or non-proteinaceous; the latter generally being generated using functional groups on the antigen binding protein (*see* the discussion on covalent modifications of the antigen binding proteins) and on the conjugate partner. For example linkers are known in the art; for example, homo-or hetero-bifunctional linkers as are well known (*see*,

1994 Pierce Chemical Company catalog, technical section on cross-linkers, pages 155-200, incorporated herein by reference).

[0079] Suitable conjugates include, but are not limited to, labels as described below, drugs and cytotoxic agents including, but not limited to, cytotoxic drugs (*e.g.*, chemotherapeutic agents) or toxins or active fragments of such toxins. Suitable toxins and their corresponding fragments include diptheria A chain, exotoxin A chain, ricin A chain, abrin A chain, curcin, crotin, phenomycin, enomycin and the like. Cytotoxic agents also include radiochemicals made by conjugating radioisotopes to antigen binding proteins, or binding of a radionuclide to a chelating agent that has been covalently attached to the antigen binding protein. Additional embodiments utilize calicheamicin, auristatins, geldanamycin and maytansine.

[0080] In one embodiment, the IL-18 antigen binding protein is an antibody analog, sometimes referred to as "synthetic antibodies." For example, a variety of recent work utilizes either alternative protein scaffolds or artificial scaffolds with grafted CDRs. Such scaffolds include, but are not limited to, mutations introduced to stabilize the three-dimensional structure of the binding protein as well as wholly synthetic scaffolds consisting for example of biocompatible polymers. *See*, for example, Korndorfer *et al.*, 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129. Roque *et al.*, 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold. Alternate scaffolds that may be used to produce an IL-18 antigen binding protein are reviewed in Hey *et al.*, 2005, *Trends Biotechnol.* 23:514-22 and Binz *et al.*, *Nature Biotechnology* 23:1257-68 (both incorporated herein by reference in their entirety).

3. CDR Variants

[0081] Also included within the invention are variants of the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 amino acid sequences depicted in SEQ ID NOs:89-190. Thus variant CDRs are included within the definition of CDR as used herein. These variants fall into one or more of three classes: substitutional, insertional or deletional variants, with the former being specific.

[0082] As it is known in the art, a number of different programs can be used to identify the degree of sequence identity or similarity a protein or nucleic acid has to a known sequence.

[0083] For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Nat. Acad. Sci. U.S.A.* 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence

program described by Devereux *et al.*, 1984, *Nucl. Acid Res.* 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc.

[0084] An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, 1987, *J. Mol. Evol.* 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, *CABIOS* 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

[0085] Another example of a useful algorithm is the BLAST algorithm, described in: Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-410; Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402; and Karin *et al.*, 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5787. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul *et al.*, 1996, *Methods in Enzymology* 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=II. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

[0086] An additional useful algorithm is gapped BLAST as reported by Altschul *et al.*, 1993, *Nucl. Acids Res.* 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; X_u set to 16, and X_g set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

[0087] Generally, the amino acid homology, similarity, or identity between individual variant CDRs are at least 80% to the sequences depicted herein, and more typically with preferably increasing homologies or identities of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and almost 100%.

[0088] In a similar manner, "percent (%) nucleic acid sequence identity" with respect to the nucleic acid sequence of the binding proteins identified herein is defined as the percentage of nucleotide residues in a candidate sequence that are identical with the nucleotide residues in the coding sequence of the antigen binding protein. A specific method utilizes the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

[0089] Generally, the nucleic acid sequence homology, similarity, or identity between the nucleotide sequences encoding individual variant CDRs and the nucleotide sequences depicted herein are at least 60%, and more typically with preferably increasing homologies or identities of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and almost 100%.

[0090] Homology between nucleotide sequences is often defined by their ability to hybridize to each other. The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof in accordance with the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein.

[0091] High stringency conditions are known in the art; *see*, for example Sambrook *et al.*, 2001, *supra*, and *Short Protocols in Molecular Biology*, Second Edition, Ausubel *et al.* eds., John Wiley & Sons, 1992, both of which are hereby incorporated by reference. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Techniques In Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes*, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993).

[0092] Generally, stringent conditions are selected to be about 5-10^{0}C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at Tm, 50% of the probes are occupied at equilibrium). Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium Ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30^{0}C for short probes (*e.g.*, 10 to 50 nucleotides) and at least about 60^{0}C for long probes (*e.g.,* greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

[0093] In another embodiment, less stringent hybridization conditions are used; for example, moderate or low stringency conditions may be used, as are known in the art; *see*, Sambrook *et al.*, 2001, *supra*; Ausubel *et al.*, 1992**,** *supra*, and Tijssen, 1993, *supra*.

[0094] The variants according to the invention are ordinarily prepared by site specific mutagenesis of nucleotides in the DNA encoding the antigen binding protein, using cassette or PCR mutagenesis or other techniques well known in the art, to produce DNA encoding the variant, and thereafter expressing the recombinant DNA in cell culture as outlined herein. However, antigen binding protein fragments comprising variant CDRs having up to about 100-150 residues may be prepared by *in vitro* synthesis using established techniques. The variants typically exhibit the same qualitative biological

activity as the naturally occurring analogue, *e.g.*, binding to IL-18 receptor and inhibiting signaling, although variants can also be selected which have modified characteristics as will be more fully outlined below.

[0095] Thus, a "variant CDR" is one with the specified homology, similarity, or identity to the parent CDR of the invention, and shares biological function, including, but not limited to, at least 90, 91, 92, 93, 94, 95, 96, 97, 98% or 99% of the specificity and/or activity of the parent CDR. For example, the variants typically will bind to the same IL-18 receptor epitope outlined below, with a similar inhibition of IL-18 receptor signaling.

[0096] While the site or region for introducing an amino acid sequence variation is predetermined, the mutation *per se* need not be predetermined. For example, in order to optimize the performance of a mutation at a given site, random mutagenesis may be conducted at the target codon or region and the expressed antigen binding protein CDR variants screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis. Screening of the mutants is done using assays of antigen binding protein activities, such as IL-18 receptor binding.

[0097] Amino acid substitutions are typically of single residues; insertions usually will be on the order of from about one (1) to about twenty (20) amino acid residues, although considerably larger insertions may be tolerated. Deletions range from about one (1) to about twenty (20) amino acid residues, although in some cases deletions may be much larger.

[0098] Substitutions, deletions, insertions or any combination thereof may be used to arrive at a final derivative or variant. Generally these changes are done on a few amino acids to minimize the alteration of the molecule, particularly the immunogenicity and specificity of the antigen binding protein. However, larger changes may be tolerated in certain circumstances. When small alterations in the characteristics of the CDR of the antigen binding protein are desired, substitutions are generally made in accordance with the following chart depicted as TABLE 2.

TABLE 2

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

[0099] Substantial changes in function or immunological identity are made by selecting substitutions that are less conservative than those shown in TABLE 2. For example, substitutions may be made which more significantly affect: the structure of the polypeptide backbone in the area of the alteration, for example the alpha-helical or beta-sheet structure; the charge or hydrophobicity of the molecule at the target site; or the bulk of the side chain. The substitutions which in general are expected to produce the greatest changes in the polypeptide's properties are those in which (a) a hydrophilic residue, *e.g.,* seryl or threonyl, is substituted for (or by) a hydrophobic residue, *e.g.*, leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, *e.g.*, lysyl, arginyl, or histidyl, is substituted for (or by) an electronegative residue, *e.g.*, glutamyl or aspartyl; or (d) a residue having a bulky side chain, *e.g.*, phenylalanine, is substituted for (or by) one not having a side chain, *e.g.*, glycine.

[00100] The variants typically exhibit the same qualitative biological activity and will elicit the same immune response as the naturally-occurring analogue, although variants also are selected to modify the characteristics of the antigen binding protein proteins as needed. Alternatively, the variant may be designed such that the biological activity of the antigen binding protein is altered. For example, glycosylation sites may be altered or removed as discussed herein.

4. VH And VL Variants

[00101] As outlined above, in some embodiments the invention provides antigen binding proteins comprising, or consisting of, a heavy chain variable region of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 and/or a light chain variable region of SEQ ID NO:18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, or 34, respectively, or fragments thereof as defined above. Thus, in those embodiments, the antigen binding protein comprises not only at least one CDR or variant thereof depicted in SEQ ID NOs:1-34, but also at least part of a depicted framework sequence. In addition, the invention encompasses variants of such heavy chain variable sequences or light chain variable sequences.

[00102] A "variant VH" or "variant heavy chain variable region," and a "variant VL" or "variant light chain variable region" generally shares an amino acid homology, similarity, or identity of at least 80% with those depicted herein, and more typically with preferably increasing homologies or identities of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% and almost 100%. The nucleic acid sequence homology, similarity, or identity between the nucleotide sequences encoding individual variant VHs and VLs and the nucleic acid sequences depicted herein are at least 60% with those depicted herein, and more typically with preferably increasing homologies or identities of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% and almost 100%. In addition, a "variant VH" or "variant heavy chain variable region," and a "variant VL" or "variant light chain variable region" typically shares the biological function, including, but not limited to, at least 90, 91, 92, 93, 94, 95, 96, 97, 98% or 99% of the specificity and/or activity of the parent CDR. For example, the variants typically will bind to the same IL-18 receptor epitopes outlined below, with a similar inhibition of IL-18 receptor signaling.

[00103] Methods of generating variants, as well as methods of determining sequence homology, similarity, and identitiy, are outlined *supra, see Section V.B.1.*

[00104] In some embodiments, constant region variants may also be included. Preferred constant region variants include those that alter a biological function of the antibody containing the variation. For example, the antibody may contain a variation that alters the antibody's ability to activate complement or induce antibody-dependent cellular cytotoxicity (ADCC). Such variants may include those that result in an alteration of the glycosylation of the antibody.

C. IL-18 Receptor and IL-18 Receptor Epitopes

[00105] By "IL-18 receptor" or "IL-18R" herein is meant the cell surface receptor that binds to a ligand, including, but not limited to, IL-18 and as a result initiates a signal transduction pathway within the cell. The IL-18 receptor complex is made up of an IL-18 binding chain termed "α-IL-18 receptor" (α-IL-18R) or "IL-18Rα chain," and a signaling chain, termed β-IL-18 receptor "β-IL-18 receptor" ("β-IL-

18R") or "IL-18Rβ chain." As used herein, the term "IL-18 receptor" collectively refers to both the α- and the β-IL-18 receptor.

[00106] The antigen binding proteins disclosed herein bind to the IL-18Rα chain, the human amino acid sequence of which is depicted in SEQ ID NO:69 (its nucleic acid sequence is depicted in SEQ ID NO:70), or the IL-18Rβ chain, the human amino acid sequence of which is depicted in SEQ ID NO:71 (its nucleic acid sequence is depicted in SEQ ID NO:72). In a specific embodiment, the IL-18 receptor is human, although in some cases, other species may be used. In addition, as described below, IL-18 receptor proteins may also include fragments.

[00107] As is described below, binding of antigen binding proteins to specific epitopes is specific.

[00108] By "epitope", "antigenic determinant", and grammatical equivalents herein are meant a region of an antigen, *e.g.*, IL-18 receptor, which can be specifically bound by an antigen binding protein. As the skilled artisan will appreciate, an epitope can be linear or conformational. "Linear epitope" refers to an epitope comprising a sequence of at least about five (5) and not more than about twenty (20) amino acids connected in a linear fashion, which amino acids, by themselves or as part of a larger sequence, bind to an antigen binding protein of the invention. "Conformational epitope" refers to an epitope whose three dimensional, secondary and/or tertiary structure can be a substantial aspect of antibody binding. Generally but not uniformly, amino acids that comprise a conformational epitope do not comprise a linear sequence of a protein's primary structure. Thus, a conformational epitope may be shared by proteins having non-homologous linear amino acid sequences. Without being bound by theory, a conformational epitope can be shared because the tertiary structure recognized by an antibody can be shared between two or more amino acid sequences. In one embodiment, suitable IL-18 receptor epitopes include any which are recognized by the antigen binding proteins of the present invention.

[00109] The invention provides antigen binding proteins recognizing and binding to a conformational epitope in the third Ig domain of human IL-18Rα, in particular, the region defined by amino acid residues 243-271, made up by amino acid residues 250-253 (*i.e.*, residues MFGE) and amino acid residues 267-271 (*i.e.*, residues MRIMT) of SEQ ID NO:69. The amino acid structure of this epitope is depicted in FIGURE 5. Antigen binding proteins that bind to this epitope are particularly effective at blocking the interaction of IL-18 with the IL-18R. Methods of determining the binding epitope of an antigen binding protein are well known in the art and one such method is described in Example 4 herein.

[00110] Example 4 demonstrates that certain human IL-18R antigen binding proteins had significantly reduced ability to bind the human IL-18Rα when residues within the epitope defined by amino acids 243-271, *e.g.*, 250-253 or 267-271, were changed to the corresponding mouse residues. Thus, provided herein are antigen binding proteins that bind human IL-18R but such binding is reduced when residues 250-253 of the human IL-18Rα chain are substituted with the corresponding mouse

amino acids. Also provided herein are antigen binding proteins that bind human IL-18R but such binding is reduced when residues 267-271 of the human IL-18Rα chain are substituted with the corresponding mouse amino acids.

D. Covalent Modifications of Antigen Binding Protein

[00111] Covalent modifications of antigen binding proteins are included within the scope of this invention, and are generally, but not always, done post-translationally. For example, several types of covalent modifications of the antigen binding protein are introduced into the molecule by reacting specific amino acid residues of the antigen binding protein with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

[00112] Cysteinyl residues most commonly are reacted with α-haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone, α-bromo-β-(5-imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

[00113] Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1M sodium cacodylate at pH 6.0.

[00114] Lysinyl and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

[00115] Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pK_a of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

[00116] The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ^{125}I or ^{131}I to prepare labeled proteins for use in radioimmunoassay, the chloramine T method described above being suitable.

[00117] Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'—N=C=N--R'), where R and R' are optionally different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

[00118] Derivatization with bifunctional agents is useful for crosslinking antigen binding proteins to a water-insoluble support matrix or surface for use in a variety of methods. Commonly used crosslinking agents include, *e.g.*, 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

[00119] Glutaminyl and asparaginyl residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

[00120] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, pp. 79-86 [1983]), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

1. Glycosylation

[00121] Another type of covalent modification of the antigen binding protein included within the scope of this invention comprises altering the glycosylation pattern of the protein. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (*e.g.*, the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

[00122] Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the

sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[00123] Addition of glycosylation sites to the antigen binding protein is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein amino acid sequence is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[00124] Another means of increasing the number of carbohydrate moieties on the antigen binding protein is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 published Sep. 11, 1987, and in Aplin and Wriston, 1981, *CRC Crit. Rev. Biochem.*, pp. 259-306.

[00125] Removal of carbohydrate moieties present on the starting antigen binding protein may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin *et al.*, 1987, *Arch. Biochem. Biophys.* 259:52 and by Edge *et al.*, 1981, *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, 1987, *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin *et al.*, 1982, *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

2. PEGylation

[00126] Another type of covalent modification of the antigen binding protein comprises linking the antigen binding protein to various nonproteinaceous polymers, including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. In addition, as is known in the art, amino acid substitutions may be made in various positions within the antigen binding protein to facilitate the addition of polymers such as PEG.

3. Labels And Effector Groups

[00127] In some embodiments, the covalent modification of the antigen binding proteins of the invention comprises the addition of one or more labels.

[00128] The term "labeling group" means any detectable label. Examples of suitable labelling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labelling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used in performing the present invention.

[00129] The term "effector group" means any group coupled to an antigen binding protein that acts as a cytotoxic agent. Examples for suitable effector groups are radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I). Other suitable groups include toxins, therapeutic groups, or chemotherapeutic groups. Examples of suitable groups include calicheamicin, auristatins, geldanamycin and maytansine. In some embodiments, the effector group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance.

[00130] In general, labels fall into a variety of classes, depending on the assay in which they are to be detected: a) isotopic labels, which may be radioactive or heavy isotopes; b) magnetic labels (*e.g.,* magnetic particles); c) redox active moieties; d) optical dyes; enzymatic groups (*e.g.* horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase); e) biotinylated groups; and f) predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.). In some embodiments, the labelling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used in performing the present invention.

[00131] Specific labels include optical dyes, including, but not limited to, chromophores, phosphors and fluorophores, with the latter being specific in many instances. Fluorophores can be either "small molecule" fluores, or proteinaceous fluores.

[00132] By "fluorescent label" is meant any molecule that may be detected *via* its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade BlueJ, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640,

Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, OR), FITC, Rhodamine, and Texas Red (Pierce, Rockford, IL), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, PA). Suitable optical dyes, including fluorophores, are described in Molecular Probes Handbook by Richard P. Haugland, hereby expressly incorporated by reference.

[00133] Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a Renilla, Ptilosarcus, or Aequorea species of GFP (Chalfie *et al.*, 1994, *Science* 263:802-805), EGFP (Clontech Laboratories, Inc., Genbank Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc. 1801 de Maisonneuve Blvd. West, 8th Floor, Montreal, Quebec, Canada H3H 1J9; Stauber, 1998, *Biotechniques* 24:462-471; Heim *et al.*, 1996, *Curr. Biol.* 6:178-182), enhanced yellow fluorescent protein (EYFP, Clontech Laboratories, Inc.), luciferase (Ichiki *et al.*, 1993, *J. Immunol.* 150:5408-5417), β galactosidase (Nolan *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:2603-2607) and Renilla (WO92/15673, WO95/07463, WO98/14605, WO98/26277, WO99/49019, U.S. Patent Nos. 5292658, 5418155, 5683888, 5741668, 5777079, 5804387, 5874304, 5876995, 5925558). All of the above-cited references are expressly incorporated herein by reference.

E. Polynucleotides Encoding IL-18 Receptor Antigen Binding Proteins

[00134] In certain aspects, the invention provides nucleic acid molecules encoding the IgGs, variable regions and CDRs of SEQ ID NOs:1-34, 73, 75, 77, 79, 81, 83, 85, 87, 89-190. In one embodiment, the nucleic acids have the nucleotide sequence of any of SEQ ID NOs:35-68, 74, 76, 78, 80, 82, 84, 86, 88, and 191-292.

[00135] As described herein, a variable region or CDR nucleic acid encodes a variable region or CDR protein, respectively. By "nucleic acid" herein is meant any nucleic acid, including both DNA and RNA. Nucleic acids of the present invention are typically polynucleic acids; that is, polymers of individual nucleotides that are covalently joined by 3', 5' phosphodiester bonds.

[00136] Depending on its use, the nucleic acid may be double stranded, single stranded, or contain portions of both double stranded or single stranded sequence. As will be appreciated by those in the art, the depiction of a single strand ("Watson") also defines the sequence of the other strand ("Crick"); thus the nucleic acid sequences depicted in SEQ ID NOs:35-68 also include the complement of these sequences. By the term "recombinant nucleic acid" herein is meant nucleic acid, originally formed *in vitro*, in general, by the manipulation of nucleic acid by endonucleases, in a form not normally found in nature. Thus an isolated antigen binding protein nucleic acid, in a linear form, or an expression vector formed *in vitro* by ligating DNA molecules that are not normally joined, are both considered recombinant for the purposes of this invention. It is understood that once a recombinant nucleic acid

is made and reintroduced into a host cell or organism, it will replicate non-recombinantly, *i.e.*, using the *in vivo* cellular machinery of the host cell rather than *in vitro* manipulations; however, such nucleic acids, once produced recombinantly, although subsequently replicated non-recombinantly, are still considered recombinant for the purposes of the invention.

[00137] As will be appreciated by those in the art, due to the degeneracy of the genetic code, an extremely large number of nucleic acids may be made, all of which encode the CDRs (and heavy and light chains or other components of the antigen binding protein) of the present invention. Thus, having identified a particular amino acid sequence, such as SEQ ID NOs:1-34, those skilled in the art could make any number of different nucleic acids, by simply modifying the sequence of one or more codons in a way which does not change the amino acid sequence of the encoded protein.

F. Methods of Producing Antigen Binding Proteins

[00138] The present invention also provides expression systems and constructs in the form of plasmids, expression vectors, transcription or expression cassettes which comprise at least one polynucleotide as above. In addition, the invention provides host cells comprising such expression systems or constructs.

[00139] Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

[00140] Optionally, the vector may contain a "tag"-encoding sequence, *i.e.*, an oligonucleotide molecule located at the 5' or 3' end of the IL-18 receptor antigen binding protein coding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis), or another "tag" such as FLAG, HA (hemaglutinin influenza virus), or *myc*, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the IL-18 receptor antigen binding protein from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified IL-18 receptor antigen binding protein by various means such as using certain peptidases for cleavage.

[00141] Flanking sequences may be homologous (*i.e.*, from the same species and/or strain as the host cell), heterologous (*i.e.*, from a species other than the host cell species or strain), hybrid (*i.e.*, a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

[00142] Flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

[00143] Whether all or only a portion of the flanking sequence is known, it may be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Chatsworth, CA), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

[00144] An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, MA) is suitable for most gram-negative bacteria, and various viral origins (*e.g.*, SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

[00145] A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

[00146] A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene may also be used for selection in both prokaryotic and eukaryotic host cells.

[00147] Other selectable genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thyrnidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as an antigen binding protein antibody that binds to IL-18 receptor polypeptide. As a result, increased quantities of a polypeptide such as an IL-18 receptor antigen binding protein are synthesized from the amplified DNA.

[00148] A ribosome-binding site is usually necessary for translation initiation of rnRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed.

[00149] In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various pre- or prosequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also may affect glycosylation. The final protein product may have, in the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

[00150] Expression and cloning vectors of the invention will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding the IL-18 receptor antigen binding protein. Promoters are untranscribed sequences located upstream (*i.e.*, 5') to the

start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding heavy chain or light chain comprising an IL-18 receptor antigen binding protein of the invention by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

[00151] Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus and most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

[00152] Additional promoters which may be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, 1981, *Nature* 290:304-310); CMV promoter (Thornsen *et al.*, 1984, *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, 1980, *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner *et al.*, 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-1445); promoter and regulatory sequences from the metallothionine gene Prinster *et al.*, 1982, *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff *et al.*, 1978, *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer *et al.*, 1983, *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift *et al.*, 1984, *Cell* 38:639-646; Ornitz *et al.*, 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, 1987, *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl *et al.*, 1984, *Cell* 38:647-658; Adames *et al.*, 1985, *Nature* 318:533-538; Alexander *et al.*, 1987, *Mol. Cell. Biol.* 7:1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, 1986, *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert *et al.*, 1987, *Genes and Devel.* 1 :268-276); the alpha-feto-protein gene control region that is active in liver (Krumlauf *et al.*, 1985, *Mol. Cell. Biol.* 5:1639-1648; Hammer *et al.*, 1987, *Science* 253:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey *et al.*, 1987, *Genes and Devel.* 1:161-171); the beta-

globin gene control region that is active in myeloid cells (Mogram *et al.*, 1985, *Nature* 315:338-340; Kollias *et al.*, 1986, *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead *et al.*, 1987, *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason *et al.*, 1986, *Science* 234:1372-1378).

[00153] An enhancer sequence may be inserted into the vector to increase transcription of DNA encoding light chain or heavy chain comprising an IL-18 receptor antigen binding protein of the invention by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (*e.g.*, globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antibody. The choice of signal peptide or leader depends on the type of host cells in which the antibody is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 (IL-7) described in US Patent No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman *et al.,*1984, *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Patent No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846.

[00154] Expression vectors of the invention may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

[00155] After the vector has been constructed and a nucleic acid molecule encoding light chain, a heavy chain, or a light chain and a heavy chain comprising an IL-18 receptor antigen binding sequence has been inserted into the proper site of the vector, the completed vector may be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for an IL-18 receptor antigen binding protein into a selected host cell may be accomplished by well known methods including transfection, infection, calcium phosphate co-

precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook *et al.*, 2001, *supra*.

[00156] A host cell, when cultured under appropriate conditions, synthesizes an IL-18 receptor antigen binding protein that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

[00157] Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and constitutively produce antigen binding proteins with IL-18 receptor binding properties. In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be selected.

G. Use Of IL-18 Receptor Antigen Binding Proteins For Diagnostic And Therapeutic Purposes

[00158] Antigen binding proteins of the invention are useful for detecting IL-18 receptor in biological samples and identification of cells or tissues that produce IL-18 receptor protein. Antigen binding proteins of the invention that specifically bind to IL-18 receptor may be used in treatment of IL-18 receptor mediated diseases in a patient in need thereof. For one, the IL-18 receptor antigen binding proteins of the invention can be used in diagnostic assays, *e.g.*, binding assays to detect and/or quantify IL-18 receptor expressed in a tissue or cell. In addition, the IL-18 receptor antigen binding protein of the invention can be used to inhibit IL-18 receptor from forming a complex with its ligand, *e.g.*, IL-18, thereby modulating the biological activity of IL-18 receptor in a cell or tissue. Antigen binding proteins that bind to IL-18 receptor thus may modulate and/or block interaction with other binding compounds and as such may have therapeutic use in ameliorating IL-18 receptor mediated diseases. In specific embodiments, IL-18 receptor antigen binding proteins may block IL-18 binding to its receptor, which may result in disruption of the IL-18 receptor induced signal transduction cascade.

1. Indications

[00159] Increased levels of IL-18 and/or involvement of IL-18 mediated signals in disease pathogenesis have been demonstrated in a variety of conditions and diseases. The antigen binding proteins of the present invention thus serve to regulate or suppress an immune response and have efficacy in the treatment and prevention of various diseases caused by an excessive immune response (*see*, WO2004/002519; WO2005/063290; WO2004/034988; Mallat *et al.*, 2002, *Circ. Res.* 91:441-448). Accordingly, the IL-18 receptor antigen binding proteins of the present invention can be used for the diagnosis, prevention or treatment of diseases or conditions associated with the IL-18.

[00160] A disease or condition associated with IL-18 means any disease or condition whose onset in a patient is caused by or prevented by the interaction of IL-18 with the IL-18 receptor. The severity of the disease or condition can also be increased or decreased by the interaction of IL-18 with the IL-18 receptor. For example, IL-18 is associated with autoimmune diseases (WO2004/002519; WO2005/063290; WO2004/034988; Mallat *et al.*, 2002, *Circ. Res.* 91:441-448), hepatic disease (Finitto *et al.*, 2004, *Liver* 53:392-400; Tsutsui *et al.,* 2000, *Immunological Reviews* 174:192-209; Ludwiczek *et al.*, 2002, *J. Clinical Immunology* 22:331-337), pancreatic disease and cardiovascular diseases (Gerdes *et al*, 2002, *J. Exp. Med.* 195:245-257; WO03/080104; WO02/060479; WO01/85201; Raeburn *et al.*, *2002, Am. J. Physiol. Heart Circ. Physiol.* 283:H650-H657).

[00161] Examples of autoimmune diseases that are associated with IL-18 include psoriasis, inflammatory arthritis such as rheumatoid arthritis (WO2005/063290; Cannetti *et al.*, 2003, *J. Immunol.* 171:1009-1015; Charles *et al.*, 1999, *J. Immunol.* 163: 1521-1528; Cunnane *et al.,* 2000, *Online J. Rheumatol.* 27 :58-63; Yoshimoto, 1998, *J. Immunol.* 161: 3400-3407), lupus (WO2005/063290), Type I diabetes, Type II diabetes, Crohn's disease (Niederau, 1997, *Online NLM*), inflammatory bowel disease (WO2004/002519), multiple sclerosis, autoimmune hepatitis (Tsutsui *et al.,* 2000, *supra)*, primary biliary cirrhosis (PBC), acquired immune deficiency syndrome (AIDS), atopic dermatitis (Konishi *et al.*, 2002, *Proc. Natl. Acad. Sci. U.S.A.* 99:11340-11345), myasthenia gravis, and sarcoidosis.

[00162] In rheumatoid arthritis, elevated levels of mature IL-18 have been demonstrated in patient sera and synovial fluid. In some studies, IL-18 levels were shown to correlate with disease activity and response to disease modifying treatment. Extremely elevated serum levels of IL-18 have consistently been measured in systemic Juvenile Idiopathic Arthritis and the closely related Adult-Onset Still's Disease. WO2005/063290; Cannetti *et al.*, 2003, *J. Immunol.* 171:1009-1015; Charles *et al.*, 1999, *J. Immunol.* 163: 1521-1528; Cunnane *et al.,* 2000, *Online J. Rheumatol.* 27 :58-63; Yoshimoto, 1998, *J. Immunol.* 161: 3400-3407.

[00163] Other forms of arthritis that are associated with IL-18 include for example ankylosing spondylitis, back pain, carpal deposition syndrome, Ehlers-Danlos-Syndrome, gout, juvenile arthritis, lupus erythematosus, myositis, osteogenesis imperfecta, osteoporosis, polyartheritis; polymyositis,

psoriatic arthritis, Reiter's syndrome, scleroderma, arthritis with bowel disease, Behcets's disease, children's arthritis, degenerative joint disease, fibromyalgia, infectious arthritis, Lyme disease, Marfan syndrome, osteoarthritis, osteonecrosis, Pagets Disease, Polymyalgia rheumatica, pseudogout, reflex sympathetic dystrophy, rheumatoid arthritis, rheumatism, Sjogren's syndrome, familial adenomatous polyposis and the like. Dai *et al.,* 2004, *Arthritis Rheum.* 50:432-443; Kawashima *et al.*, 2004, *Online Arthritis Res. Ther.* 6:R39-R45; Myers *et al.*, 2004, *Rheumatology* 43:272-276; Wei *et al.*, 2001, *American Association Of Immunologists,* pp. 517-521.

[00164] Elevated levels of IL-18 have also been found in patients with Crohn's disease when compared with patients with ulcerative colitis or non-inflammatory intestinal conditions. Both intestinal epithelial cells and lamina propria mononuclear cells have been identified as the source of increased IL-18 production *in situ*. Crohn's disease lesions have been shown to be infiltrated with IL-18R expressing cells. Niederau, 1997, *Online NLM*.

[00165] IL-18 has also been implicated as being associated with ulcerative colitis and Coeliac Disease.

[00166] Central Nervous System (CNS) lesions, cerebrospinal fluid, and sera from patients with Multiple Sclerosis have been shown to contain increased levels of IL-18 message or protein. Within lesions, microglia and macrophages are thought to be the source of IL-18. IL-18 cannot be detected in control tissue biopsies from individuals with non-inflammatory CNS diseases. Particularly high levels of IL-18 has been found in the patient subset with relapsing-remitting disease; and IL-18 levels have been found to increase during relapses compared to periods of remission. Huang *et al.*, 2004, *Mult. Scler.* 10:482-7; Karni *et al.*, 2002, *J. Neuroimmunol.* 125:134-40; Losy *et al.*, 2001, *Acta Neurol. Scand.* 104:171-3; Nicoletti *et al.*, 2001, *Neurology* 57:342-4; Fassbender *et al.*, 1999, *Neurology* 53:1104-6.

[00167] In patients with psoriasis, serum levels of IL-18 were reported to be increased, correlating with the extent of skin lesions and PASI score. Overexpression of both IL-18 and IL-18R mRNA has been demonstrated in lesional skin compared with non-lesional or normal skin controls. Documented overexpression of IFN-γ and TNF-α in psoriatic skin is consistent with biological activities exerted by IL-18. Arican *et al.*, 2005, *Mediators Inflamm.* 2005:273-9; Piskin *et al.*, 2004, *Exp. Dermatol.* 13:764-72; Companjen *et al.*, 2004 *Eur. Cytokine Netw.* 15:210-6; Pietrzak *et al.*, 2003, *Acta Derm. Venereol.* 83:262-5.

[00168] Various other autoimmune diseases have been associated with increased levels of IL-18 either in diseased tissue or in the serum. These include Systemic Lupus Erythematosus, atopic dermatitis, myasthenia gravis, type I diabetes, and sarcoidosis. IL-18 may also be involved in asthma, Alzheimer's Disease, allergic rhinitis, Idiopathic Thrombocytopenic Purpura (ITP), transplantation and GvHD.

[00169] IL-18 has also been implicated in a liver or hepatic diseases and in conditions associated with liver damage or injury. Liver damage or injury may have diverse causes. It may be due to viral or bacterial infections, alcohol abuse, immunological disorders, or cancer, for example. Liver injury also includes damages of the bile ducts, and damage to the liver in conditions such as alcoholic hepatitis, liver cirrhosis, viral hepatitis, primary biliary cirrhosis, and alcohol-related hepatic necro-inflammation. Finitto *et al.*, 2004, *Liver* 53:392-400; Tsutsui *et al.,* 2000, *Immunological Reviews* 174:192-209; Ludwiczek *et al.*, 2002, *J. Clinical Immunology* 22:331-337.

[00170] Hepatic diseases that are associated with IL-18 include hepatitis C and hepatitis B. IL-18 has been implicated in the pathogenesis of both autoimmune and infectious hepatitis. It is thought to contribute to hepatocyte death *via* upregulation of proapoptotic molecules, including FasL. It has been suggested that the beneficial effect of interferon-alpha in hepatitis C may be mediated through reduced levels of IL-18. In contrast, IL-18 administration had a beneficial effect in a transgenic model of hepatitis B, improving viral clearance through increased NK and CTL activity. Finitto *et al.*, 2004, *Liver* 53:392-400; Tsutsui *et al.,* 2000, *Immunological Reviews* 174:192-209; Ludwiczek *et al.*, 2002, *J. Clinical Immunology* 22:331-337.

[00171] Apart from Hepatitis B and C virus, at least four other viruses causing virus-associated hepatitis have been discovered so far, called Hepatitis A, D, E and G-Virus.

[00172] IL-18 is also associated with cardiovascular disease, including atheromatous plaque rupture, post-ischemic heart failure, reperfusion injury, atherosclerosis, chronic heart failure, cardiovascular complications of rheumatoid arthritis and other cardiovascular disorders. IL-18 is thought to markedly depress cardiac output in the setting of sepsis or endotoxin shock. IL-18 is an important link between inflammatory processes and atherogenesis, which is particularly relevant given the accumulating evidence for large excess mortality from cardiovascular causes in patients with chronic inflammatory conditions, including RA and lupus. IL-18 levels have been shown to be a strong independent predictor of death from cardiac events (with better predictive power than CRP levels). Gerdes *et al*, 2002, *J. Exp. Med.* 195:245-257; WO03/080104; WO02/060479; WO01/85201; Raeburn *et al.*, *2002, Am. J. Physiol. Heart Circ. Physiol.* 283:H650-H657.

[00173] IL-18 may also be associated with pulmonary diseases such as, for example, Chronic Obstructed Pulmonary Disease (COPD), chronic severe asthma and Acute Respiratory Distress Syndrome (ARDS).

2. Diagnostic Methods

[00174] The antigen binding proteins of the invention can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or conditions associated with IL-18 or the IL-18 receptor. The invention provides for the detection of the presence of the IL-18 receptor in a sample using classical immunohistological methods known to those of skill in the art (*e.g.*, Tijssen, 1993, *Practice and Theory*

of *Enzyme Immunoassays*, vol 15 (Eds R.H. Burdon and P.H. van Knippenberg, Elsevier, Amsterdam); Zola, 1987, *Monoclonal Antibodies: A Manual of Techniques*, pp. 147-158 (CRC Press, Inc.); Jalkanen *et al.*, 1985, *J. Cell. Biol.* 101:976-985; Jalkanen *et al.*, 1987, *J. Cell Biol.* 105:3087-3096). The detection of the IL-18 receptor can be performed *in vivo* or *in vitro*.

[00175] Diagnostic applications provided herein include use of the antigen binding proteins to detect expression of the IL-18 receptor and binding of the ligands to the IL-18 receptor. Examples of methods useful in the detection of the presence of the IL-18 receptor include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

[00176] For diagnostic applications, the antigen binding protein typically will be labeled with a detectable labeling group. Suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labelling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used in performing the present invention.

[00177] One aspect of the invention provides for identifying a cell or cells that express the IL-18 receptor. In a specific embodiment, the antigen binding protein is labeled with a labeling group and the binding of the labeled antigen binding protein to the IL-18 receptor is detected. In a further specific embodiment, the binding of the antigen binding protein to the IL-18 receptor detected *in vivo*. In a further specific embodiment, the antigen binding protein-IL-18 receptor is isolated and measured using techniques known in the art. *See,* for example, *Harlow and Lane*, 1988, *Antibodies: A Laboratory Manual,* New York: Cold Spring Harbor (ed. 1991 and periodic supplements); *John E. Coligan, ed.*, 1993, *Current Protocols In Immunology* New York: John Wiley & Sons.

[00178] Another aspect of the invention provides for detecting the presence of a test molecule that competes for binding to the IL-18 receptor with the antigen binding proteins of the invention. An example of one such assay would involve detecting the amount of free antigen binding protein in a solution containing an amount of IL-18 receptor in the presence or absence of the test molecule. An increase in the amount of free antigen binding protein (*i.e.*, the antigen binding protein not bound to the IL-18 receptor) would indicate that the test molecule is capable of competing for IL-18 receptor binding with the antigen binding protein. In one embodiment, the antigen binding protein is labeled with a labeling group. Alternatively, the test molecule is labeled and the amount of free test molecule is monitored in the presence and absence of an antigen binding protein.

3. Methods Of Treatment: Pharmaceutical Formulations,

Routes Of Administration

[00179] In some embodiments, the invention provides pharmaceutical compositions comprising a therapeutically effective amount of one or a plurality of the antigen binding proteins of the invention together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. In addition, the invention provides methods of treating a patient by administering such pharmaceutical composition. The term "patient" includes human and animal subjects.

[00180] Preferably, acceptable formulation materials are nontoxic to recipients at the dosages and concentrations employed. In specific embodiments, pharmaceutical compositions comprising a therapeutically effective amount of IL-18 receptor antigen binding proteins are provided.

[00181] In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. *See,* REMINGTON'S PHARMACEUTICAL SCIENCES, 18" Edition, (A.R. Genrmo, ed.), 1990, Mack Publishing Company.

[00182] In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. *See*, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*. In certain embodiments, such compositions may influence the physical state, stability, rate of *in vivo* release and rate of *in vivo* clearance of the antigen binding proteins of the invention. In certain

embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor. In certain embodiments of the invention, IL-18 receptor antigen binding protein compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, the IL-18 receptor antigen binding protein product may be formulated as a lyophilizate using appropriate excipients such as sucrose.

[00183] The pharmaceutical compositions of the invention can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art.

[00184] The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[00185] When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired IL-18 receptor antigen binding protein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the IL-18 receptor antigen binding protein is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or sustained release of the product which can be delivered *via* depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antigen binding protein.

[00186] Pharmaceutical compositions of the invention can be formulated for inhalation. In these embodiments, IL-18 receptor antigen binding proteins are advantageously formulated as a dry, inhalable powder. In specific embodiments, IL-18 receptor antigen binding protein inhalation solutions may also be formulated with a propellant for aerosol delivery. In certain embodiments, solutions may be nebulized. Pulmonary administration and formulation methods therefore are further described in International Patent Application No. PCT/US94/001875, which is incorporated by reference and

describes pulmonary delivery of chemically modified proteins. It is also contemplated that formulations can be administered orally. IL-18 receptor antigen binding proteins that are administered in this fashion can be formulated with or without carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the IL-18 receptor antigen binding protein. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

[00187] A pharmaceutical composition of the invention is preferably provided to comprise an effective quantity of one or a plurality of IL-18 receptor antigen binding proteins in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[00188] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving IL-18 receptor antigen binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. *See*, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, *e.g.*, films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Patent No. 3,773,919 and European Patent Application Publication No. EP 058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, 1983, *Biopolymers* 2:547-556), poly (2-hydroxyethyl-inethacrylate) (Langer *et al.*, 1981, *J. Biomed. Mater. Res.* 15:167-277 and Langer, 1982, *Chem. Tech.* 12:98-105), ethylene vinyl acetate (Langer *et al.*, 1981, *supra*) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. *See, e.g.*, Eppstein *et al.*, 1985, *Proc. Natl. Acad. Sci. U.S.A.* 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949, incorporated by reference.

[00189] Pharmaceutical compositions used for *in vivo* administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to

or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[00190] Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) that is reconstituted prior to administration. The invention also provides kits for producing a single-dose administration unit. The kits of the invention may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments of this invention, kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes) are provided.

[00191] The therapeutically effective amount of an IL-18 receptor antigen binding protein-containing pharmaceutical composition to be employed will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will vary depending, in part, upon the molecule delivered, the indication for which the IL-18 receptor antigen binding protein is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 µg/kg to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage may range from 0.1 µg/kg up to about 30 mg/kg, optionally from 1 µg/kg up to about 30 mg/kg or from 10 µg/kg up to about 5 mg/kg.

[00192] Dosing frequency will depend upon the pharmacokinetic parameters of the particular IL-18 receptor antigen binding protein in the formulation used. Typically, a clinician administers the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion *via* an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages may be ascertained through use of appropriate dose-response data. In certain embodiments, the antigen binding proteins of the invention can be administered to patients throughout an extended time period. Chronic administration of an antigen binding protein of the invention minimizes the adverse immune or allergic response commonly associated with antigen binding proteins that are not fully human, for example an antibody raised against a human antigen in a non-human animal, for example, a non-fully human antibody or non-human antibody produced in a non-human species.

[00193] The route of administration of the pharmaceutical composition is in accord with known methods, *e.g.*, orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device.

[00194] The composition also may be administered locally *via* implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be *via* diffusion, timed-release bolus, or continuous administration.

[00195] It also may be desirable to use IL-18 receptor antigen binding protein pharmaceutical compositions according to the invention *ex vivo*. In such instances, cells, tissues or organs that have been removed from the patient are exposed to IL-18 receptor antigen binding protein pharmaceutical compositions after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[00196] In particular, IL-18 receptor antigen binding proteins can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptide. In certain embodiments, such cells may be animal or human cells, and may be autologous, heterologous, or xenogeneic. In certain embodiments, the cells may be immortalized. In other embodiments, in order to decrease the chance of an immunological response, the cells may be encapsulated to avoid infiltration of surrounding tissues. In further embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

[00197] All references cited within the body of the instant specification are hereby expressly incorporated by reference in their entirety.

[00198] The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the invention.

VI. EXAMPLES

A. Example 1: Production Of IgG2 And IgG4 Versions Of Anti-IL-18 Receptor Antibodies Using pVE414N Transient Expression Constructs

[00199] The following example describes the generation of transient expression constructs used to produce IgG2 and IgG4 versions of various anti-IL18 receptor binding proteins, and experimental approaches to test their binding characteristics and potency.

1. Generation Of Constructs

[00200] Expression constructs for transient expression of IgG4 versions of AM_H9/AM_L9, AM_H11/AM_L7, AM_H3/AM_L14, and AM_H6/AM_L12 were generated by subcloning the polynucleotide sequences of SEQ ID NOs:74, 76, 78, 80, 82, 84, 86 and 88 into a transient expression vector. IgG2 versions of the same variable regions were generated by subcloning the polynucleotide portions encoding the variable regions of those IgGs into a separate transient expression vector.

2. Transient Roller Bottle Tranfections

[00201] Eight roller bottle transfections into CosPKB cell line for each of the antibodies were performed. The titers for the IgG2's were as follows:

IgG2	Titer
AM_H9/AM_L9	33.5
AM_H11/AM_L7	35.1
AM_H3/AM_L14	42.9
AM_H6/AM_L12	41.5

3. Assays For Potency And Cross Reactivity Of Various Antibodies

[00202] ***KG-1 IFNγ Release Assay***. The various IgG constructs were tested to determine their inhibitory activity in an *in vitro* Interferon-γ (IFNγ) release assay. The IFNγ release assay works on the principle that human myelomonocytic KG-1 cells that express the endogenous IL-18R release IFNγ in response to IL-18.

[00203] Briefly, reagents such as affinity-purified scFv are pre-incubated with KG-1 cells in a 96-well tissue culture plate. IL-18 (+TNFα) is added to the cells to induce IFNγ release. TNFα is added with the IL-18 to increase the IFNγ response and therefore makes the assay more sensitive by allowing a lower concentration of IL-18 to be used. This is at least in part, likely due to TNFα induced upregulation of IL-18R surface expression.

[00204] After a defined incubation period, the cell supernatants are harvested and analyzed for IFNγ content using ELISA. Test compounds that inhibit IL-18R mediated signaling can be assessed in this assay by showing a reduction in IFNγ release.

[00205] KG-1 cells were obtained from the European Collection of Cell Cultures (ECACC, 86111306). The cells were propagated in supplemented Iscove's Dulbecco modified medium (IMDM), and were maintained at 1-2 x 10^6 cells/ml. Recombinant human IL-18 was obtained from Peprotech (200-18) and the recombinant human TNFα was purchased from R&D Systems (210-TA). The amount of IFNγ released in response to 1nM IL-18 (+1.1nM TNFα) was monitored in each experiment, and ranged from approximately 250 to 4000 pg/ml.

[00206] The KG-1 assay was carried out in 96 flat bottom well cell culture plates (Costar). Test solutions of antibody (in duplicate) were used neat (or diluted to the required concentration in Dulbecco's PBS) in a volume of 50 μl. The antibodies were then titrated in a 6-9 point 1/3 dilution series (using KG-1 medium), followed by the addition of 50 μl KG-1 cells with gentle mixing. A "no antibody" control with only IL-18 and a "cells only" control were always included. After incubation of the antibody/cell mixture for 30-60 minutes at 37°C with 5% CO_2, 100 μl of IL-18 +TNFα diluted in KG-1 medium was added with gentle mixing. The final concentration of IMAC-purified scFv typically ranged between 25-200 μg/ml. Three reference inhibitors were used in all assays. The first two were monoclonal antibodies against the two different chains of the IL-18R, RP1 (R&Dsystems, MAB840) and AcPL (R&D Systems, MAB1181). These antibodies were used as described above for scFv, except that the final starting concentration for the dilution series was 10-20 μg/ml. In addition, a recombinant IL-18BP/Fc chimera (R&D Systems, 119-BP) was used to neutralize IL-18. In this case, 50μl of KG-1 medium was added to the cell culture plate, followed by 50μl of cells and the cells were incubated as above for the antibodies. In a separate 96 well "U" bottom cell culture plate, the IL-18BP/Fc was titrated in a 6-9 point ½ dilution series (using KG-1 medium) in a volume of 60 μl/well. An equal volume of IL-18+TNFα was added to the IL-18BP/Fc dilution series. After incubation of the IL-18BP/Fc /IL-18 mixture for 30-60 minutes at 37°C with 5% CO_2, 100μl/ well was added to the KG-1 cell plate with gentle mixing. The final starting concentration of the IL-18BP/Fc for the dilution series was 1mg/ml. The final concentration of the KG-1 cells was 1.5 x 10^6 cells/ml (*i.e.* 3 x 10^5/well) and IL-18 was used at a final concentration of 1nM (+1.1nM TNFα).

[00207] IL-18 was also titrated to determine the EC50 of the IFNγ response. The IL-18 was titrated in a 6-10 point ½ dilution series (using KG-1 medium), with the TNFα held constant at 1.1 nM. In this case 50 ml of KG-1 medium was added to the cell culture plate, followed by 50 ml of cells. The cell plate was incubated for 30-60 minutes at 37°C with 5% CO_2, then 100 ml of the titrated IL-18 was added with gentle mixing. The final concentration of IL-18 started at 5 nM for the dilution series. Typically, the EC_{50} for IL-18 (+TNFα) was in the range of 0.5-1 nM, although minimum and maximum EC_{50} values of down to 0.3 nM or up to 5 nM were occasionally seen.

[00208] The KG-1 cell plates were incubated at 37°C with 5% CO_2 overnight. The cell supernatants were harvested by removal of 180 ml medium into a clean "U" bottom 96-well plate, which was then sealed and centrifuged at 1200 rpm for 5 minutes. 160 ml of the cell free supernatant was then transferred to another clean "U" bottom 96-well plate, and the clarified supernatants tested immediately or frozen at –20°C.

[00209] The amount of IFNγ in the KG-1 cell supernatants was determined by a standard sandwich ELISA based assay, using a time-resolved fluorometric readout. FLUORONUNC flat bottom 96-well plates (NUNC, 437958) were coated using 100ml/well of the IFNγ specific monoclonal capture antibody (R&D Systems, MAB2851) at 4mg/ml and left at +4°C overnight. The plates were rinsed with Dulbecco's PBS, then non-specific protein binding was blocked by the addition of 200 ml/well of 3% milk powder in PBS and incubation at RT (RT) for 1-2 hours. The recombinant human IFNγ standard (R&D Systems, 285-IF-100) was diluted to 16,000 pg/ml in reagent diluent (0.1% BSA, 0.05% Tween-20, 20 mM Tris, 150 mM NaCl; pH 7.2-7.4), then titrated in a 12 point ½ dilution series. The blocking buffer was removed from the capture antibody coated plates, and 100ml/well of the IFNγ standard or clarified cell supernatants was added. Reagent diluent was added for the "blank" control. After incubation for 1-2 hours at RT, the plates were washed 3X with PBS containing 0.1% Tween-20. The biotinylated anti-human IFNγ polyclonal detection antibody (R&D Systems, BAF285) was diluted to 100 ng/ml in reagent diluent supplemented with 2% normal goat serum, and 100ml/well was added. After incubation for 1 hour at RT, the plates were washed 3X with PBS containing 0.1% Tween-20. Streptavidin-Europium (Perkin-Elmer, 4001-0010) was diluted 1/1000 in DELFIA assay buffer (Perkin-Elmer, 4002-0010), and 100 ml/well was added. After 30-60 minutes incubation at RT, the plates were washed 7X with DELFIA wash buffer (Perkin-Elmer, 1244-114). DELFIA Enhancement solution (Perkin-Elmer, 4001-0010) was added at 100 ml/well and the plates were left for at least 10 min at RT. The resulting fluorescent signal was measured using dissociation-enhanced time-resolved fluorometryusing the Victor2 V plate reader (PerkinElmer).

[00210] The average value for the ELISA "blank" control was subtracted from the results for the IFNγ standard, while the average value for the "cells alone" control was subtracted for the cell supernatant results. GraphPad PRISM (GraphPad Software, Inc.) was used to calculate the IFNγ standard curve using non-linear regression (with a variable slope). The concentration of IFNγ in the cell supernatants was then determined by using an "unknown X from Y" output for the IFNγ standard curve. The EC50 for IFNγ release from KG-1 cells in response to IL-18 was calculated using non-linear regression (with a variable slope) and constraining the top and bottom as necessary. Inhibition of IFNγ release from KG-1 cells by test compound was normalised as a percentage of the average value of the "no antibody" IL-18 alone control, using the fluorescent counts data. The IC_{50} values for test compounds could then be calculated using non-linear regression (with a variable slope),and constraining the bottom and top to 0 and 100% respectively.

[00211] The IgG2 versions of antibodies AM_H9/AM_L9, AM_H11/AM_L7, AM_H3/AM_L14, and AM_H6/AM_L12 have at least equivalent potency as the original IgG4 versions in an assay measuring their effect on the IFN-γ production by KG1 cells. Furthermore, the IgG2 versions have at least equivalent potency as the original IgG4s in an assay measuring INF-γ production by human NK cells.

[00212] The IgG2 versions of the antibodies have equivalent potency as the original IgG4s in an assay measuring their effect on IL-18 induced INF-γ production by cynomolgus PBMC#010182 cells. This confirms that the conversion to IgG2 did not affect the cyno cross reactivity of the tested antibodies.

4. Assays For Specificity

[00213] IgGs of various antibodies were analyzed for cross-reactivity by ELISA against a panel of proteins.

[00214] Test antigens were coated onto Protein Immobiliser 96-well plates (Exiqon, Prd# 10203-111-60) at 1 µg/ml in PBS (Dulbecco's w/o Ca and Mg, Invitrogen, Cat#14190-086) in duplicate, 50 µl per well, overnight at 4˚C.

[00215] Plates were washed three times with 300µl PBS-Tween (0.1%) (PBS-T) and three times with 300 µl PBS per well using a 96-well plate washer (BIO-TEK, ELX405UV). To the washed plates, 300 µl of 3% Marvel PBS (MPBS) was added per well as a blocking agent. Plates were blocked at room temperature (RT) for 1 hour.

[00216] Plates were washed three times with PBS-T and three times with PBS as previously stated.

[00217] Antibodies ($huIgG_4$) were diluted to 0.5µg/ml in 3% MPBS. 50µl of diluted $huIgG_4$ were added per well. Plates were incubated at RT for 1 hour. Plates were washed as previously stated.

[00218] Primary detection antibody (Monoclonal anti-human IgG4 clone HP-6025 biotin conjugate, Sigma, Cat#B-3648) was diluted 1:15,000 in 3%MPBS and added to plates at 50µl per well. Incubation with primary detection antibody was at RT for 1 hour. Plates were washed previously stated.

[00219] Secondary detection antibody (ExtrAvidin peroxidase conjugate, Sigma, Cat#E-2886), was diluted 1:1,000 in 3%MPBS and added to plates at 50 µl per well. Incubation with secondary detection antibody was at RT for 30 minutes. Plates were washed previously stated.

[00220] 50µl per well Tetramethyl-benzidine (TMB) (Liquid substrate for ELISA, Sigma, Cat#T-0440) was added and incubated at RT for 10 minutes. To stop the enzyme color reaction, 50µl 0.5 M H_2SO_4 per well was added.

[00221] Plates were read at 450nm on a 96-well plate reader (Victor^2 V plate reader (PerkinElmer).

[00222] The specific anti-IL-18 receptor IgG4 antibodies were positive against human and cynomolgus IL-18 receptor protein only. There was no cross-reactivity with other species. An IgG2 version of an above antibody had the same cross-reactivity properties, *i.e.*, it cross-reacted with cynomolgus IL-18 receptor only.

B. Example 2: Characterization Of The Binding Affinity Of An IL-18 Receptor Antibody

[00223] This Example provides an exemplary method of determining the binding affinity of an IL-18 receptor antigen binding protein to cell surface-expressed human IL-18Rα. An IL-18 receptor antibody was iodinated using [^{125}I]-Bolton-Hunter Reagent (diiodinated; PerkinElmer Life Sciences, Inc., Boston, MA). One millicurie of [^{125}I]-Bolton-Hunter Reagent supplied in anhydrous benzene was evaporated to dryness under a nitrogen stream. Five microliters of IL-18 receptor antibody (16 micrograms) was diluted with an equal volume of borate buffered saline and then added to the dried [^{125}I]-Bolton-Hunter Reagent in its original vial. After an overnight incubation at 4ºC, 10 microliters of PBS, 0.1% gelatin was added and the entire sample transferred to an equilibrated 2 mL P6 column (BioRad; Hercules, CA) where iodinated IL-18 receptor antibody was separated from free ^{125}I by gel filtration with 0.1% gelatin as a carrier protein. Fractions containing iodinated antibody were pooled, diluted to a concentration of 100 nM in binding media (RPMI 1640 containing 2.5% bovine albumin, Fraction V, 20 mM Hepes, and 0.2% sodium azide, pH 7.2), and stored at 4ºC. A specific activity of 3.5 x 10^{15} cpm/mmol was calculated based on an initial protein concentration of antibody by amino acid analysis, and a recovery of 70% from a control experiment in which an aliquot of iodiniated antibody was put through the iodination protocol with omission of [^{125}I]-Bolton-Hunter Reagent.

1. Direct Equilibrium Binding

[00224] KG-1 cells were stimulated for 20 hours at 37ºC in 5% CO_2 in IMDM medium containing 20% fetal calf serum in the presence of 20 ng/mL of human TNFα. The stimulated KG-1 cells (5 x 10^5 cells/ 150 microliters final) were washed twice with PBS, and then incubated with a range of concentrations of iodinated antibody. Nonspecific binding was measured at a single concentration of iodinated antibody (~350 pM, in triplicate) in the presence of a 1000-fold molar excess of unlabeled antibody, and assumed to be a linear function of the concentration of iodinated antibody present. All reagents were diluted in binding media containing sodium azide (0.2%) to inhibit potential internalization of iodinated antibody by the cells.

[00225] Cells were incubated in 96-well round-bottom microtiter plates at 37ºC, 5% CO_2 on a miniorbital shaker. After 4 hours, two 60 microliter aliquots of each mixture were transferred to chilled 400 microliter polyethylene centrifuge tubes containing 200 microliters phthalate oil (1.5 parts dibutylphthalate: 1 part dioctylphthalate) and spun for 1.5 minutes in a 4ºC tabletop microfuge (Sorvall, Asheville, NC) at 10,000 rpm to separate cell associated iodinated antibody from free

iodinated antibody. The oil tubes were cut, and each cell pellet and supernatant was collected in individual 12 x 75 mm glass tubes and loaded on a COBRA gamma counter (Packard Instrument Company; Boston, MA) for cpm measurements. Cpm from duplicate aliquots for each well were averaged for analysis. Data were fir to a simple 1-site binding equation via nonlinear regression in Prism version 3.03 (GraphPad Software, Inc; San Diego, CA).

[00226] The iodinated antibody bound to stimulated KG-1 cells at 37ºC with a K_D of 81 pM and ~4700 sites/cell.

2. Competition Assay

[00227] Stimulated and washed KG-1 cells (5 x 10^5 cells/150 microliters final) were incubated with a single concentration of iodinated antibody (15.6 pM) and varying concentrations of unlabeled antibody in binding media. Nonspecific binding was determined in the presence of a 1000-fold molar excess of unlabeled antibody. Iodinated and unlabeled antibody were mixed just prior to the addition of cells, *i.e.*, there was no pre-incubation step.

[00228] Cells were incubated in 96-well round-bottom microtiter plates at 37ºC, 5% CO_2 on a miniorbital shaker. After 4 hours, two 60 microliter aliquots of each mixture were transferred to chilled 400 microliter polyethylene centrifuge tubes containing 200 microliters phthalate oil (1.5 parts dibutylphthalate: 1 part dioctylphthalate) and spun for 1.5 minutes in a 4ºC tabletop microfuge (Sorvall, Asheville, NC) at 10,000 rpm to separate cell associated iodinated antibody from free iodinated antibody. The oil tubes were cut, and each cell pellet and supernatant was collected in individual 12 x 75 mm glass tubes and loaded on a COBRA gamma counter (Packard Instrument Company; Boston, MA) for cpm measurements. Cpm from duplicate aliquots for each well were averaged for analysis. Data were fit to a single competitive inhibition equation via nonlinear regression using the Kd value of 81 pM in Prism.

[00229] The K_I of unlabeled antibody binding was 53 pM.

C. Example 3: Characterization Of The Activity Of Anti-IL-18 Receptor Antibodies

[00230] A IFNγ release assay was performed as described in Example 1, Section 3 for various IgG constructs, as described below.

1. Comparison Of The Inhibition Of INFγ Release By KG1 Cells With AM_H2/AM_L16, AM_H2/AM_L17, AM_H1/AM_L16, and AM_H1/AM_L17 Constructs

[00231] Inhibition of INF-γ release by KG1 cells when treated with AM_H/AM_L antigen binding protein constructs AM_H2/AM_L16, AM_H2/AM_L17, AM_H1/AM_L16, and AM_H1/AM_L17 was compared with control

treatment with IL-18 binding protein (BP). The AM_H/AM_L antigen binding proteins were significantly more efficacious at inhibiting IFNγ release, all demonstrating an ED_{50} between 6 and 10 pM compared to an ED_{50} for IL-18 BP of 520 pM.

2. Comparison Of The Inhibition Of INFγ Release By KG1 Cells With AM_H4/AM_L14, AM_H4/AM_L15, AM_H3/AM_L14, and AM_H3/AM_L15 Constructs

[00232] Inhibition of INF-γ release by KG1 cells when treated with AM_H/AM_L antigen binding protein constructs AM_H4/AM_L14, AM_H4/AM_L15, AM_H3/AM_L14, and AM_H3/AM_L15 was compared with control treatment with IL-18 binding protein (BP). The AM_H/AM_L antigen binding proteins were significantly more efficacious at inhibiting IFNγ release, all demonstrating an ED_{50} between 3 and 7 pM compared to an ED_{50} for IL-18 BP of 520 pM.

3. Comparison Of The Inhibition Of INFγ Release By KG1 Cells With AM_H6/AM_L12, AM_H6/AM_L13, AM_H5/AM_L12, and AM_H5/AM_L13 Constructs

[00233] Inhibition of INF-γ release by KG1 cells when treated with AM_H/AM_L antigen binding protein constructs AM_H6/AM_L12, AM_H6/AM_L13, AM_H5/AM_L12, and AM_H5/AM_L13 was compared with control treatment with IL-18 binding protein (BP). The AM_H/AM_L antigen binding proteins were significantly more efficacious at inhibiting IFNγ release, all demonstrating an ED_{50} between 2.9 and 11.3 pM compared to an ED_{50} for IL-18 BP of 520 pM.

4. Inhibition Of INFγ Release By KG1 Cells By AM_H8/AM_L11, AM_H9/AM_L9, AM_H10/AM_L8, and AM_H11/AM_L7 IgGs

[00234] Inhibition of INF-γ release by KG1 cells with AM_H/AM_L IgG antigen binding protein constructs comprising combinations of AM_H8/AM_L11, AM_H9/AM_L19, AM_H10/AM_L8, and AM_H11/AM_L7 IgGs was compared with control treatment with IL-18 binding protein (BP). The AM_H/AM_L antigen binding proteins were significantly more efficacious at inhibiting IFNγ release, all demonstrating an ED_{50} between 3 and 45 pM compared to an ED_{50} for IL-18 BP of 520 pM.

5. Inhibition Of INFγ Release By KG1 Cells By AM_H15/AM_L3, AM_H13/AM_L4, AM_H13/AM_L5, and AM_H16/AM_L2 IgGs

[00235] Inhibition of INF-γ release by KG1 cells with AM_H/AM_L IgG antigen binding protein constructs comprising combinations of AM_H15/AM_L3, AM_H13/AM_L4, AM_H13/AM_L5, and AM_H16/AM_L2 IgGs was compared with control treatment with IL-18 binding protein (BP). The AM_H/AM_L antigen binding proteins were significantly more efficacious at inhibiting IFNγ release, all demonstrating an ED_{50} between 17 and 320 pM compared to an ED_{50} for IL-18 BP of 520 pM.

D. Example 4: Identification Of The Binding Epitope Of The Described IL-18 Receptor Antibodies

[00236] Experiments were carried out to determine the amino acids residues present in human IL-18 receptor (IL-18R) that are important for binding to one or more of the IL-18 receptor binding proteins. An exemplary antibody bound with high affinity to human IL-18R but did not bind the mouse ortholog of IL-18R. Experiments were directed towards examining the amino acids that differ between human and mouse IL-18R. This was coupled with analysis of a three dimensional computational model of the IL-18R to determine which of those amino acids lie on the surface of the receptor and are therefore more likely to interact with the antibody. Candidate amino acids were examined for their contribution to antibody recognition by using site-specific mutagenesis to change the particular amino acids from the human sequence to mouse sequence and then testing the mutant IL-18R molecules for binding to antibody. The relative ability of antibody to bind the different mutations was assessed using antibody dose-response curves and subsequent determination of EC_{50} concentrations (the concentration of antibody required for 50% of the maximal binding signal).

[00237] A region on the surface of human IL-18R was identified that is particularly important for antibody binding and thus contributes to the epitope. This region contains amino acids 243-271 (shown in bold in Figure 5). When specific amino acids in this region were mutated to mouse sequence, antibody binding was diminished (effects on antibody binding reported in TABLE 3). Amino acids 250-253 (MFGE mutant) and 267-271 (MRIMT mutation) had the most profound influence on antibody binding however neither completely influenced antibody binding alone (*see*, underlined amino acid residues). When the receptor was mutated at all four of the specific sites tested, antibody binding was virtually abolished. Binding of a control anti-IL-18R receptor antibody was not significantly affected by the mutations indicating that the overall structure of the receptor had not been disrupted by the mutations. Amino acids 243-271 encode one of the predicted IL-18 contact points and thus this epitope is consistent with the antibody's ability to block IL-18 binding to the receptor.

TABLE 3

Results of Antibody Binding Assay with IL-18R and Mutated IL-18R

(the mouse amino acids corresponding to each mutation is provided in parenthesis)

	Exemplary Ab binding: avg. EC50 (pM)	Fold decrease in binding ability relative to hulL18R	Control Ab binding: avg. EC50 (pM)
hulL18R	15.7 +/- 9.0	0	7.9 +/- 4.7
EEDV mutation (KDDL)	25.3 +/- 11.9	1.6	6.7 +/- 4.4
MFGE mutation (SIRK)	57.9 +/-26.7	3.7	5.9 +/- 3.7
MRIMT mutation (TTTWI)	177.5 +/- 58.9	11.3	8.5 +/- 5.1
STGGT (NEEAI)	15.7 +/- 8.5	0	10.0 +/- 6.2
EEDV + MRIMT + STGGT	2615.1	2287.3	7.9 +/- 5.1
EEDV + MRIMT + MFGE + STGGT	too low to measure	N/A	10.3 +/- 5.5
Mouse IL18R	does not bind	N/A	N/A

[00238] Human IL18R was mutated to mouse IL18R sequence at the indicated residues and recombinant mutated receptors with and avidin tag were immobilized on biotin-coated beads. Immobilized receptor was then used to determine relative antibody binding ability in a soluble binding assay. Binding was also performed using an anti-hull_-18R antibody that recognizes a distinct epitope from the exemplary antibody. Binding experiments were all performed at least two times. The average EC50 represents the concentration of antibody required to achieve 50% of maximal binding.

[0239] Throughout the specification and claims, unless the context requires otherwise, the word “comprise” or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

[0240] Each document, reference, patent application or patent cited in this text is expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness.

[0241] Reference to cited material or information contained in the text should not be understood as a concession that the material or information was part of the common general knowledge or was known in Australia or any other country.

WHAT IS CLAIMED IS:

1. An isolated antigen binding protein that binds a human IL-18 receptor, wherein said antigen binding protein comprises:

a heavy chain amino acid sequence that comprises: (a) a CDRH1 of SEQ ID NO: 104, (b) a CDRH2 of SEQ ID NO: 105 and (c) a CDRH3 of SEQ ID NO: 106; and

a light chain amino acid sequence that comprises: (a) a CDRL1 of SEQ ID NO: 173, (b) a CDRL2 of SEQ ID NO: 174, and (c) a CDRL3 of SEQ ID NO: 175; or

a heavy chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:6; and

a light chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:29.

2. The antigen binding protein according to claim 1, wherein said antigen binding protein comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 6 or a light chain variable region amino acid sequence of SEQ ID NO: 29.

3. The antigen binding protein according to claim 1, wherein said antigen binding protein comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 6 and a light chain variable region amino acid sequence of SEQ ID NO: 29.

4. An isolated antigen binding protein comprising an IgG heavy chain of SEQ ID NO: 73, or an IgG light chain of SEQ ID NO: 75.

5. The antigen binding protein according to any one of claims 1 to 4 wherein said antigen binding protein is a monoclonal antibody, a human antibody, a recombinant antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or a fragment thereof.

6. The antigen binding protein according to any one of claims 1 to 5, wherein said antigen binding protein is of an IgG2-type.

7. An isolated nucleic acid molecule encoding the heavy chain, light chain, or both the heavy chain and the light chain of the antigen binding protein according to any one of claims 1 to 6.

8. A host cell transformed with a vector comprising the nucleic acid according to claim 7.

9. An isolated antigen binding protein that binds to a three-dimensional structure formed by amino acid residues 250-253 and 267-271 of mature IL-18 receptor (SEQ ID NO:69).

10. The antigen binding protein according to claim 9, wherein said antigen binding protein is a monoclonal antibody, a human antibody, a recombinant antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or a fragment thereof.

11. The antigen binding protein according to claim 9 or 10, wherein said antigen binding protein is of an IgG2-type.

12. A pharmaceutical composition comprising at least one antigen binding protein according to any one of claims 1 to 6 or 9 to 11 and pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to claim 7 for use in a method for preventing or treating a condition associated with IL-18 receptor in a patient.

14. A pharmaceutical composition for use according to claim 13 wherein said condition associated with IL-18 receptor is selected from the group consisting of psoriasis, rheumatoid arthritis, lupus, Type 1 diabetes, Crohn's disease, inflammatory bowel disease, multiple sclerosis, autoimmune hepatitis, HIV, atopic dermatitis, myasthenia gravis, sarcoidosis, COPD and asthma.

15. A method when used in preventing or treating a condition associated with IL-18 receptor in a patient, comprising administering to a patient in need thereof a pharmaceutical composition according to claim 12.

16. The method according to claim 15 wherein the condition is selected from the group consisting of an autoimmune disease, a hepatic disease, a pancreatic disease, and a cardiovascular disease.

17. The method according to claim 16, wherein said autoimmune disease is selected from the group consisting of psoriasis, rheumatoid arthritis, lupus, Type I diabetes, Crohn's disease, inflammatory bowel disease, multiple sclerosis, autoimmune hepatitis, HIV, atopic dermatitis, myasthenia gravis, and sarcoidosis.

18. The method according to claim 16, wherein said cardiovascular disease is selected from the group consisting of heart disease including acute heart attacks, atheromatous plaque rupture, post-ischemic heart failure, reperfusion injury, vascular inflammation, and atherogenesis.

19. A method of inhibiting the binding of IL-18 to IL-18 receptor comprising contacting an IL-18 receptor with the antigen binding protein according to any one of claims 1 to 6 or claims 9 to 11, wherein said antigen binding protein binds said IL-18 receptor and prevents binding of said IL-18 receptor to IL-18.

20. An isolated nucleic acid molecule encoding the heavy chain, light chain, or both the heavy chain and the light chain of the antigen binding protein according to any one of claims 9 to 11.

21. A host cell transformed with the vector comprising the nucleic acid according to claim 20.

22. Use of isolated antigen binding protein that binds a human IL-18 receptor, wherein said antigen binding protein comprises:

a heavy chain amino acid sequence that comprises: (a) a CDRH1 of SEQ ID NO: 104, (b) a CDRH2 of SEQ ID NO: 105 and (c) a CDRH3 of SEQ ID NO: 106; and a light chain amino acid sequence that comprises: (a) a CDRL1 of SEQ ID NO: 173, (b) a CDRL2 of SEQ ID NO: 174, and (c) a CDRL3 of SEQ ID NO: 175; or a heavy chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:6; and a light chain amino acid sequence that comprises a variable domain at least 90% identical to SEQ ID NO:19; or

an IgG heavy chain of SEQ ID NO: 73, or an IgG light chain of SEQ ID NO: 75

in the treatment or prevention of a condition associated with IL-18 receptor in a patient.

23. Use of an isolated antigen binding protein that binds to a three-dimensional structure formed by amino acid residues 250-253 and 267-271 of mature IL-18 receptor (SEQ ID NO:69) in the treatment or prevention of a condition associated with IL-18 receptor in a patient.

24. The use of an isolated antigen binding protein according to any one of claims 1 to 6 or claims 9 to 11 in the preparation of a medicament in the treatment or prevention of a condition associated with IL-18 receptor in a patient.

25. The use according to any one of claims 22 to 24 wherein the condition is selected from the group consisting of an autoimmune disease, a hepatic disease, a pancreatic disease, and a cardiovascular disease.

26. The use according to claim 25, wherein said autoimmune disease is selected from the group consisting of psoriasis, rheumatoid arthritis, lupus, Type I diabetes, Crohn's disease, inflammatory bowel disease, multiple sclerosis, autoimmune hepatitis, HIV, atopic dermatitis, myasthenia gravis, and sarcoidosis.

27. The use according to claim 25, wherein said cardiovascular disease is selected from the group consisting of heart disease including acute heart attacks, atheromatous plaque rupture, post-ischemic heart failure, reperfusion injury, vascular inflammation, and atherogenesis.

28. An isolated antigen binding protein according to any one of claims 1, 4 or 9 substantially as herein before described with reference to the Examples.

AM_H1 polynucleotide sequence (SEQ ID:35)

```
caggtgcagctggtgcagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 Q  V  Q  L  V  Q  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgacccagtccctggaccactgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  T  Q  S  L  D  H  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H1 amino acid sequence (SEQ ID:1)

```
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY        60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTQSLDHWGQGTTVTV       120
SS                                                                   122
```

AM_H2 polynucleotide sequence (SEQ ID:36)

```
gaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 E  V  Q  L  V  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgacccagtccctggaccactgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  T  Q  S  L  D  H  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H2 amino acid sequence (SEQ ID NO:2)

```
EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY        60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTQSLDHWGQGTTVTV       120
SS                                                                   122
```

FIGURE 1A

AM_H3 polynucleotide sequence (SEQ ID 37)

```
caggtgcagctggtgcagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 Q  V  Q  L  V  Q  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgtcgcagtccctggacggctgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  S  Q  S  L  D  G  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H3 amino acid sequence (SEQ ID NO:3)

```
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY         60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLSQSLDGWGQGTTVTV        120
SS                                                                   122
```

AM_H4 polynucleotide sequence (SEQ ID:38)

```
gaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 E  V  Q  L  V  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgtcgcagtccctggacggctgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  S  Q  S  L  D  G  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H4 amino acid sequence (SEQ ID:4)

```
EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY         60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLSQSLDGWGQGTTVTV        120
SS                                                                   122
```

FIGURE 1B

AM_H5 polynucleotide sequence (SEQ ID:39)

```
caggtgcagctggtgcagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 Q  V  Q  L  V  Q  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgacctcggccctgaacctgtgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  T  S  A  L  N  L  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H5 amino acid sequence (SEQ ID:5)

```
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY        60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTSALNLWGQGTTVTV       120
SS                                                                   122
```

AM_H6 polynucleotide sequence (SEQ ID:40)

```
gaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 E  V  Q  L  V  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctgtatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  K  G  S
agttccatatggctgacctcggccctgaacctgtgggggcaggggaccacggtcaccgtc         360
 S  S  I  W  L  T  S  A  L  N  L  W  G  Q  G  T  T  V  T  V
tcctca                                                               366
 S  S
```

AM_H6 polynucleotide sequence (SEQ ID:6)

```
EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY        60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTSALNLWGQGTTVTV       120
SS                                                                   122
```

FIGURE 1C

AM_H7 polynucleotide sequence (SEQ ID:41)

```
gaggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactc          60
 E  V  Q  L  V  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L
tcctgtgcagcgtctggattcaccttcagcggttatggcatgcactgggtccgccaggct         120
 S  C  A  A  S  G  F  T  F  S  G  Y  G  M  H  W  V  R  Q  A
ccaggcaaggggctggagtgggtggcagtaatatcaaatgatggaagtaagaaatattat         180
 P  G  K  G  L  E  W  V  A  V  I  S  N  D  G  S  K  K  Y  Y
tcagactccgtgaagggccgattcaccatctccagagacaattccaaaaacacgctgtat         240
 S  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcagatgaacagcctgagagctgaggacacggctatatattactgtgcgaaagggtcc         300
 L  Q  M  N  S  L  R  A  E  D  T  A  I  Y  Y  C  A  K  G  S
agttccatatggttcggggagaccgttgactactgggggcaggggaccacg                 351
 S  S  I  W  F  G  E  T  V  D  Y  W  G  Q  G  T  T
```

AM_H7 amino acid sequence (SEQ ID:7)

```
EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYY          60
SDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCAKGSSSIWFGETVDYWGQGTT          117
```

AM_H8 polynucleotide sequence (SEQ ID:42)

```
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtc          60
 Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S  V  K  V
tcctgcaaggtttccggatacaccctcactgaattatccatgcactgggtgcgacaggct         120
 S  C  K  V  S  G  Y  T  L  T  E  L  S  M  H  W  V  R  Q  A
cctggaaaagggcttgagtggatgggaggttttgatcgtgaagatgatgaaacaatccac         180
 P  G  K  G  L  E  W  M  G  G  F  D  R  E  D  D  E  T  I  H
gcacagaagttccagggcagagtcaccatgaccgaggacacatctacagacacagcctac         240
 A  Q  K  F  Q  G  R  V  T  M  T  E  D  T  S  T  D  T  A  Y
atggaactgagcagcctgcgatctgaggacacggccgtttattactgtgcaacagatctt         300
 M  E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  T  D  L
atggtgtggggcgatttttggatccagcactggggccaggggacactggtcaccgtctcc         360
 M  V  W  G  D  F  W  I  Q  H  W  G  Q  G  T  L  V  T  V  S
tca                                                                  363
 S
```

AM_H8 polynucleotide sequence (SEQ ID:8)

```
QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIH          60
AQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWGDFWIQHWGQGTLVTVS          120
S                                                                      121
```

FIGURE 1D

AM_H9 polynucleotide sequence (SEQ ID:43)

```
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtc        60
 Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S  V  K  V
tcctgcaaggtttccggatacaccctcactgaattatccatgcactgggtgcgacaggct       120
 S  C  K  V  S  G  Y  T  L  T  E  L  S  M  H  W  V  R  Q  A
cctggaaaagggcttgagtggatgggaggttttgatcgtgaagatgatgaaacaatccac       180
 P  G  K  G  L  E  W  M  G  G  F  D  R  E  D  D  E  T  I  H
gcacagaagttccagggcagagtcaccatgaccgaggacacatctacagacacagcctac       240
 A  Q  K  F  Q  G  R  V  T  M  T  E  D  T  S  T  D  T  A  Y
atggaactgagcagcctgcgatctgaggacacggccgtttattactgtgcaacagatctt       300
 M  E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  T  D  L
atggtgtggggcgatttttggatccagcactggggccaggggacactggtcaccgtctcc       360
 M  V  W  G  D  F  W  I  Q  H  W  G  Q  G  T  L  V  T  V  S
tca                                                                363
 S
```

AM_H9 amino acid sequence (SEQ ID:9)

```
QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIH        60
AQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWGDFWIQHWGQGTLVTVS       120
S                                                                   121
```

AM_H10 polynucleotide sequence (SEQ ID:44)

```
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtc        60
 Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S  V  K  V
tcctgcaaggtttccggatacaccctcactgaattatccatgcactgggtgcgacaggct       120
 S  C  K  V  S  G  Y  T  L  T  E  L  S  M  H  W  V  R  Q  A
cctggaaaagggcttgagtggatgggaggttttgatcgtgaagatgatgaaacaatccac       180
 P  G  K  G  L  E  W  M  G  G  F  D  R  E  D  D  E  T  I  H
gcacagaagttccagggcagagtcaccatgaccgaggacacatctacagacacagcctac       240
 A  Q  K  F  Q  G  R  V  T  M  T  E  D  T  S  T  D  T  A  Y
atggaactgagcagcctgcgatctgaggacacggccgtttattactgtgcaacagatctt       300
 M  E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  T  D  L
atggcctgggactacccgcccatccagcactggggccaggggacactggtcaccgtctcc       360
 M  A  W  D  Y  P  P  I  Q  H  W  G  Q  G  T  L  V  T  V  S
tca                                                                363
 S
```

AM_H10 amino acid sequence (SEQ ID:10)

```
QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIH        60
AQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMAWDYPPIQHWGQGTLVTVS       120
S                                                                   121
```

FIGURE 1E

AM_H11 polynucleotide sequence (SEQ ID:45)

```
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtc      60
 Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S  V  K  V
tcctgcaaggtttccggatacaccctcactgaattatccatgcactgggtgcgacaggct      120
 S  C  K  V  S  G  Y  T  L  T  E  L  S  M  H  W  V  R  Q  A
cctggaaaagggcttgagtggatgggaggttttgatcgtgaagatgatgaaacaatccac      180
 P  G  K  G  L  E  W  M  G  G  F  D  R  E  D  D  E  T  I  H
gcacagaagttccagggcagagtcaccatgaccgaggacacatctacagacacagcctac      240
 A  Q  K  F  Q  G  R  V  T  M  T  E  D  T  S  T  D  T  A  Y
atggaactgagcagcctgcgatctgaggacacggccgtttattactgtgcaacagatctt      300
 M  E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  T  D  L
atggtgtggaacttccccccccatccagcactggggccaggggacactggtcaccgtctcc      360
 M  V  W  N  F  P  P  I  Q  H  W  G  Q  G  T  L  V  T  V  S
tca                                                               363
 S
```

AM_H11 amino acid sequence (SEQ ID:11)

```
QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIH      60
AQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWNFPPIQHWGQGTLVTVS      120
S                                                                 121
```

AM_H12 polynucleotide sequence (SEQ ID:46)

```
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtc      60
 Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S  V  K  V
tcctgcaaggtttccggatacaccctcactgaattatccatgcactgggtgcgacaggct      120
 S  C  K  V  S  G  Y  T  L  T  E  L  S  M  H  W  V  R  Q  A
cctggaaaagggcttgagtggatgggaggttttgatcgtgaagatgatgaaacaatccac      180
 P  G  K  G  L  E  W  M  G  G  F  D  R  E  D  D  E  T  I  H
gcacagaagttccagggcagagtcaccatgaccgaggacacatctacagacacagcctac      240
 A  Q  K  F  Q  G  R  V  T  M  T  E  D  T  S  T  D  T  A  Y
atggaactgagcagcctgcgatctgaggacacggccgtttattactgtgcaacagatctt      300
 M  E  L  S  S  L  R  S  E  D  T  A  V  Y  Y  C  A  T  D  L
atggtgtggggcgatttttggatccagcactggggcaaggggacaatg                  348
 M  V  W  G  D  F  W  I  Q  H  W  G  K  G  T  M
```

AM_H12 amino acid sequence (SEQ ID:12)

```
QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIH      60
AQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAOVYYCATDLMVWGDFWIQHWGKGTM       111
```

FIGURE 1F

AM_H13 polynucleotide sequence (SEQ ID:47)

```
gaggtgcagctgttggagtctgggggaggcttggtacagcctgggggtccctgagactc      60
 E  V  Q  L  L  E  S  G  G  G  L  V  Q  P  G  G  S  L  R  L
tcctgtgcagcctctggattcacctttagcagctatgccatgagctgggtccgccaggct     120
 S  C  A  A  S  G  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A
ccagggaaggggctggagtgggtctcagctattagtggtagtggtggtggcacatactac     180
 P  G  K  G  L  E  W  V  S  A  I  S  G  S  G  G  G  T  Y  Y
gcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtat     240
 A  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagaattcgg     300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  R  I  R
ggcgactaccggacggacatctggggccagggaaccacggtcaccgtctcctca          354
 G  D  Y  R  T  D  I  W  G  Q  G  T  T  V  T  V  S  S
```

AM_H13 amino acid sequence (SEQ ID:13)

```
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGGTYY      60
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIRGDYRTDIWGQGTTVTVSS      118
```

AM_H14 polynucleotide sequence (SEQ ID:48)

```
gaggtgcagctgttggagtctgggggaggcttggtacagcctgggggtccctgagactc      60
 E  V  Q  L  L  E  S  G  G  G  L  V  Q  P  G  G  S  L  R  L
tcctgtgcagcctctggattcacctttagcagctatgccatgagctgggtccgccaggct     120
 S  C  A  A  S  G  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A
ccagggaaggggctggagtgggtctcagctattagtggtagtggtggtggcacatactac     180
 P  G  K  G  L  E  W  V  S  A  I  S  G  S  G  G  G  T  Y  Y
gcagactccgtgaagggccggtccaccatctccagagacaattccaagaacacgctgtat     240
 A  D  S  V  K  G  R  S  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagaattcgg     300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  R  I  R
ggggactaccggacggacatctggggccggggaaccctggtcaccgtctcctca          354
 G  D  Y  R  T  D  I  W  G  R  G  T  L  V  T  V  S  S
```

AM_H14 amino acid sequence (SEQ ID:14)

```
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGGTYY      60
ADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCARIRGDYRTDIWGRGTLVTVSS      118
```

FIGURE 1G

AM_H15 polynucleotide sequence (SEQ ID:49)

```
gaggtgcagctgttggagtctgggggaggcttggcacagcctgggggtccctgagactc      60
 E  V  Q  L  L  E  S  G  G  G  L  A  Q  P  G  G  S  L  R  L
tcctgtgcagcctctgggttcacctttagcagctatgccatgagctgggtccgccaggct     120
 S  C  A  A  S  G  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A
ccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactac     180
 P  G  K  G  L  E  W  V  S  A  I  S  G  S  G  G  S  T  Y  Y
gcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtat     240
 A  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagagttcgg     300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  R  V  R
ggggactaccggacggacatctggggccggggaaccctggtcaccgtctcctca          354
 G  D  Y  R  T  D  I  W  G  R  G  T  L  V  T  V  S  S
```

AM_H15 amino acid sequence (SEQ ID:15)

```
EVQLLESGGGLAQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYY      60
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGDYRTDIWGRGTLVTVSS      118
```

AM_H16 polynucleotide sequence (SEQ ID:50)

```
gaggtgcagctgttggagtctgggggaggcttggtacagcctgggggtccctgagactc      60
 E  V  Q  L  L  E  S  G  G  G  L  V  Q  P  G  G  S  L  R  L
tcctgtgcagcctctagattcacctttagcagctatgccatgagctgggtccgccaggct     120
 S  C  A  A  S  R  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A
ccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactac     180
 P  G  K  G  L  E  W  V  S  A  I  S  G  S  G  G  S  T  Y  Y
gcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtat     240
 A  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagagttcgg     300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  R  V  R
ggggactaccggacggacatctggggccggggaaccctggtcaccgtctcctca          354
 G  D  Y  R  T  D  I  W  G  R  G  T  L  V  T  V  S  S
```

AM_H16 amino acid sequence (SEQ ID:16)

```
EVQLLESGGGLVQPGGSLRLSCAASRFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYY      60
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGDYRTDIWGRGTLVTVSS      118
```

FIGURE 1H

AM_H17 polynucleotide sequence (SEQ ID:51)

```
gaggtgcagctgttggagtctgggggaggcttggtacagcctgggggtccctgagactc      60
 E  V  Q  L  L  E  S  G  G  G  L  V  Q  P  G  G  S  L  R  L
tcctgtgcagcctctagattcacctttagcagctatgccatgagctgggtccgccaggct     120
 S  C  A  A  S  R  F  T  F  S  S  Y  A  M  S  W  V  R  Q  A
ccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactac     180
 P  G  K  G  L  E  W  V  S  A  I  S  G  S  G  G  S  T  Y  Y
gcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtat     240
 A  D  S  V  K  G  R  F  T  I  S  R  D  N  S  K  N  T  L  Y
ctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagagttcgg     300
 L  Q  M  N  S  L  R  A  E  D  T  A  V  Y  Y  C  A  R  V  R
ggcatatacggtatggacgtctggggccggggaaccctg                         339
 G  I  Y  G  M  D  V  W  G  R  G  T  L
```

AM_H17 amino acid sequence (SEQ ID:17)

```
EVQLLESGGGLVQPGGSLRLSCAASRFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYY      60
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGIYGMDVWGRGTL          113
```

AM_L1 polynucleotide sequence (SEQ ID:52)

```
cagcctgtgctgactcagccccctcagtgtccgtgtccccaggacagactgccagcatc      60
 Q  P  V  L  T  Q  P  P  S  V  S  V  S  P  G  Q  T  A  S  I
acctgctctggagataaattgggggataaatatgcttcctggtatcagcagaagccaggc     120
 T  C  S  G  D  K  L  G  D  K  Y  A  S  W  Y  Q  Q  K  P  G
aagtcccctgtactggtcatctatcaagattccaatcggccctcagggatccctgagcga     180
 K  S  P  V  L  V  I  Y  Q  D  S  N  R  P  S  G  I  P  E  R
ttctctggctccaactctgggaacacagccactctgaccatcagcgggacccaggctagg     240
 F  S  G  S  N  S  G  N  T  A  T  L  T  I  S  G  T  Q  A  R
gatgaggctgactattactgtcaggcgtgggacagcagcactgcatcggtgttcggcgga     300
 D  E  A  D  Y  Y  C  Q  A  W  D  S  S  T  A  S  V  F  G  G
gggaccaag                                                       309
 G  T  K
```

AM_L1 amino acid sequence (SEQ ID:18)

```
QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGKSPVLVIYQDSNRPSGIPER      60
FSGSNSGNTATLTISGTQARDEADYYCQAWDSSTASVFGGGTK                     103
```

FIGURE 1I

AM_L2 polynucleotide sequence (SEQ ID:53)

```
cagcctgtgctgactcagccccctcagtgtccgtgtccccaggacagactgccagcatc          60
 Q  P  V  L  T  Q  P  P  S  V  S  V  S  P  G  Q  T  A  S  I
acctgctctggagataaattgggggataaatatgcttcctggtatcagcagaagccaggc         120
 T  C  S  G  D  K  L  G  D  K  Y  A  S  W  Y  Q  Q  K  P  G
aagtcccctgtactggtcatctatcaagattccaatcggccctcagggatccctgagcga         180
 K  S  P  V  L  V  I  Y  Q  D  S  N  R  P  S  G  I  P  E  R
ttctctggctccaactctgggaacacagccactctgaccatcagcgggacccaggctagg         240
 F  S  G  S  N  S  G  N  T  A  T  L  T  I  S  G  T  Q  A  R
gatgaggctgactattactgtcaggcgtgggaccactccttgcagcacaggttcggcgga         300
 D  E  A  D  Y  Y  C  Q  A  W  D  H  S  L  Q  H  R  F  G  G
gggaccaaggtcaccgtcctaggt                                             324
 G  T  K  V  T  V  L  G
```

AM_L2 amino acid sequence (SEQ ID:19)

```
QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGKSPVLVIYQDSNRPSGIPER      60
FSGSNSGNTATLTISGTQARDEADYYCQAWDHSLQHRFGGGTKVTVLG                  108
```

AM_L3 polynucleotide sequence (SEQ ID:54)

```
cagcctgtgctgactcagccccctcagtgtccgtgtccccaggacagactgccagcatc          60
 Q  P  V  L  T  Q  P  P  S  V  S  V  S  P  G  Q  T  A  S  I
acctgctctggagataaattgggggataaatatgcttcctggtatcagcagaagccaggc         120
 T  C  S  G  D  K  L  G  D  K  Y  A  S  W  Y  Q  Q  K  P  G
cagacccctgtactggtcatctatcaagattccaatcggccctcagggatccctgagcga         180
 Q  T  P  V  L  V  I  Y  Q  D  S  N  R  P  S  G  I  P  E  R
ttctctggctccaactccgggaacacagccactctgaccatcagcgggacccaggctagg         240
 F  S  G  S  N  S  G  N  T  A  T  L  T  I  S  G  T  Q  A  R
gatgaggctgactattactgtcaggcgtggaccagcgccctgaactcgcagttcggcgga         300
 D  E  A  D  Y  Y  C  Q  A  W  T  S  A  L  N  S  Q  F  G  G
gggaccaaggtcaccgtcctaggt                                             324
 G  T  K  V  T  V  L  G
```

AM_L3 amino acid sequence (SEQ ID:20)

```
QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQTPVLVIYQDSNRPSGIPER      60
FSGSNSGNTATLTISGTQARDEADYYCQAWTSALNSQFGGGTKVTVLG                  108
```

FIGURE 1J

AM_L4 polynucleotide sequence (SEQ ID:55)

```
cagcctgtgctgactcagccccctcagtgtccgtgtccccaggacagactgccagcatc      60
 Q  P  V  L  T  Q  P  P  S  V  S  V  S  P  G  Q  T  A  S  I
acctgctctggagataaattgggggataaatatgcttcctggtatcagcagaagccaggc     120
 T  C  S  G  D  K  L  G  D  K  Y  A  S  W  Y  Q  Q  K  P  G
cagtcccctgtactggtcatctatcaagattccaatcggccctcagggatccctgagcga     180
 Q  S  P  V  L  V  I  Y  Q  D  S  N  R  P  S  G  I  P  E  R
ttctctggctccaactctggggacacagccactctgaccatcagcgggacccaggctagg     240
 F  S  G  S  N  S  G  D  T  A  T  L  T  I  S  G  T  Q  A  R
gatgaggctgactattactgtcaggcgtggacgcactccctcagcacgttgttcggcgga     300
 D  E  A  D  Y  Y  C  Q  A  W  T  H  S  L  S  T  L  F  G  G
gggaccaaggtcaccgtcctaggt                                        324
 G  T  K  V  T  V  L  G
```

AM_L4 amino acid sequence (SEQ ID:21)

```
QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDSNRPSGIPER      60
FSGSNSGDTATLTISGTQARDEADYYCQAWTHSLSTLFGGGTKVTVLG                 108
```

AM_L5 polynucleotide sequence (SEQ ID:56)

```
tcctatgagctgactcagccccctcagtgtccgtgtccccaggacagactgccagcatc      60
 S  Y  E  L  T  Q  P  P  S  V  S  V  S  P  G  Q  T  A  S  I
acctgctctggagataaattgggggataaatatgcttcctggtatcagcagaagccaggc     120
 T  C  S  G  D  K  L  G  D  K  Y  A  S  W  Y  Q  Q  K  P  G
cagtcccctgtactggtcatctatcaagattccaatcggccctcagggatccctgagcga     180
 Q  S  P  V  L  V  I  Y  Q  D  S  N  R  P  S  G  I  P  E  R
ttctctggctccaactctgggaacacagccactctgaccatcagcgggacccaggctatg     240
 F  S  G  S  N  S  G  N  T  A  T  L  T  I  S  G  T  Q  A  M
gatgaggctgactattactgtcaggcgtggacccacagcctgagcacgttgttcggcgga     300
 D  E  A  D  Y  Y  C  Q  A  W  T  H  S  L  S  T  L  F  G  G
gggaccaagctgaccgtcctaggt                                        324
 G  T  K  L  T  V  L  G
```

AM_L5 amino acid sequence (SEQ ID:22)

```
SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDSNRPSGIPER      60
FSGSNSGNTATLTISGTQAMDEADYYCQAWTHSLSTLFGGGTKLTVLG                 108
```

FIGURE 1K

AM_L6 polynucleotide sequence (SEQ ID:57)

```
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatc          60
 Q  S  V  L  T  Q  P  P  S  A  S  G  T  P  G  Q  R  V  T  I
tcttgttctggaaggaactccaacatcggaagttatactgtaacctggtaccagcagctc         120
 S  C  S  G  R  N  S  N  I  G  S  Y  T  V  T  W  Y  Q  Q  L
ccaggaacggcccccaaactcctcatctatagtaatagtcagcggccctcaggggtccct         180
 P  G  T  A  P  K  L  L  I  Y  S  N  S  Q  R  P  S  G  V  P
gaccgattctcaggctccaagtctggcacctcagcctccttggccatcagtgggctccag         240
 D  R  F  S  G  S  K  S  G  T  S  A  S  L  A  I  S  G  L  Q
tctgaagatgaggctgattattactgtgcagcatgggatgacagcctgaatggcccggtg         300
 S  E  D  E  A  D  Y  Y  C  A  A  W  D  D  S  L  N  G  P  V
ttcggcggagggaccaag                                                   318
 F  G  G  G  T  K
```

AM_L6 amino acid sequence (SEQ ID:23)

```
QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVP          60
DRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGPVFGGGTK                       106
```

AM_L7 polynucleotide sequence (SEQ ID:58)

```
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatc          60
 Q  S  V  L  T  Q  P  P  S  A  S  G  T  P  G  Q  R  V  T  I
tcttgttctggaaggaactccaacatcggaagttatactgtaacctggtaccagcagctc         120
 S  C  S  G  R  N  S  N  I  G  S  Y  T  V  T  W  Y  Q  Q  L
ccaggaacggcccccaaactcctcatctatagtaatagtcagcggccctcaggggtccct         180
 P  G  T  A  P  K  L  L  I  Y  S  N  S  Q  R  P  S  G  V  P
gaccgattctcaggctccaagtctggcacctcagcctccttggccatcagtgggctccag         240
 D  R  F  S  G  S  K  S  G  T  S  A  S  L  A  I  S  G  L  Q
tctgaagatgaggctgattattactgtgtggtgtgggatgacgtgctgaatggcccggtg         300
 S  E  D  E  A  D  Y  Y  C  V  V  W  D  D  V  L  N  G  P  V
ttcggcggagggaccaagctgaccgtcctaggt                                    333
 F  G  G  G  T  K  L  T  V  L  G
```

AM_L7 amino acid sequence (SEQ ID:24)

```
QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVP          60
DRFSGSKSGTSASLAISGLQSEDEADYYCVVWDDVLNGPVFGGGTKLTVLG                 111
```

FIGURE 1L

AM_L8 polynucleotide sequence (SEQ ID:59)

```
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatc      60
 Q  S  V  L  T  Q  P  P  S  A  S  G  T  P  G  Q  R  V  T  I
tcttgttctggaaggaactccaacatcggaagttatactgtaacctggtaccagcagctc     120
 S  C  S  G  R  N  S  N  I  G  S  Y  T  V  T  W  Y  Q  Q  L
ccaggaacggcccccaaactcctcatctatagtaatagtcagcggccctcaggggtccct     180
 P  G  T  A  P  K  L  L  I  Y  S  N  S  Q  R  P  S  G  V  P
gaccgattctcaggctccaagtctggcacctcagcctccttggccatcagtgggctccag     240
 D  R  F  S  G  S  K  S  G  T  S  A  S  L  A  I  S  G  L  Q
tctgaagatgaggctgattattactgtgtcgtgtgggatgacaagctgaatggcccggtg     300
 S  E  D  E  A  D  Y  Y  C  V  V  W  D  D  K  L  N  G  P  V
ttcggcggagggaccaagctgaccgtcctaggt                               333
 F  G  G  G  T  K  L  T  V  L  G
```

AM_L8 polynucleotide sequence (SEQ ID:25)

```
QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVP      60
DRFSGSKSGTSASLAISGLQSEDEADYYCVVWDDKLNGPVFGGGTKLTVLG              111
```

AM_L9 polynucleotide sequence (SEQ ID:60)

```
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatc      60
 Q  S  V  L  T  Q  P  P  S  A  S  G  T  P  G  Q  R  V  T  I
tcttgttctggaaggaactccaacatcggaagttatactgtaacctggtaccagcagctc     120
 S  C  S  G  R  N  S  N  I  G  S  Y  T  V  T  W  Y  Q  Q  L
ccaggaacggcccccaaactcctcatctatagtaatagtcagcggccctcaggggtccct     180
 P  G  T  A  P  K  L  L  I  Y  S  N  S  Q  R  P  S  G  V  P
gaccgattctcaggctccaagtctggcacctcagcctccttggccatcagtgggctccag     240
 D  R  F  S  G  S  K  S  G  T  S  A  S  L  A  I  S  G  L  Q
tctgaagatgaggctgattattactgtgtggtgtgggacgagatcctgaatggcccggtg     300
 S  E  D  E  A  D  Y  Y  C  V  V  W  D  E  I  L  N  G  P  V
ttcggcggagggaccaagctgaccgtcctaggt                               333
 F  G  G  G  T  K  L  T  V  L  G
```

AM_L9 amino acid sequence (SEQ ID:26)

```
QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVP      60
DRFSGSKSGTSASLAISGLQSEDEADYYCVVWDEILNGPVFGGGTKLTVLG              111
```

FIGURE 1M

AM_L10 polynucleotide sequence (SEQ ID:61)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatc        60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  I
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga       120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga       180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa       240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaagctgactattactgtaactcccgggacagcagtaaccatgtggtattcggcgga       300
 D  E  A  D  Y  Y  C  N  S  R  D  S  S  N  H  V  V  F  G  G
gggaccaag                                                          309
 G  T  K
```

AM_L10 amino acid sequence (SEQ ID:27)

```
SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR       60
FSGSSSGNTASLTITGAQAEDEADYYCNSRDSSNHVVFGGGTK                       103
```

AM_L11 polynucleotide sequence (SEQ ID:62)

```
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatc        60
 Q  S  V  L  T  Q  P  P  S  A  S  G  T  P  G  Q  R  V  T  I
tcttgttctggaaggaactccaacatcggaagttatactgtaacctggtaccagcagctc       120
 S  C  S  G  R  N  S  N  I  G  S  Y  T  V  T  W  Y  Q  Q  L
ccaggaacggcccccaaactcctcatctatagtaatagtcagcggccctcaggggtccct       180
 P  G  T  A  P  K  L  L  I  Y  S  N  S  Q  R  P  S  G  V  P
gaccgattctcaggctccaagtctggcacctcagcctccttggccatcagtgggctccag       240
 D  R  F  S  G  S  K  S  G  T  S  A  S  L  A  I  S  G  L  Q
tctgaagatgaggctgattattactgtctcgtgtgggacgacgtcctgaatggcccggtg       300
 S  E  D  E  A  D  Y  Y  C  L  V  W  D  D  V  L  N  G  P  V
ttcggcggagggaccaagctgaccgtcctaggt                                  333
 F  G  G  G  T  K  L  T  V  L  G
```

AM_L11 amino acid sequence (SEQ ID:28)

```
QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVP       60
DRFSGSKSGTSASLAISGLQSEDEADYYCLVWDDVLNGPVFGGGTKLTVLG              111
```

FIGURE 1N

AM_L12 polynucleotidesequence (SEQ ID:63)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatc        60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  I
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga       120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga       180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa       240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgtcccggaacggctggaaccatgtggtattcggcgga       300
 D  E  A  D  Y  Y  C  A  S  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                           324
 G  T  K  L  T  V  L  G
```

AM_L12 amino acid sequence (SEQ ID:29)

```
SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR        60
FSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG                   108
```

AM_L13 polynucleotide sequence (SEQ ID:64)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcagggtc        60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  V
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga       120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga       180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa       240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgtcccggaacggctggaaccatgtggtattcggcgga       300
 D  E  A  D  Y  Y  C  A  S  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                           324
 G  T  K  L  T  V  L  G
```

AM_L13 amino acid sequence (SEQ ID:30)

```
SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR        60
FSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG                   108
```

FIGURE 1O

AM_L14 polynucleotide sequence (SEQ ID:65)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatc      60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  I
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga     120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga     180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa     240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgtcccggaacggctggaaccatgtggtattcggcgga     300
 D  E  A  D  Y  Y  C  A  S  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                        324
 G  T  K  L  T  V  L  G
```

AM_L14 amino acid sequence (SEQ ID:31)

```
SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR      60
FSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG                 108
```

AM_L15 polynucleotide sequence (SEQ ID:66)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcagggtc      60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  V
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga     120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga     180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa     240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgtcccggaacggctggaaccatgtggtattcggcgga     300
 D  E  A  D  Y  Y  C  A  S  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                        324
 G  T  K  L  T  V  L  G
```

AM_L15 amino acid sequence (SEQ ID:32)

```
SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR      60
FSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG                 120
```

FIGURE 1P

AM_L16 polynucleotide sequence (SEQ ID:67)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatc        60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  I
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga       120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga       180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa       240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgacccggaacggctggaaccatgtggtattcggcgga       300
 D  E  A  D  Y  Y  C  A  T  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                           324
 G  T  K  L  T  V  L  G
```

AM_L16 amino acid sequence (SEQ ID:33)

```
SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR      60
FSGSSSGNTASLTITGAQAEDEADYYCATRNGWNHVVFGGGTKLTVLG                 108
```

AM_L17 polynucleotide sequence (SEQ ID:68)

```
tcgtctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcagggtc        60
 S  S  E  L  T  Q  D  P  A  V  S  V  A  L  G  Q  T  V  R  V
acatgccaaggagacagcctcagaagctattatgcaagctggtaccagcagaagccagga       120
 T  C  Q  G  D  S  L  R  S  Y  Y  A  S  W  Y  Q  Q  K  P  G
caggcccctgtacttgtcatctctgctaaaaacaaccggccctcagggatcccagaccga       180
 Q  A  P  V  L  V  I  S  A  K  N  N  R  P  S  G  I  P  D  R
ttctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaa       240
 F  S  G  S  S  S  G  N  T  A  S  L  T  I  T  G  A  Q  A  E
gatgaggctgactattactgtgcgacccggaacggctggaaccatgtggtattcggcgga       300
 D  E  A  D  Y  Y  C  A  T  R  N  G  W  N  H  V  V  F  G  G
gggaccaagctgaccgtcctaggt                                           324
 G  T  K  L  T  V  L  G
```

AM_L17 amino acid sequence (SEQ ID:34)

```
SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDR      60
FSGSSSGNTASLTITGAQAEDEADYYCATRNGWNHVVFGGGTKLTVLG                 108
```

FIGURE 1Q

AM_H1 amino acid sequence (SEQ ID:1)

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTQSLDHWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H2 amino acid sequence (SEQ ID NO:2)

EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTQSLDHWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H3 amino acid sequence (SEQ ID NO:3)

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLSQSLDGWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H4 amino acid sequence (SEQ ID:4)

EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMKWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLSQSLDGWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H5 amino acid sequence (SEQ ID:5)

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTSALNLWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H6 (amino acid) sequence (SEQ ID:6)

EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSSSIWLTSALNLWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H7 amino acid sequence (SEQ ID:7)

EVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCAKGSSSIWFGETVDYWGQGTT
CDR1 CDR2 CDR3

FIGURE 2A

AM_H8 amino acid sequence (SEQ ID:8)

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWGDFWIQHWGQGTLVTVSS
CDR1 CDR2 CDR3

AM_H9 amino acid sequence (SEQ ID:9)

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWGDFWIQHWGQGTLVTVSS
CDR1 CDR2 CDR3

AM_H10 amino acid sequence (SEQ ID:10)

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMAWDYPPIQHWGQGTLVTVSS
CDR1 CDR2 CDR3

AM_H11 amino acid sequence (SEQ ID:11)

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATDLMVWNFPPIQHWGQGTLVTVSS
CDR1 CDR2 CDR3

AM_H12 amino acid sequence (SEQ ID:12)

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYMELSSLRSEDTAVVYYCATDLMVWGDFWIQHWGKGTM
CDR1 CDR2 CDR3

AM_H13 amino acid sequence (SEQ ID:13)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIRGDYRTDIWGQGTTVTVSS
CDR1 CDR2 CDR3

AM_H14 amino acid sequence (SEQ ID:14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGGTYYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCARIRGDYRTDIWGRGTLVTVSS
CDR1 CDR2 CDR3

FIGURE 2B

AM_H15 amino acid sequence (SEQ ID:15)

EVQLLESGGGLAQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGDYRTDIWGRGTLVTVSS
CDR1 CDR2 CDR3

AM_H16 amino acid sequence (SEQ ID:16)

EVQLLESGGGLVQPGGSLRLSCAASRFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGDYRTDIWGRGTLVTVSS
CDR1 CDR2 CDR3

AM_H17 amino acid sequence (SEQ ID:17)

EVQLLESGGGLVQPGGSLRLSCAASRFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRGIYGMDVWGRGTL
CDR1 CDR2 CDR3

AM_L1 amino acid sequence (SEQ ID:18)

QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGKSPVLVIYQDSNRPSGIPERFSGSNSGNTATLTISGTQARDEADYYCQAWDSSIASVFGGGTK
CDR1 CDR2 CDR3

AM_L2 amino acid sequence (SEQ ID:19)

QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGKSPVLVIYQDSNRPSGIPERFSGSNSGNTATLTISGTQARDEADYYCQAWDHSLQHRFGGGTKVTVLG
CDR1 CDR2 CDR3

AM_L3 amino acid sequence (SEQ ID:20)

QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQTPVLVIYQDSNRPSGIPERFSGSNSGNTATLTISGTQARDEADYYCQANTSALNSQFGGGTKVTVLG
CDR1 CDR2 CDR3

AM_L4 amino acid sequence (SEQ ID:21)

QPVLTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDSNRPSGIPERFSGSNSGDTATLTISGTQARDEADYYCQAWTHSLSTLFGGGTKVTVLG
CDR1 CDR2 CDR3

FIGURE 2C

AM_L5 amino acid sequence (SEQ ID:22)

SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDSNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWTHSLSTLFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L6 amino acid sequence (SEQ ID:23)

QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGPVFGGGTK
CDR1 CDR2 CDR3

AM_L7 amino acid sequence (SEQ ID:24)

QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCVVWDDVLNGPVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L8 amino acid sequence (SEQ ID:25)

QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCVVWDDKLNGPVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L9 amino acid sequence (SEQ ID:26)

QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCVVWDELLNGPVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L10 amino acid sequence (SEQ ID:27)

SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLIITGAQAEDEADYYCNSRDSSNHVVFGGGTK
CDR1 CDR2 CDR3

AM_L11 amino acid sequence (SEQ ID:28)

QSVLTQPPSASGTPGQRVTISCSGRNSNIGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCLVWDDVLNGPVFGGGTKLTVLG
CDR1 CDR2 CDR3

FIGURE 2D

AM_L12 amino acid sequence (SEQ ID:29)

SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L13 amino acid sequence (SEQ ID:30)

SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L14 amino acid sequence (SEQ ID:31)

SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L15 amino acid sequence (SEQ ID:32)

SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCASRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L16 amino acid sequence (SEQ ID:33)

SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCATRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

AM_L17 amino acid sequence (SEQ ID:34)

SSELTQDPAVSVALGQTVRVTCQGDSLRSYYASWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCATRNGWNHVVFGGGTKLTVLG
CDR1 CDR2 CDR3

FIGURE 2E

Heavy Chain

	1			CDR1		CDR2	70
AM$_H$1 SEQ ID NO: 1	QVQLVQSGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$2 SEQ ID NO: 2	EVQLVESGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$3 SEQ ID NO: 3	QVQLVQSGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$4 SEQ ID NO: 4	EVQLVESGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$5 SEQ ID NO: 5	QVQLVQSGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$6 SEQ ID NO: 6	EVQLVESGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$15 SEQ ID NO:15	EVQLLESGGG	LAQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGSTYY	ADSVKGRFTI
AM$_H$16 SEQ ID NO:16	EVQLLESGGG	LVQPGGSLRL	SCAASRFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGSTYY	ADSVKGRFTI
AM$_H$13 SEQ ID NO:13	EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGGTYY	ADSVKGRFTI
AM$_H$14 SEQ ID NO:14	EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGGTYY	ADSVKGRSTI
AM$_H$8 SEQ ID NO: 8	QVQLVQSGAE	VKKPGASVKV	SCKVSGYTLT	ELSMHWVRQA	PGKGLEWMGG	FDREDDETIH	AQKFQGRVTM
AM$_H$9 SEQ ID NO: 9	QVQLVQSGAE	VKKPGASVKV	SCKVSGYTLT	ELSMHWVRQA	PGKGLEWMGG	FDREDDETIH	AQKFQGRVTM
AM$_H$10 SEQ ID NO:10	QVQLVQSGAE	VKKPGASVKV	SCKVSGYTLT	ELSMHWVRQA	PGKGLEWMGG	FDREDDETIH	AQKFQGRVTM
AM$_H$11 SEQ ID NO:11	QVQLVQSGAE	VKKPGASVKV	SCKVSGYTLT	ELSMHWVRQA	PGKGLEWMGG	FDREDDETIH	AQKFQGRVTM
AM$_H$7 SEQ ID NO: 7	EVQLVESGGG	VVQPGRSLRL	SCAASGFTFS	GYGMHWVRQA	PGKGLEWVAV	ISNDGSKKYY	SDSVKGRFTI
AM$_H$12 SEQ ID NO:12	QVQLVQSGAE	VKKPGASVKV	SCKVSGYTLT	ELSMHWVRQA	PGKGLEWMGG	FDREDDETIH	AQKFQGRVTM
AM$_H$17 SEQ ID NO:17	EVQLLESGGG	LVQPGGSLRL	SCAASRFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGSTYY	ADSVKGRFTI

	71			CDR3		122		
AM$_H$1 SEQ ID NO: 1	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLTQSLD	HWGQGTTVTV	SS........	....	...
AM$_H$2 SEQ ID NO: 2	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLTQSLD	HWGQGTTVTV	SS........	....	...
AM$_H$3 SEQ ID NO: 3	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLSQSLD	GWGQGTTVTV	SS........	....	...
AM$_H$4 SEQ ID NO: 4	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLSQSLD	GWGQGTTVTV	SS........	....	...
AM$_H$5 SEQ ID NO: 5	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLTSALN	LWGQGTTVTV	SS........	....	...
AM$_H$6 SEQ ID NO: 6	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKGS	SSIWLTSALN	LWGQGTTVTV	SS........	....	...
AM$_H$15 SEQ ID NO:15	SRDNSKNTLY	LQMNSLRAED	TAVYYCARVR	GDY....RTD	IWGRGTLVTV	SS........	....	...
AM$_H$16 SEQ ID NO:16	SRDNSKNTLY	LQMNSLRAED	TAVYYCARVR	GDY....RTD	IWGRGTLVTV	SS........	....	...
AM$_H$13 SEQ ID NO:13	SRDNSKNTLY	LQMNSLRAED	TAVYYCARIR	GDY....RTD	IWGQGTTVTV	SS........	....	...
AM$_H$14 SEQ ID NO:14	SRDNSKNTLY	LQMNSLRAED	TAVYYCARIR	GDY....RTD	IWGRGTLVTV	SS........	....	...
AM$_H$8 SEQ ID NO: 8	TEDTSTDTAY	MELSSLRSED	TAVYYCATDL	M.VWGDFWIQ	HWGQGTLVTV	SS........	....	...
AM$_H$9 SEQ ID NO: 9	TEDTSTDTAY	MELSSLRSED	TAVYYCATDL	M.VWGDFWIQ	HWGQGTLVTV	SS........	....	...
AM$_H$10 SEQ ID NO:10	TEDTSTDTAY	MELSSLRSED	TAVYYCATDL	M.AWDYPPIQ	HWGQGTLVTV	SS........	....	...
AM$_H$11 SEQ ID NO:11	TEDTSTDTAY	MELSSLRSED	TAVYYCATDL	M.VWNFPPIQ	HWGQGTLVTV	SS........	....	...
AM$_H$7 SEQ ID NO: 7	SRDNSKNTLY	LQMNSLRAED	TAIYYCAKGS	SSIWFGETVD	YWGQGTT...	....	....	...
AM$_H$12 SEQ ID NO:12	TEDTSTDTAY	MELSSLRSED	TAVYYCATDL	M VWGDFWIQ	HWGKGTM...	....	....	...
AM$_H$17 SEQ ID NO:17	SRDNSKNTLY	LQMNSLRAED	TAVYYCAR..	..VRGIYGMD	VWGRGTL...	....	....	...

FIGURE 3A

Light Chain

		1		CDR1			CDR2	70
AM_L17	SEQ ID NO:34	SSELTQDPAV	SVALGQTVRV	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L16	SEQ ID NO:33	SSELTQDPAV	SVALGQTVRI	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L15	SEQ ID NO:32	SSELTQDPAV	SVALGQTVRV	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L13	SEQ ID NO:30	SSELTQDPAV	SVALGQTVRV	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L14	SEQ ID NO:31	SSELTQDPAV	SVALGQTVRI	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L12	SEQ ID NO:29	SSELTQDPAV	SVALGQTVRI	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L3	SEQ ID NO:20	QPVLTQPPSV	SVSPGQTASI	TCSG..DKLG	DKYASWYQQK	PGQTPVLVIY	QDSNRPSGIP	ERFSGSNSGN
AM_L4	SEQ ID NO:21	QPVLTQPPSV	SVSPGQTASI	TCSG..DKLG	DKYASWYQQK	PGQSPVLVIY	QDSNRPSGIP	ERFSGSNSGD
AM_L2	SEQ ID NO:19	QPVLTQPPSV	SVSPGQTASI	TCSG..DKLG	DKYASWYQQK	PGKSPVLVIY	QDSNRPSGIP	ERFSGSNSGN
AM_L5	SEQ ID NO:22	SYELTQPPSV	SVSPGQTASI	TCSG..DKLG	DKYASWYQQK	PGQSPVLVIY	QDSNRPSGIP	ERFSGSNSGN
AM_L11	SEQ ID NO:28	QSVLTQPPSA	SGTPGQRVTI	SCSGRNSNIG	SYTVTWYQQL	PGTAPKLLIY	SNSQRPSGVP	DRFSGSKSGT
AM_L7	SEQ ID NO:24	QSVLTQPPSA	SGTPGQRVTI	SCSGRNSNIG	SYTVTWYQQL	PGTAPKLLIY	SNSQRPSGVP	DRFSGSKSGT
AM_L9	SEQ ID NO:26	QSVLTQPPSA	SGTPGQRVTI	SCSGRNSNIG	SYTVTWYQQL	PGTAPKLLIY	SNSQRPSGVP	DRFSGSKSGT
AM_L8	SEQ ID NO:25	QSVLTQPPSA	SGTPGQRVTI	SCSGRNSNIG	SYTVTWYQQL	PGTAPKLLIY	SNSQRPSGVP	DRFSGSKSGT
AM_L10	SEQ ID NO:27	SSELTQDPAV	SVALGQTVRI	TCQG..DSLR	SYYASWYQQK	PGQAPVLVIS	AKNNRPSGIP	DRFSGSSSGN
AM_L1	SEQ ID NO:18	QPVLTQPPSV	SVSPGQTASI	TCSG..DKLG	DKYASWYQQK	PGKSPVLVIY	QDSNRPSGIP	ERFSGSNSGN
AM_L6	SEQ ID NO:23	QSVLTQPPSA	SGTPGQRVTI	SCSGRNSNIG	SYTVTWYQQL	PGTAPKLLIY	SNSQRPSGVP	DRFSGSKSGT

		51		CDR3		129		
AM_L17	SEQ ID NO:34	TASLTITGAQ	AEDEADYYCA	TRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L16	SEQ ID NO:33	TASLTITGAQ	AEDEADYYCA	TRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L15	SEQ ID NO:32	TASLTITGAQ	AEDEADYYCA	SRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L13	SEQ ID NO:30	TASLTITGAQ	AEDEADYYCA	SRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L14	SEQ ID NO:31	TASLTITGAQ	AEDEADYYCA	SRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L12	SEQ ID NO:29	TASLTITGAQ	AEDEADYYCA	SRNGWNH.VV	FGGGTKLTVL	G.........	....	....
AM_L3	SEQ ID NO:20	TATLTISGTQ	ARDEADYYCQ	AWTSALN.SQ	FGGGTKVTVL	G.........	....	....
AM_L4	SEQ ID NO:21	TATLTISGTQ	ARDEADYYCQ	AWTHSLS.TL	FGGGTKVTVL	G.........	....	....
AM_L2	SEQ ID NO:19	TATLTISGTQ	ARDEADYYCQ	AWDHSLQ.HR	FGGGTKVTVL	G.........	....	....
AM_L5	SEQ ID NO:22	TATLTISGTQ	AMDEADYYCQ	AWTHSLS.TL	FGGGTKLTVL	G.........	....	....
AM_L11	SEQ ID NO:28	SASLAISGLQ	SEDEADYYCL	VWDDVLNGPV	FGGGTKLTVL	G.........	....	....
AM_L7	SEQ ID NO:24	SASLAISGLQ	SEDEADYYCV	VWDDVLNGPV	FGGGTKLTVL	G.........	....	....
AM_L9	SEQ ID NO:26	SASLAISGLQ	SEDEADYYCV	VWDEILNGPV	FGGGTKLTVL	G.........	....	....
AM_L8	SEQ ID NO:25	SASLAISGLQ	SEDEADYYCV	VWDDKLNGPV	FGGGTKLTVL	G.........	....	....
AM_L10	SEQ ID NO:27	TASLTITGAQ	AEDEADYYCN	SRDSS.NHVV	FGGGTK....	....	....	....
AM_L1	SEQ ID NO:18	TATLTISGTQ	ARDEADYYCQ	AWDSS.TASV	FGGGTK....	....	....	....
AM_L6	SEQ ID NO:23	SASLAISGLQ	SEDEADYYCA	AWDDSLNGPV	FGGGTK....	....	....	....

FIGURE 3B

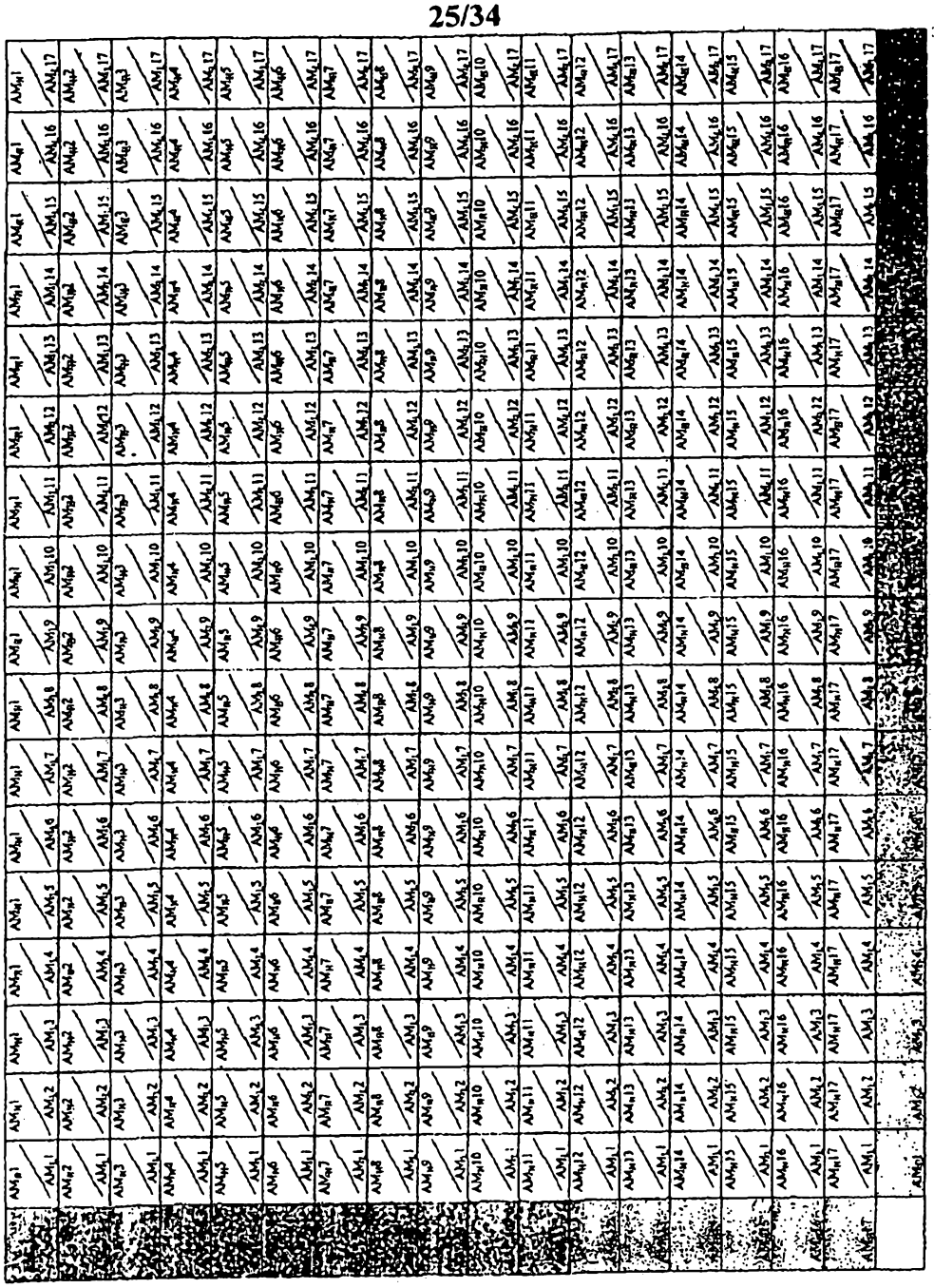

FIGURE 4

MNCRELPLTLWVLISVSTAESCTSRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYKSSGSQEHVELNPR
SSSRIALHDCVLEFWPVELNDTGSYFFQMKNYTQKWKLNVIRRNKHSCFTERQVTSKIVEVKKFFQITCE
NSYYQTLVNSTSLYKNCKKLLLENNKNPTIKKNAEFEDQGYYSCVHFLHHNGKLFNITKTFNITIVEDRSNI
VPVLLGPKLNHVAVELGKNVRLNCSALLNEEDVIYWMFGEENGSDPNIHEEKEMRIMTPEGKWHASKVL
RIENIGESNLNVLYNCTVASTGGTDTKSFILVRKADMADIPGHVFTRGMIIAVLILVAVVCLVTVCVIYRVDLV
LFYRHLTRRDETLTDGKTYDAFVSYLKECRPENGEEHTFAVEILPRVLEKHFGYKLCIFERDVVPGGAVVD
EIHSLIEKSRRLIIVLSKSYMSNEVRYELESGLHEALVERKIKIILIEFTPVTDFTFLPQSLKLLKSHRVLKWKA
DKSLSYNSRFWKNLLYLMPAKTVKPGRDEPEVLPVLSES

Amino acids of the human IL-18 receptor sequence that contribute to the antigen binding epitope are shown in bold (Amino Acids 243-271). Specific amino acids that were experimentally determined to influence binding are in bold.

FIGURE 5

AM_H6 (SEQ ID NO:74)

GTCGACGCCGCCACCATGGGGTCAACCGCCATCCTTGGCCTCCTCCTGGCTGT
CCTGCAGGGAGGGCGCGCCGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGT
GGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCT
TCAGCGGTTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGA
GTGGGTGGCAGTAATATCAAATGATGGAAGTAAGAAATATTATTCAGACTCC
GTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAAAACACGCTGTATC
TGCAGATGAACAGCCTGAGAGCTGAGGACACGGCTGTATATTACTGTGCGAA
AGGGTCCAGTTCCATATGGCTGACCTCGGCCCTGAACCTGTGGGGGCAGGGG
ACCACGGTCACCGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCT
GGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTC
TGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCT
ACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAG
TTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGC
AGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCT
CCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCC
CGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG
ACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCC
TCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT
CTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAA
GGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAG
ATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACA
AGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG
TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTC
TCCGGGTAAATGAGCGGCCGC

AM_H6 (SEQ ID NO:73)

MGSTAILGLLLAVLQGGRA^EVQLVESGGGVVQPGRSLRLSCAASGFTFSG
YGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYL
QMNSLRAEDTAVYYCAKGSSSIWLTSALNLWGQGTTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPA
PIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

FIGURE 6

AM_L12 (SEQ ID NO:76)

GTCGACGTTTAAACGCCGCCACCATGGAGACAGACACACTCCTGCTATGGGT
ACTGCTGCTCTGGGTTCCAGGTTCCACTGGTTCGTCTGAGCTGACTCAGGACC
CTGCTGTGTCTGTGGCCTTGGGACAGACAGTCAGGATCACATGCCAAGGAGA
CAGCCTCAGAAGCTATTATGCAAGCTGGTACCAGCAGAAGCCAGGACAGGCC
CCTGTACTTGTCATCTCTGCTAAAAACAACCGGCCCTCAGGGATCCCAGACC
GATTCTCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGGCT
CAGGCGGAAGATGAGGCTGACTATTACTGTGCGTCCCGGAACGGCTGGAACC
ATGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGCCAACCGAAAGC
GGCGCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACA
AGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT
GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCAC
ACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTG
ACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATG
AAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAGGCGG
CCGC

AM_L12 (SEQ ID NO:75)

METDTLLLWVLLLWVPGSTG^SSELTQDPAVSVALGQTVRITCQGDSLRSYYA
SWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADY
YCASRNGWNHVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS
HRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 7

AM_H4 (SEQ ID NO:78)

ATGGGGTCAACCGCCATCCTTGGCCTCCTCCTGGCTGTCCTGCAGGGAGGGC
GCGCCGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGA
GGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGCGGTTATGGC
ATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTAA
TATCAAATGATGGAAGTAAGAAATATTATTCAGACTCCGTGAAGGGCCGATT
CACCATCTCCAGAGACAATTCCAAAAACACGCTGTATCTGCAGATGAACAGC
CTGAGAGCTGAGGACACGGCTGTATATTACTGTGCGAAAGGGTCCAGTTCCA
TATGGCTGTCGCAGTCCCTGGACGGCTGGGGGCAGGGGACCACGGTCACCGT
CTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCA
GGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT
CCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTG
CACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTA
GATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT
TGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCT
TCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAG
GTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA
ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGG
AGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCA
CCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGG
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACC
AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCC
CATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGC
TCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

AM_H4 (SEQ ID NO:77)

MGSTAILGLLLAVLQGGRA^EVQLVESGGGVVQPGRSLRLSCAASGFTFSG
YGMHWVRQAPGKGLEWVAVISNDGSKKYYSDSVKGRFTISRDNSKNTLYL
QMNSLRAEDTAVYYCAKGSSSIWLSQSLDGWGQGTTVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPA
PIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

FIGURE 8

AM_L14 (SEQ ID NO:80)

ATGGAGACAGACACACTCCTGCTATGGGTACTGCTGCTCTGGGTTCCAGGTTC
CACTGGTTCGTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGAC
AGACAGTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGCTATTATGCAAG
CTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTACTTGTCATCTCTGCTAAA
AACAACCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCAGCTCAGGAA
ACACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTA
TTACTGTGCGTCCCGGAACGGCTGGAACCATGTGGTATTCGGCGGAGGGACC
AAGCTGACCGTCCTAGGCCAACCGAAAGCGGCGCCCTCGGTCACTCTGTTCC
CGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCAT
AAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGC
CCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC
AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCC
ACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGA
CAGTGGCCCCTACAGAATGTTCATAGGCGGCCGC

AM_L14 (SEQ ID NO:79)

METDTLLLWVLLLWVPGSTG^SSELTQDPAVSVALGQTVRITCQGDSLRSYYA
SWYQQKPGQAPVLVISAKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADY
YCASRNGWNHVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI
SDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS
HRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 9

AM_H9 (SEQ ID NO:82)

ATGGGGTCAACCGCCATCCTTGGCCTCCTCCTGGCTGTCCTGCAGGGAGGGC
GCGCCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGC
CTCAGTGAAGGTCTCCTGCAAGGTTTCCGGATACACCCTCACTGAATTATCCA
TGCACTGGGTGCGACAGGCTCCTGGAAAAGGGCTTGAGTGGATGGGAGGTTT
TGATCGTGAAGATGATGAAACAATCCACGCACAGAAGTTCCAGGGCAGAGTC
ACCATGACCGAGGACACATCTACAGACACAGCCTACATGGAACTGAGCAGCC
TGCGATCTGAGGACACGGCCGTTTATTACTGTGCAACAGATCTTATGGTGTGG
GGCGATTTTTGGATCCAGCACTGGGGCCAGGGGACACTGGTCACCGTCTCCT
CAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG
CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC
GAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACA
CCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTG
ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATC
ACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGT
CGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGG
TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG
CAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGG
ACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGG
AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCCCA
TGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG
AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC
TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

AM_H9 (SEQ ID NO:81)

MGSTAILGLLLAVLQGGRA^QVQLVQSGAEVKKPGASVKVSCKVSGYTLTE
LSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYM
ELSSLRSEDTAVYYCATDLMVWGDFWIQHWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAP
IEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

FIGURE 10

AM_L9 (SEQ ID NO:84)

ATGGAGACAGACACACTCCTGCTATGGGTACTGCTGCTCTGGGTTCCAGGTTC
CACTGGTGCTAGCCAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCC
CCGGGCAGAGGGTCACCATCTCTTGTTCTGGAAGGAACTCCAACATCGGAAG
TTATACTGTAACCTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTC
ATCTATAGTAATAGTCAGCGGCCCTCAGGGGTCCCTGACCGATTCTCAGGCTC
CAAGTCTGGCACCTCAGCCTCCTTGGCCATCAGTGGGCTCCAGTCTGAAGAT
GAGGCTGATTATTACTGTGTGGTGTGGGACGAGATCCTGAATGGCCCGGTGT
TCGGCGGAGGGACCAAGCTGACCGTCCTAGGCCAACCGAAAGCGGCGCCCTC
GGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGA
AGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCA
AACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTG
AGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGA
GCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAG

AM_L9 (SEQ ID NO:83)

METDTLLLWVLLLWVPGSTG^ASQSVLTQPPSASGTPGQRVTISCSGRNSN
IGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISG
LQSEDEADYYCVVWDEILNGPVFGGGTKLTVLGQPKAAPSVTLFPPSSEE
LQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA
SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 11

AM_H11 (SEQ ID NO:86)

ATGGGGTCAACCGCCATCCTTGGCCTCCTCCTGGCTGTCCTGCAGGGAGGGC
GCGCCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGC
CTCAGTGAAGGTCTCCTGCAAGGTTTCCGGATACACCCTCACTGAATTATCCA
TGCACTGGGTGCGACAGGCTCCTGGAAAAGGGCTTGAGTGGATGGGAGGTTT
TGATCGTGAAGATGATGAAACAATCCACGCACAGAAGTTCCAGGGCAGAGTC
ACCATGACCGAGGACACATCTACAGACACAGCCTACATGGAACTGAGCAGCC
TGCGATCTGAGGACACGGCCGTTTATTACTGTGCAACAGATCTTATGGTGTGG
AACTTCCCCCCCATCCAGCACTGGGGCCAGGGGACACTGGTCACCGTCTCCT
CAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG
CACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC
GAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACA
CCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTG
ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATC
ACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGT
CGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
GTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGG
TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG
CAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGG
ACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCC
AGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTC
AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCCCATGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

AM_H11 (SEQ ID NO:85)

MGSTAILGLLLAVLQGGRA^QVQLVQSGAEVKKPGASVKVSCKVSGYTLTE
LSMHWVRQAPGKGLEWMGGFDREDDETIHAQKFQGRVTMTEDTSTDTAYM
ELSSLRSEDTAVYYCATDLMVWNFPPIQHWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAP
IEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

FIGURE 12

AM_L7 (SEQ ID NO:88)

ATGGAGACAGACACACTCCTGCTATGGGTACTGCTGCTCTGGGTTCCAGGTTC
CACTGGTGCTAGCCAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCC
CCGGGCAGAGGGTCACCATCTCTTGTTCTGGAAGGAACTCCAACATCGGAAG
TTATACTGTAACCTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTC
ATCTATAGTAATAGTCAGCGGCCCTCAGGGGTCCCTGACCGATTCTCAGGCTC
CAAGTCTGGCACCTCAGCCTCCTTGGCCATCAGTGGGCTCCAGTCTGAAGAT
GAGGCTGATTATTACTGTGTGGTGTGGGATGACGTGCTGAATGGCCCGGTGTT
CGGCGGAGGGACCAAGCTGACCGTCCTAGGCCAACCGAAAGCGGCGCCCTC
GGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGA
AGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCA
AACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTG
AGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGA
GCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAG

AM_L7 (SEQ ID NO:87)

METDTLLLWVLLLWVPGSTG^ASQSVLTQPPSASGTPGQRVTISCSGRNSN
IGSYTVTWYQQLPGTAPKLLIYSNSQRPSGVPDRFSGSKSGTSASLAISG
LQSEDEADYYCVVWDDVLNGPVFGGGTKLTVLGQPKAAPSVTLFPPSSEE
LQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA
SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 13