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(54) Title: HUMAN ANTIBODIES TO HUMAN INTERLEUKIN 18 RECEPTOR ALPHA AND BETA

(57) Abstract: Provided are antibodies or fragments thereof having binding specificity to anti-IL-18 receptor alpha or beta. Methods of using the antibodies or fragments thereof for treating and diagnosing diseases such as cancer and inflammatory and autoimmune diseases are also provided.

HUMAN ANTIBODIES TO HUMAN INTERLEUKIN 18 RECEPTOR ALPHA AND BETA

The present invention claims the priority of the PCT/CN2018/091780, filed on June 19, 2018, the contents of which are incorporated herein by its entirety.

BACKGROUND

The interleukins (ILs) are a class of soluble cytokines used for leukocyte communication in shaping immune responses. Since their discovery in the late 1970's, more than 40 distinct proteins have been classified as ILs according to their sequence identity with other ILs or their functional activity.

IL-18 was originally discovered as a pro-inflammatory, IFN-γ-inducing cytokine that shares biological functions and acts synergistically with IL-12. As a member of the IL-1 family of cytokines, IL-18 is thought to play a role in early inflammatory responses and is synthesized by a range of both hematopoietic and non-hematopoietic cells (e.g., macrophages, dendritic cells, Kupffer cells, keratinocytes, osteoblasts, astrocytes, adrenal cortex cells, intestinal epithelial cells, microglial cells, and synovial fibroblasts) both constitutively and in response to lipopolysaccharide and other cytokines such as TNF-α, and is post-translationally cleaved by the caspase-1 for functional activity of the mature 18 kDa species. Active IL-18 then targets cells that express the IL-18 receptor which is widely expressed on both hematopoietic and non-hematopoietic tissues.

The IL-18 receptor is a heterodimeric transmembrane protein comprised of a ligand binding IL-18R alpha (IL-18Rα) subunit and a non-ligand binding IL-18R beta (IL-18Rβ) subunit that is essential for functional signaling. Ligand-induced activation of the receptor results in recruitment and activation of intracellular myeloid differentiation 88 (MyD88) and IL-1R-associated kinase (IRAK) that simultaneously triggers at least two divergent phosphorylation cascades that activate the PI3K pathway and the MAPK pathway including activation of Akt, p38 and SAPK/JNK. Activation of these pathways culminate in NF-κB activation and transcription of its downstream genes that includes IFN-γ, chemokines, transcription factors, G protein and cell surface receptors. IL-18 shares elements of its signaling pathway with IL-1 but also bears distinct elements.

On hematopoietic cells such as T cells, B cell, natural killer (NK) cells, macrophages, and neutrophils, IL-18 ligand stimulation can enhance T and NK cell maturation, cytokine secretion, cytotoxicity and adhesion. Differentiation of naive T cells induced by IL-18 can induce either Th1 or Th2 lineages independently of either IL-4 or IL-12. In differentiated Th1 clones, IL-18 can induce the production and secretion of IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), or tumor necrosis factor (TNF); however, it does so primarily in synergy with IL-12. In neutrophils, IL-18 has been shown to induce the expression and secretion of cytokines and chemokines, up-regulate the expression of the cell surface adhesion molecule - CD11b, and potentiate the neutrophil respiratory burst. Importantly, the IL-18 receptor itself can be up-regulated on naive T, Th1 and B cells by IL-12 which explains, in part, the synergy between these two cytokines. IL-18 also acts synergistically with IL-2 inducing expression of IL-13 (in an IFN-γ-dependent manner) and IL-10 (in an IFN-γ independent manner). Together, these results underscore the role of IL-18 in both innate and adaptive immune responses.

In non-hematopoietic cells such as endothelial and epithelial cells, synovial fibroblasts and chondrocytes, IL-18 can up-regulate the expression of adhesion molecules (such as E-selectin, ICAM and VCAM), other cytokines, chemokines (CXCL8, CXCL5, CXCL1, CXCL12, CCL, CCL20) and angiogenic mediators such as vascular endothelial growth factor (VEGF) and thrombospondin. Overall, the effects of IL-18 induction of these effectors are to increase leukocyte recruitment, cellular adhesion, extravasation of immune cells, and promotion of cellular migration and formation of new blood vessels.

Mouse studies on IL-18 and its receptors have been facilitated by a reasonable degree of identity between both mouse and human ligands and their cognate receptors. Alignment of mouse and human IL-18 revealed a 63.5% identity between orthologs while alignment of mouse and human IL-18Rα and IL-18Rβ reveals a 64% and 65% sequence identity, respectively.

IL-18 can be induced by interaction of pattern recognition receptors with the repeating subunits of numerous different microbes including hepatitis C, chikungunya, mycobacterium tuberculosis, human immunodeficiency virus, heliobacteria and more.

Mouse models of infection suggest that pathogen-associated molecular patterns (PAMPs) recognized by Toll receptors (TLRs) and Nod-like receptors (NLRs) can activate caspase-1 in

the inflammasome leading to the cleavage and maturation of IL-18 (and IL-1β) which may help to limit immunopathologic responses. Studies of gram-negative bacterium *Burkholderia pseudomallei* in IL-18 -/- mice suggest that IL-18-mediated production of IFN-γ is essential for survival. Alternately, studies on the obligate intracellular bacterium *Ixodes Ovatus Ehrlichia* (IOE) in IL-18R-/- mice revealed decreased immunopathogenic responses and enhanced control of infection suggesting that IL-18 may play a greater role in regulating the immune response rather than conferring protection against infection. Interestingly, a host of orthopoxviruses encodes a functional homolog of the naturally occurring inhibitor IL-18 binding protein (IL-18BP), which enhances virulence of these viruses by inhibiting IL-18 signals.

In the context of numerous inflammatory diseases, IL-18 has been shown to be upregulated, to correlate with disease or to be a risk factor for disease development. Examples include in Crohn's disease, rheumatoid arthritis, systemic lupus erythrites, cardiovascular disease. Increased IL-18 levels have been observed in individuals at risk of developing either Type I (T1D) or Type 2 diabetes (T2D). Elevated IL-18 has also been observed in the serum, urine and islets of juvenile and adult T1D and T2D patients, correlating with the severity of disease, and the development of sequelae such as diabetic nephropathy. Studies on Alzheimer's patients have revealed expression of IL-18 is increased in the brain and is thought to contribute to immune and inflammatory processes that enhance oxidative stress and alter the expression of proteins that contribute to amyloid beta (Aβ) formation.

Recognizing the potential role of IL-18 in immunopathogenesis of inflammatory diseases several studies have undertaken pre-clinical evaluation of IL-18 abrogation via either genetic knockout or anti-IL-18 antagonists. A mouse model of collagen-induced arthritis in which IL-18 levels increase within 4-8 days after collagen injection was used to obtain pre-clinical insights into the efficacy of two distinct modalities of IL-18 inhibition including an anti-mouse rabbit polyclonal antibody and a recombinant anti-IL-18-binding protein. The authors concluded that both modalities were capable of impeding gross measures of pathologic progression such as inflammatory paw swelling and histological measures of disease severity such as degree of cartilage erosion. These results were further confirmed by serological measures that noted a decrease in serum IFN-γ, IL-6, TNF-α and cartilage oligomeric matrix protein (COMP) with both treatments. This provides both strong rationale and a clear pathway for pre-clinical assessment.

In experimental mouse models of sepsis, dual genetic IL-18 and IL-1β deficiencies were shown to protect mice from lethal doses of lipopolysaccharide (LPS), TNF-α or a surgical procedure that induces septic-like conditions referred to cecal ligation and puncture. Sepsis is often viewed as an 'unbridled hyper-inflammatory response' mediated by cytokines and is one of the leading causes of mortality in intensive care units. Importantly, the loss of either IL-1β or IL-18 provided only partial protection against septic lethality in contrast to the full protection offered by dual knockout, underscoring the complementary roles of these two pro-inflammatory cytokines.

Together, these studies suggest that inflammatory disorders may represent a class of pathologies that blockade of anti-IL-18-mediated signals through the use of antagonizing anti-IL-18 may show efficacy and for which there are ample opportunities for clearly defined pre-clinical study.

Studies in pre-clinical models of cancer suggest that anti-tumor activity of IL-18 arises from its ability to potentiate effector cells such as T cells and NK cells and have supported its use in clinical studies, though results thus far, provide modest support for a positive role for IL-18 in cancer. High IL-18 levels can be observed in numerous cancers either at the tumor site or systemically including breast, esophageal, gastrointestinal, lung, hepatic, ovarian and others.

SUMMARY

The present disclosure provides antibodies and antigen-binding fragments that are specific to IL-18 receptor alpha and beta subunits. These antibodies and fragments are capable of disrupting the IL-18 receptor linked downstream signaling pathway and thus can be used for treating certain diseases and conditions associated with expression or over-expression of IL-18 or the receptors, such as inflammatory and autoimmune diseases and cancer.

In one embodiment, therefore, the present disclosure provides an antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor beta (IL-18Rβ) protein having the amino acid sequence of SEQ ID NO:1, wherein the binding comprises at least: an amino acid residue selected from the group consisting of L167, D213 and T242, an amino acid residue selected from the group consisting

of V244, G245 and D246, and an amino acid residue selected from the group consisting of G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1.

In some embodiments, the binding comprises at least: an amino acid residue selected from the group consisting of D213 and T242, an amino acid residue selected from the group consisting of V244, G245 and D246, and an amino acid residue selected from the group consisting of G278, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1.

In some embodiments, the binding comprises at least: an amino acid residue selected from the group consisting of D213 and T242, the amino acid residue V244, and an amino acid residue selected from the group consisting of G278, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1. In some embodiments, the binding comprises at least the amino acid residues D213, T242, V244, G278, R281, V282, F283, N284, P285, S310, E315 and I317 of SEQ ID NO:1. In some embodiments, the binding comprises at least the amino acid residues L167, D213, T242, V244, G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317 of SEQ ID NO:1.

In some embodiments, the antibody or fragment thereof further is capable of binding to a mouse IL-18Rβ protein.

Another embodiment of the present disclosure provides an antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor beta (IL-18Rβ) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-27 of **Table B** or each of the combinations 1-27 in which each of the CDRL3, CDRH1, CDRH2, and CDRH3 includes one, two, or three amino acid addition, deletion, conservative amino acid substitution or the combinations thereof.

In some embodiments, the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combination 1 of **Table B** or have one amino acid substitution. In some embodiments, the substitutions are selected from **Table B1**. In some embodiments, the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combinations 1-27 of **Table B** or any combination of

Table 9. In some embodiments, the CDRL1 and CDRL2 have sequences of QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively.

Yet another embodiment of the present disclosure provides an antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor alpha (IL-18Rα) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-12 of **Table C** or each of the combinations 1-12 in which each of the CDRL3, CDRH1, CDRH2, and CDRH3 includes one, two, or three amino acid addition, deletion, conservative amino acid substitution or the combinations thereof.

In some embodiments, the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combination 11 of **Table C** or have one amino acid substitution. In some embodiments, the substitutions are selected from **Table C1**. In some embodiments, the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combinations 1-12 of **Table C**. In some embodiments, the CDRL1 and CDRL2 have sequences of QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively.

In some embodiments, the antibody or fragment thereof of the present disclosure comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, and 321 or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, and 321.

In some embodiments, the antibody or fragment thereof comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320.

In some embodiments, it comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:42, or a peptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:42. In some embodiments, the antibody or fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:44, or a peptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:44.

In some embodiments, the antibody or fragment thereof further comprises a second specificity to a second target protein. In some embodiments, the second target protein can be other pro-inflammatory cytokines, including but not limited to, IL-1, IL-4, IL-5, IL-6, IL13, IL-17 and IL36. Other examples include but not limited to CD3, CD16, CD19, CD20, CD28, CD64, PD-1, CTLA-4, LAG-3 (also known as CD223), CD28, CD122, 4-1BB (also known as CD137), TIM3, OX-40 or OX40L, CD40 or CD40L, LIGHT, ICOS/ICOSL, GITR/GITRL, TIGIT, CD27, VISTA, B7H3, B7H4, HEVM or BTLA (also known as CD272), killer-cell immunoglobulin-like receptors (KIRs), and CD47.

Also provided, in one embodiment, is a composition comprising the antibody or fragment thereof of the present disclosure and a pharmaceutically acceptable carrier. Also provided is an isolated cell comprising one or more polynucleotide encoding the antibody or fragment thereof of the present disclosure.

Methods and uses of treatments are also provided. In one embodiment, provided is a method of treating an autoimmune or inflammatory disease in a patient in need thereof, comprising administering to the patient the antibody or fragment thereof of the present disclosure. In some embodiments, the autoimmune or inflammatory disease is selected from the group consisting of a Parkinson's disease, arthritis, rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, lupus, systemic lupus erythematous, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, Grave's disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, dermatomyositis, multiple sclerosis, myasthenia gravis, pernicious anemia, Sjogren syndrome, type I diabetes, type II diabetes, vasculitis, uveitis, sepsis, atherosclerosis and ankylosing spondylitis.

In one embodiment, a method of treating cancer in a patient in need thereof is provided, comprising administering to the patient the antibody or fragment thereof of the present disclosure. In some embodiments, the cancer is selected from the group consisting of bladder cancer, liver cancer, colon cancer, rectal cancer, endometrial cancer, leukemia, lymphoma, pancreatic cancer, small cell lung cancer, non-small cell lung cancer, breast cancer, urethral cancer, head and neck cancer, gastrointestinal cancer, stomach cancer, oesophageal cancer, ovarian cancer, renal cancer, melanoma, prostate cancer and thyroid cancer.

Still further provided is a method of detecting expression of IL-18 receptor in a sample, comprising contacting the sample with an antibody or fragment thereof of the present disclosure under conditions for the antibody or fragment thereof to bind to the IL-18 receptor, and detecting the binding which indicates expression of IL-18 receptor in the sample.

In some embodiments, the sample is isolated from a human patient. In some embodiments, the detection indicates a disease associated with abnormal expression of the IL-18 receptor. In some embodiments, the disease is selected from the group consisting of infection, an autoimmune or inflammatory disease, or cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A-B. Evaluation of Fab-mediated inhibition of NF-κB signaling by luciferase assay. An IL-18 responsive luciferase reporter assay was used to assess the effects of **A**) anti-IL-18Rα–and **B**) anti-IL-18Rβ-binding Fabs on transcriptional activation of NF-kB by IL-18. NF-κB-induced luciferase signals by IL-18 (10ng/mL) in transfected cells were compared to

cells pre-treated with Fab and are expressed as normalized relative luciferase units. Errors bars represent standard deviation of replicate samples.

FIG. 2A-D. Antibody binding and epitope mapping. The EC_{50} and IC_{50} values of Fab binding to both IL-18Rα (red trace) and IL-18Rβ (black trace) were determined by **A**) multipoint direct binding and **B**) competitive binding ELISA following incubation with a two-fold dilutions series of soluble receptor. Generated curves were fit using appropriate models and values extracted from fit curves. **C**) The kinetics of anti Il-18Rβ Fab binding were determined to cognate human receptor by biolayer interferometry (BLI) to confirm EC_{50}/IC_{50} estimates. Kinetics of the interaction between the anti-IL-18Rα Fab and its cognate human receptor was similarly determined by surface plasmon resonance (SPR). **D**) To assess overlap of the indicated anti-IL-18Rβ-binding Fabs, IgG binding to hIL-18Rβ was measured by ELISA (white bars) and compared with IgG-binding signals obtained in the presence of saturating Fab (black bars). Error bars represent standard deviation of replicate measurements.

FIG. 3A-D. IgG binding to ectopically-expressed, cell surface IL-18R by immunofluorescence and flow cytometry. Anti-IL18Rα IgGs or an isotype control IgG were used to immunostain HEK293 cells transfected with **A**) hIL-18Rα-GFP or **B**) hIL-18Rβ-GFP constructs. Fluorochrome signals from GFP expression (green) and IgG-binding (red) were measured in the Cy3 and Cy5 channels and merged in the far-right column vs DAPI-stained nuclei (blue). Cell binding was also characterized at 400 nM IgG by flow cytometry using receptor-expressing or non-transfected HEK293 cells versus isotype control IgG or secondary alone in (**C**) for hIL-18Rα and in (**D**) for hIL-18Rβ. Median fluorescence intensity of IgG or control binding was measured in the Cy3 (IgG), APC (control anti-18Rα), or PE3 (control IL-18β) channels and visualized as histograms.

FIG. 4A-F. IgG-mediated Inhibition of IL-18 signals and function A) IL-18-induced phospho-signals were assayed to assess the effects of cell pre-incubation with IgG and compared to levels of non-phosphorylated parent protein by Western blot. Band intensities determined by densitometry were used to calculate normalized ratios of phospho signals versus controls untreated with either IL-18 or antibody and plotted as bar graphs for phospho **B**) -IKKα/β, **C**) -p38 and **D**) SAPK/JNK. The statistical significance in the change of IL-18 induced phosphorylation of downstream effectors - IKK-α/β, p38 MARK and SAPK/JNK in

comparison to no IL-18 control was assessed by t-test and * indicates a $p < 0.05$. The cellular effects of antibody pre-incubation on IL-18-induced stimulation of IFN-γ secretion was assessed over a range of IgG concentrations on both **E**) KG-1 myeloblasts and **F**) isolated PBMCs.

FIG. 5. Purification of the extracellular domain (ECD) of IL-18Rβ in complex with scFv 3131. A) The ECD of IL-18Rβ in complex with scFv 3131 was purified from size exclusion chromatography column (S200 26/600, GE). **B**) SDS-PAGE profile of size exclusion chromatography.

FIG. 6. Structural analysis of antibody binding reveals a novel mode of non-competitive antagonism. A) The structure of the IL-18 ternary signaling complex from PDB ID 3WO4 is shown for reference. **B**) A refined model of IgG 3131 reformatted as scFv in complex with IL-18Rβ (PDB ID 5ZX7) reveals a novel mode of inhibition in which binding to the hinge region of the receptor between domains 2 and 3 locks IL-18Rβ into a non-binding conformation for IL-18Rα. The D3 domain of IL-18Rβ in both structures is shown in the same orientation.

FIG. 7 shows the cellular effects of IgG 3131 pre-incubation on rhesus IL-18 (50 ng/ml) plus rhesus IL-12 (5 ng/ml) induced stimulation of IFN-γ secretion which was assessed over a range of IgG concentrations on isolated fresh cynomolgus monkey PBMCs. The mean and the standard deviation (SD) were calculated from three different monkeys. IC_{50} values were estimated from the dose response curves by curve fitting in GraphPad Prism (Version5.0).

FIG. 8 shows the individual serum concentration-time curve of IgG 3131 in male monkey following dosing of IgG 3131.

FIG. 9 shows the binding competition results for assessing the epitopes of AM2 antibody variants developed in Example 7 relative to parent 3131 antibody. The binding signals for purified AM2 Fab clones (white bars) to recombinant human IL-18Rb were compared to those obtained in the presence of saturating IgG 3131 (black bars). Fab 3131 was used as a positive control. Error bars represent standard deviation of replicate measurements.

DETAILED DESCRIPTION

Definitions

It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "an antibody," is understood to represent one or more antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

As used herein, the term "polypeptide" is intended to encompass a singular "polypeptide" as well as plural "polypeptides," and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term "polypeptide" refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, peptides, dipeptides, tripeptides, oligopeptides, "protein," "amino acid chain," or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of "polypeptide," and the term "polypeptide" may be used instead of, or interchangeably with any of these terms. The term "polypeptide" is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non- naturally occurring amino acids. A polypeptide may be derived from a natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis.

The term "isolated" as used herein with respect to cells, nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term "isolated" as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to cells or polypeptides which are isolated from other cellular proteins or tissues. Isolated polypeptides is meant to encompass both purified and recombinant polypeptides.

As used herein, the term "recombinant" as it pertains to polypeptides or polynucleotides intends a form of the polypeptide or polynucleotide that does not exist naturally, a non-limiting example of which can be created by combining polynucleotides or polypeptides that would not normally occur together.

"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present disclosure.

A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, 60 %, 65 %, 70 %, 75 %, 80 %, 85 %, 90 %, 95 %, 98 % or 99 %) of "sequence identity" to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in Ausubel *et al.* eds. (2007) Current Protocols in Molecular Biology. Preferably, default parameters are used for alignment. One alignment program is BLAST, using default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + SwissProtein + SPupdate + PIR. Biologically equivalent polynucleotides are those having the above-noted specified percent homology and encoding a polypeptide having the same or similar biological activity.

The term "an equivalent nucleic acid or polynucleotide" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology, or sequence identity, with the nucleotide sequence of the nucleic acid or complement thereof. A homolog of a double stranded nucleic acid is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with or with the complement thereof. In one aspect, homologs of nucleic acids are capable of hybridizing to the nucleic acid or complement

thereof. Likewise, "an equivalent polypeptide" refers to a polypeptide having a certain degree of homology, or sequence identity, with the amino acid sequence of a reference polypeptide. In some aspects, the sequence identity is at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%. In some aspects, the equivalent polypeptide or polynucleotide has one, two, three, four or five additions, deletions, substitutions and their combinations thereof as compared to the reference polypeptide or polynucleotide. In some aspects, the equivalent sequence retains the activity (*e.g.*, epitope-binding) or structure (*e.g.*, salt-bridge) of the reference sequence.

Hybridization reactions can be performed under conditions of different "stringency". In general, a low stringency hybridization reaction is carried out at about 40°C in about 10 x SSC or a solution of equivalent ionic strength/temperature. A moderate stringency hybridization is typically performed at about 50°C in about 6 x SSC, and a high stringency hybridization reaction is generally performed at about 60°C in about 1 x SSC. Hybridization reactions can also be performed under "physiological conditions" which is well known to one of skill in the art. A non-limiting example of a physiological condition is the temperature, ionic strength, pH and concentration of Mg^{2+} normally found in a cell.

A polynucleotide is composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); thymine (T); and uracil (U) for thymine when the polynucleotide is RNA. Thus, the term "polynucleotide sequence" is the alphabetical representation of a polynucleotide molecule. This alphabetical representation can be input into databases in a computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a "polymorphic region of a gene". A polymorphic region can be a single nucleotide, the identity of which differs in different alleles.

The terms "polynucleotide" and "oligonucleotide" are used interchangeably and refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides or analogs thereof. Polynucleotides can have any three-dimensional structure and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: a gene or gene fragment (for example, a probe, primer, EST or SAGE tag), exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA,

dsRNA, siRNA, miRNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes and primers. A polynucleotide can comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure can be imparted before or after assembly of the polynucleotide. The sequence of nucleotides can be interrupted by non-nucleotide components. A polynucleotide can be further modified after polymerization, such as by conjugation with a labeling component. The term also refers to both double- and single-stranded molecules. Unless otherwise specified or required, any embodiment of this disclosure that is a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form.

The term "encode" as it is applied to polynucleotides refers to a polynucleotide which is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment thereof. The antisense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

As used herein, an "antibody" or "antigen-binding polypeptide" refers to a polypeptide or a polypeptide complex that specifically recognizes and binds to an antigen. An antibody can be a whole antibody and any antigen binding fragment or a single chain thereof. Thus the term "antibody" includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule having biological activity of binding to the antigen. Examples of such include, but are not limited to a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein.

The terms "antibody fragment" or "antigen-binding fragment", as used herein, is a portion of an antibody such as $F(ab')_2$, $F(ab)_2$, Fab', Fab, Fv, scFv and the like. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the intact antibody. The term "antibody fragment" includes aptamers, spiegelmers, and diabodies. The term "antibody fragment" also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex.

A "single-chain variable fragment" or "scFv" refers to a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of immunoglobulins. In some aspects, the regions are connected with a short linker peptide of ten to about 25 amino acids. The linker can be rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the V_H with the C-terminus of the V_L, or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker. ScFv molecules are known in the art and are described, *e.g.*, in US patent 5,892,019.

The term antibody encompasses various broad classes of polypeptides that can be distinguished biochemically. Those skilled in the art will appreciate that heavy chains are classified as gamma, mu, alpha, delta, or epsilon (γ, μ, α, δ, ε) with some subclasses among them (*e.g.*, γ l- γ4). It is the nature of this chain that determines the "class" of the antibody as IgG, IgM, IgA IgD, or IgE, respectively. The immunoglobulin subclasses (isotypes) *e.g.*, IgG_1, IgG_2, IgG_3 and IgG_4. are well characterized and are known to confer functional specialization. Modified versions of each of these classes and isotypes are readily discernable to the skilled artisan in view of the instant disclosure and, accordingly, are within the scope of the instant disclosure. All immunoglobulin classes are clearly within the scope of the present disclosure, the following discussion will generally be directed to the IgG class of immunoglobulin molecules. With regard to IgG, a standard immunoglobulin molecule comprises two identical light chain polypeptides of molecular weight approximately 23,000 Daltons, and two identical heavy chain polypeptides of molecular weight 53,000-70,000. The four chains are typically joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" and continuing through the variable region.

Antibodies, antigen-binding polypeptides, variants, or derivatives thereof of the disclosure include, but are not limited to, polyclonal, monoclonal, multi-specific, human, humanized, primatized, or chimeric antibodies, single chain antibodies, epitope-binding fragments, *e.g.*, Fab, Fab' and $F(ab')_2$, Fd, Fvs, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv), fragments comprising either a VK or VH domain, fragments produced by a Fab expression library, and anti- idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to LIGHT antibodies disclosed herein). Immunoglobulin or antibody molecules of

the disclosure can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgGl, IgG2, IgG3, IgG4, IgAl and IgA2) or subclass of immunoglobulin molecule.

Light chains are classified as either kappa or lambda (K, λ). Each heavy chain class may be bound with either a kappa or lambda light chain. In general, the light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated either by hybridomas, B cells or genetically engineered host cells. In the heavy chain, the amino acid sequences run from an N-terminus at the forked ends of the Y configuration to the C-terminus at the bottom of each chain.

Both the light and heavy chains are divided into regions of structural and functional homology. The terms "constant" and "variable" are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VK) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CK) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention the numbering of the constant region domains increases as they become more distal from the antigen-binding site or amino- terminus of the antibody. The N-terminal portion is a variable region and at the C-terminal portion is a constant region; the CH3 and CK domains actually comprise the carboxy-terminus of the heavy and light chain, respectively.

As indicated above, the variable region allows the antibody to selectively recognize and specifically bind epitopes on antigens. That is, the VK domain and VH domain, or subset of the complementarity determining regions (CDRs), of an antibody combine to form the variable region that defines a three-dimensional antigen-binding site. This quaternary antibody structure forms the antigen-binding site present at the end of each arm of the Y. More specifically, the antigen-binding site is defined by three CDRs on each of the VH and VK chains (*i.e.* CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3). In some instances, *e.g.*, certain immunoglobulin molecules derived from camelid species or engineered based on camelid immunoglobulins, a complete immunoglobulin molecule may consist of heavy chains only, with no light chains. *See, e.g.*, Hamers-Casterman *et al.*, *Nature* 363:446-448 (1993).

In naturally occurring antibodies, the six "complementarity determining regions" or "CDRs" present in each antigen-binding domain are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three-dimensional configuration in an aqueous environment. The remainder of the amino acids in the antigen-binding domains, referred to as "framework" regions, show less inter-molecular variability. The framework regions largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β -sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immuno-reactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids comprising the CDRs and the framework regions, respectively, can be readily identified for any given heavy or light chain variable region by one of ordinary skill in the art, since they have been precisely defined (*see* "Sequences of Proteins of Immunological Interest," Kabat, E., *et al.*, U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, *J. Mol. Biol.*, 196:901-917 (1987)).

In the case where there are two or more definitions of a term which is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term "complementarity determining region" ("CDR") to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat *et al.*, U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" (1983) and by Chothia *et al.*, *J. Mol. Biol.* 196:901-917 (1987), which are incorporated herein by reference in their entireties. The CDR definitions according to Kabat and Chothia include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth in the table below as a comparison. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

	Kabat	Chothia
CDR-H1	31-35	26-32
CDR-H2	50-65	52-58
CDR-H3	95-102	95-102
CDR-L1	24-34	26-32
CDR-L2	50-56	50-52
CDR-L3	89-97	91-96

Kabat *et al.* also defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat *et al.*, U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest" (1983).

In addition to table above, the Kabat number system describes the CDR regions as follows: CDR-H1 begins at approximately amino acid 31 (*i.e.*, approximately 9 residues after the first cysteine residue), includes approximately 5-7 amino acids, and ends at the next tryptophan residue. CDR-H2 begins at the fifteenth residue after the end of CDR-H1, includes approximately 16-19 amino acids, and ends at the next arginine or lysine residue. CDR-H3 begins at approximately the thirty third amino acid residue after the end of CDR-H2; includes 3-25 amino acids; and ends at the sequence W-G-X-G, where X is any amino acid. CDR-L1 begins at approximately residue 24 (*i.e.*, following a cysteine residue); includes approximately 10-17 residues; and ends at the next tryptophan residue. CDR-L2 begins at approximately the sixteenth residue after the end of CDR-L1 and includes approximately 7 residues. CDR-L3 begins at approximately the thirty third residue after the end of CDR-L2 (*i.e.*, following a cysteine residue); includes approximately 7-11 residues and ends at the sequence F or W-G-X-G, where X is any amino acid.

Antibodies disclosed herein may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine, donkey, rabbit, goat, guinea pig, camel, llama, horse, or chicken antibodies. In another embodiment, the variable region may be condricthoid in origin (*e.g.*, from sharks).

As used herein, the term "heavy chain constant region" includes amino acid sequences derived from an immunoglobulin heavy chain. A polypeptide comprising a heavy chain constant region comprises at least one of: a CH1 domain, a hinge (*e.g.*, upper, middle, and/or

lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant or fragment thereof. For example, an antigen-binding polypeptide for use in the disclosure may comprise a polypeptide chain comprising a CH1 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH2 domain; a polypeptide chain comprising a CH1 domain and a CH3 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH3 domain, or a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, a CH2 domain, and a CH3 domain. In another embodiment, a polypeptide of the disclosure comprises a polypeptide chain comprising a CH3 domain. Further, an antibody for use in the disclosure may lack at least a portion of a CH2 domain (*e.g.*, all or part of a CH2 domain). As set forth above, it will be understood by one of ordinary skill in the art that the heavy chain constant region may be modified such that they vary in amino acid sequence from the naturally occurring immunoglobulin molecule.

The heavy chain constant region of an antibody disclosed herein may be derived from different immunoglobulin molecules. For example, a heavy chain constant region of a polypeptide may comprise a CH1 domain derived from an IgG_1 molecule and a hinge region derived from an IgG_3 molecule. In another example, a heavy chain constant region can comprise a hinge region derived, in part, from an IgG_1 molecule and, in part, from an IgG_3 molecule. In another example, a heavy chain portion can comprise a chimeric hinge derived, in part, from an IgG_1 molecule and, in part, from an IgG_4 molecule.

As used herein, the term "light chain constant region" includes amino acid sequences derived from antibody light chain. Preferably, the light chain constant region comprises at least one of a constant kappa domain or constant lambda domain.

A "light chain-heavy chain pair" refers to the collection of a light chain and heavy chain that can form a dimer through a disulfide bond between the CL domain of the light chain and the CH1 domain of the heavy chain.

As previously indicated, the subunit structures and three-dimensional configuration of the constant regions of the various immunoglobulin classes are well known. As used herein, the term "VH domain" includes the amino terminal variable domain of an immunoglobulin heavy chain and the term "CH1 domain" includes the first (most amino terminal) constant region domain of an immunoglobulin heavy chain. The CH1 domain is adjacent to the VH domain and is amino terminal to the hinge region of an immunoglobulin heavy chain molecule.

As used herein the term "CH2 domain" includes the portion of a heavy chain molecule that extends, *e.g.*, from about residue 244 to residue 360 of an antibody using conventional numbering schemes (residues 244 to 360, Kabat numbering system; and residues 231-340, EU numbering system; *see* Kabat *et al.*, U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" (1983). The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It is also well documented that the CH3 domain extends from the CH2 domain to the C-terminal of the IgG molecule and comprises approximately 108 residues.

As used herein, the term "hinge region" includes the portion of a heavy chain molecule that joins the CH1 domain to the CH2 domain. This hinge region comprises approximately 25 residues and is flexible, thus allowing the two N-terminal antigen-binding regions to move independently. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains (Roux *et al.*, *J. Immunol* 161:4083 (1998)).

As used herein the term "disulfide bond" includes the covalent bond formed between two sulfur atoms. The amino acid cysteine comprises a thiol group that can form a disulfide bond or bridge with a second thiol group. In most naturally occurring IgG molecules, the CH1 and CK regions are linked by a disulfide bond and the two heavy chains are linked by two disulfide bonds at positions corresponding to 239 and 242 using the Kabat numbering system (position 226 or 229, EU numbering system).

As used herein, the term "chimeric antibody" will be held to mean any antibody wherein the immuno-reactive region or site is obtained or derived from a first species and the constant region (which may be intact, partial or modified in accordance with the instant disclosure) is obtained from a second species. In certain embodiments, the target binding region or site will be from a non-human source (*e.g.* mouse or primate) and the constant region is human.

As used herein, "percent humanization" is calculated by determining the number of framework amino acid differences (*i.e.*, non-CDR difference) between the humanized domain and the germline domain, subtracting that number from the total number of amino acids, and then dividing that by the total number of amino acids and multiplying by 100.

By "specifically binds" or "has specificity to," it is generally meant that an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity

between the antigen-binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D."

As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the progression of cancer. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, and zoo, sport, or pet animals such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, cows, and so on.

As used herein, phrases such as "to a patient in need of treatment" or "a subject in need of treatment" includes subjects, such as mammalian subjects, that would benefit from administration of an antibody or composition of the present disclosure used, *e.g.*, for detection, for a diagnostic procedure and/or for treatment.

Anti-IL-18R alpha and beta antibodies

Some cytokine-directed therapies have been associated with an increase in infections. This might be less of a concern with anti-IL-18-directed antibodies. Nevertheless, recent clinical studies investigating the safety and efficacy of an anti-IL-18 monoclonal antibody with 30

pM affinity was used to evaluate its ability to restore fasting plasma glucose control, insulin levels and C-reactive peptide (a proxy for insulin levels) failed to show appreciable efficacy. It is therefore not surprising that no therapeutic antibodies have been developed targeting the receptors.

Various embodiments of the present disclosure provide antibodies specific to IL-18 receptor α or β. These antibodies can be effective therapeutic agents given their unique features. Often, antagonistic antibodies impede receptor-mediated signaling by steric blockade of the ligand binding site. The anti-IL-18Rβ antibody 3131 of the present disclosure, however, targets the non-ligand binding component of the receptor, as shown in the structural data obtained herein. This subunit of the receptor does not directly contact the ligand, but rather forms intermolecular contacts with the ligand-binding IL-18Rα subunit. In doing so, it mediates the signaling function of the receptor complex and without it, no transduction of ligand signals occurs. Antibody 3131 interaction with IL-18Rβ appears to occur at the hinge region between domains 2 (D2) and 3 (D3), distorting the relative angle between them into a conformation that cannot interact with IL-18Rα. This effectively impedes formation of a functional receptor-ligand complex and inhibits downstream signaling in a new manner.

It is also interesting that the IL-18Rβ antibody 3131 exhibited appreciable affinity for its mouse ortholog. This is useful as it will enable pre-clinical evaluation of its distribution, safety and activity in a mouse model against the endogenous receptor thus facilitating development and the path to clinical evaluation.

In accordance with one embodiment of the present disclosure, antibodies and fragments thereof are provided that specifically bind to the IL-18Rβ protein. These antibodies or fragments can have binding specificity to two or more of the following regions, (1) the D1-D2 domains, (2) the hinge region, and (3) the D3 domain of a human interleukin-18 receptor beta (IL-18Rβ) protein. The hinge regions can be illustrated with an example IL-18Rβ sequence, SEQ ID NO:161 (UniProt ID O95256; **Table A**). In SEQ ID NO:1, amino acid residues 1-243 are the D1 and D2 domains. Amino acid residues 244-246 constitute the hinge region. Amino acid residues 247-356 constitute the D3 domain.

Amino acid residues in the D1-D2 domains that can be involved in binding the antibody or fragment include, without limitation, L167, D213, and T242. Amino acid residues in the hinge region that can be involved in binding the antibody or fragment include, without

limitation, V244, G245 and D246. Amino acid residues in the D3 domain that can be involved in binding the antibody or fragment include, without limitation, G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317.

In one embodiment, the antibody of fragment thereof binds to at least a residue in the D1-D2 domains (e.g., one of more of L167, D213, or T242, preferably one or more of D213 or T242) and at least a residue in the hinge region (e.g., one or more of V244, G245 or D246, preferably V244).

In one embodiment, the antibody of fragment thereof binds to at least a residue in the D1-D2 domains (e.g., one or more of L167, D213, and T242, preferably one or more of D213, and T242) and at least a residue in the D3 domain (one or more of G278, F279, R281, V282, F283, N284, P285, S310, E315 or I317, or preferably one or more of G278, R281, V282, F283, N284, P285, S310, E315 or I317).

In one embodiment, the antibody of fragment thereof binds to at least a residue in the hinge region (e.g., one or more of V244, G245 or D246, preferably V244) and at least a residue in the D3 domain (one or more of G278, F279, R281, V282, F283, N284, P285, S310, E315 or I317, or preferably one or more of G278, R281, V282, F283, N284, P285, S310, E315 or I317).

In one embodiment, the antibody of fragment thereof binds to at least a residue in the D1-D2 domains (e.g., one or more of L167, D213, or T242, preferably one or more of D213 or T242), at least a residue in the hinge region (e.g., one or more of V244, G245 or D246, preferably V244), and at least a residue in the D3 domain (one or more of G278, F279, R281, V282, F283, N284, P285, S310, E315 or I317, or preferably one or more of G278, R281, V282, F283, N284, P285, S310, E315 or I317).

In one embodiment, the antibody of fragment thereof binds to D213 and T242 of D1-D2, V244 of the hinge region, and at least two, three, four, five, six, seven or eight residues in the D3 domain selected from G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317, or from G278, R281, V282, F283, N284, P285, S310, E315 and I317.

In one embodiment, the antibody of fragment thereof binds to amino acid residues D213, T242, V244, G278, R281, V282, F283, N284, P285, S310, E315 and I317. In one

embodiment, the antibody of fragment thereof binds to amino acid residues L167, D213, T242, V244, G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317.

Table A. Example IL-18Rβ sequence

Name	Sequence
IL-18Rβ (SEQ ID NO:161)	1 MLCLGWIFLW LVAGERIKGF NISGCSTKKL LWTYSTRSEE EFVLFCDLPE 51 PQKSHFCHRN RLSPKQVPEH LPFMGSNDLS DVQWYQQPSN GDPLEDIRKS 101 YPHIIQDKCT LHFLTPGVNN SGSYICRPKM IKSPYDVACC VKMILEVKPQ 151 TNASCEYSAS HKQDLLLGST GSISCPSLSC QSDAQSPAVT WYKNGKLLSV 201 ERSNRIVVDE VYDYHQGTYV CDYTQSDTVS SWTVRAVVQV RTIVGDTKLK 251 PDILDPVEDT LEVELGKPLT ISCKARFGFE RVFNPVIKWY IKDSDLEWEV 301 SVPEAKSIKS TLKDEIIERN IILEKVTQRD LRRKFVCFVQ NSIGNTTQSV 351 QLKEKRGVVL LYILLGTIGT LVAVLAASAL LYRHWIEIVL LYRTYQSKDQ 401 TLGDKKDFDA FVSYAKWSSF PSEATSSLSE EHLALSLFPD VLENKYGYSL 451 CLLERDVAPG GVYAEDIVSI IKRSRRGIFI LSPNYVNGPS IFELQAAVNL 501 ALDDQTLKLI LIKFCYFQEP ESLPHLVKKA LRVLPTVTWR GLKSVPPNSR 551 FWAKMRYHMP VKNSQGFTWN QLRITSRIFQ WKGLSRTETT GRSSQPKEW

In some embodiments, the antibody or fragment can bind to both human and mouse IL-18Rβ proteins.

Antibodies and fragments of the present disclosure are also described with respect to their CDR sequences. In one embodiment, an antibody or fragment thereof is provided that has binding specificity to a human interleukin-18 receptor beta (IL-18Rβ) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-27 of **Table B**. The antibody or fragment disclosure herein can also include a CDRL1 and a CDRL2. A good variety of CDRL1 and CDRL2 sequences can be employed here. Non-limiting examples include QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively, as well as them with substitutions as illustrated in **Table B1**.

Table B. CDR sequences for anti-IL-18Rβ antibodies

Comb #	Fab ID	CDRL1 (SEQ ID NO:)		CDRL2 (SEQ ID NO:)		CDRL3 (SEQ ID NO:)		CDRH1 (SEQ ID NO:)		CDRH2 (SEQ ID NO:)		CDRH3 (SEQ ID NO:)	
1	F3131	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
2	F3132	QSVSSA	45	SAS	46	QQHWWASVPPFT	48	GFNISYYYI	75	SIYSYSGYTS	96	ARASAMDY	118
3	F3133	QSVSSA	45	SAS	46	QQHYWGYLIT	49	GFNLSYYSI	76	SIYSSYGYTS	97	ARSYGLDY	119
4	F3134	QSVSSA	45	SAS	46	QQHHWSYPIT	50	GFNIYSYSI	77	SIYPSYGYTS	98	ARSFGLDY	120
5	F3135	QSVSSA	45	SAS	46	QQHHHWAVLIT	51	GFNFYSYSM	78	YIYPYSGYTS	99	ARSFAMDY	121
6	F3136	QSVSSA	45	SAS	46	QQHYWGGPIT	52	GFNISSYSM	79	SIYSYYSYTS	100	ARSYAMDY	122
7	F3137	QSVSSA	45	SAS	46	QQSWGWSWLIT	53	GFNLSSYSI	80	YIYPSYGSTY	101	ARSYALDY	123
8	F3138	QSVSSA	45	SAS	46	QQHSFHSGLIT	54	GFNLYSYSM	81	YIYSYSGYTS	102	ARGFALDY	124
9	F3139	QSVSSA	45	SAS	46	QQSHGWWGFPFT	55	GFNISSYSI	82	SIYPYYGYTY	103	ARSWAMDY	125
10	F3140	QSVSSA	45	SAS	46	QQYYWASYPFT	56	GFNFYSYSM	78	SIYPSYGYTS	98	ARSFGFDY	126
11	F3141	QSVSSA	45	SAS	46	QQYYYSAALIT	57	GFNIYYSSM	83	YIYPYSGYTS	99	ARYFAMDY	127
12	F3142	QSVSSA	45	SAS	46	QQWWGGPYVLIT	58	GFNLSYSSM	84	SIYPSSSSTY	104	ARSSHSHGYYFYGIDY	128
13	F3143	QSVSSA	45	SAS	46	QQYHWGSYYPFT	59	GFNLSSYYM	85	SIYPYYGYTY	103	ARSSAMDY	129
14	F3144	QSVSSA	45	SAS	46	QQHWWGYPLIT	60	GFNLSYYSI	76	SIYSYSGYTS	96	ARSSAMDY	129
15	F3145	QSVSSA	45	SAS	46	QQHYYGSFPPIT	61	GFNFYSYSM	78	SIYSYYGYTS	105	ARSFGMDY	130
16	F3147	QSVSSA	45	SAS	46	QQHWWAALIT	62	GFNLSSYSI	80	YIYSSYGYTS	106	ARSFGMDY	130
17	F3148	QSVSSA	45	SAS	46	QQHYYSSLIT	63	GFNIYSYSM	86	SIYPYYSSTY	107	ARSSAMDY	129
18	F3150	QSVSSA	45	SAS	46	QQHSWAVPIT	64	GFNLSSYSM	87	SIYPYYGYTS	108	ARSSAFDY	131
19	F3152	QSVSSA	45	SAS	46	QQHSYSAPLIT	65	GFNIYSYSM	86	SIYPSYSYTS	109	ARSYAMDY	122
20	FA3	QSVSSA	45	SAS	46	QQSYFLIT	66	GFNLYSSYI	88	SIYSSSGYTY	110	ARSVHSYYSSAAYYAMDY	132
21	FE60	QSVSSA	45	SAS	46	QQYPSASHYLIT	67	GFNLYYYYM	89	SIYSYYGYTS	105	ARSYPSSSWGSVALDY	133
22	3131 AM1-1	QSVSSA	45	SAS	46	QQYAYHEPGLLT	68	GFNPYYSSI	90	SISPSYSSTY	111	ARSSCSHSCRFYGLDY	134
23	3131-AM1-2	QSVSSA	45	SAS	46	QQWGYRYAPLVT	69	GFNFYYSSI	91	SISSATGNTS	112	ARSSYSHGHSWYGLDY	135

24	3144-AM1-3	QSVSSA	45	SAS	46	QQHSWAYPMIT	70	GFNLTWWSI	92	TIFSGFSYTS	113	ARSSAMDY	129
25	3144-AM1-4	QSVSSA	45	SAS	46	QQHWFGYPAVT	71	GFNISQYTI	93	SIYARSRFTS	114	ARSSRMDY	136
26	3144-AM1-5	QSVSSA	45	SAS	46	QQHWWGYPMIT	72	GFNISYYTI	94	SIYSYSLYTS	115	ARSSAMDY	129
27	3144-AM1-6	QSVSSA	45	SAS	46	QQHSWRYPLIT	73	GFNLSSYSI	86	AIYAGFGSTT	116	ARSSAMDY	129

It can be readily appreciated that certain modification (e.g., one, two, or three amino acid additions, deletions, conservative amino acid substitutions) to one or more of the CDR sequences can be made while retaining the binding activity of the antibody or fragment. In some embodiments, the modifications are amino acid substitution of one, two, or three residues.

In some embodiments, the modification is substitution at no more than one hot spot position from each of the CDRs. In some embodiments, the modification is substitution at one, two or three such hot spot positions. In one embodiment, the modification is substitution at one of the hot spot positions. Such substitutions, in some embodiments, are conservative substitutions.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in an immunoglobulin polypeptide is preferably replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members.

Non-limiting examples of conservative amino acid substitutions are provided in the table below, where a similarity score of 0 or higher indicates conservative substitution between the two amino acids.

Amino Acid Similarity Matrix

	C	G	P	S	A	T	D	E	N	Q	H	K	R	V	M	I	L	F	Y	W
W	-8	-7	-6	-2	-6	-5	-7	-7	-4	-5	-3	-3	2	-6	-4	-5	-2	0	0	17
Y	0	-5	-5	-3	-3	-3	-4	-4	-2	-4	0	-4	-5	-2	-2	-1	-1	7	10	
F	-4	-5	-5	-3	-4	-3	-6	-5	-4	-5	-2	-5	-4	-1	0	1	2	9		
L	-6	-4	-3	-3	-2	-2	-4	-3	-3	-2	-2	-3	-3	2	4	2	6			
I	-2	-3	-2	-1	-1	0	-2	-2	-2	-2	-2	-2	-2	4	2	5				
M	-5	-3	-2	-2	-1	-1	-3	-2	0	-1	-2	0	0	2	6					
V	-2	-1	-1	-1	0	0	-2	-2	-2	-2	-2	-2	-2	4						
R	-4	-3	0	0	-2	-1	-1	-1	0	1	2	3	6							
K	-5	-2	-1	0	-1	0	0	0	1	1	0	5								
H	-3	-2	0	-1	-1	-1	1	1	2	3	6									
Q	-5	-1	0	-1	0	-1	2	2	1	4										
N	-4	0	-1	1	0	0	2	1	2											
E	-5	0	-1	0	0	0	3	4												
D	-5	1	-1	0	0	0	4													
T	-2	0	0	1	1	3														
A	-2	1	1	1	2															
S	0	1	1	1																
P	-3	-1	6																	
G	-3	5																		
C	12																			

Conservative Amino Acid Substitutions

For Amino Acid	**Substitution With**
Alanine	D-Ala, L-Gly, Aib, β-Ala, L-Cys, D-Cys
Arginine	D-Arg, L-Lys, D-Lys, Orn, D-Orn
Asparagine	D-Asn, L-Asp, D-Asp, L-Glu, D-Glu, L-Gln, D-Gln
Aspartic Acid	D-Asp, D-Asn, L-Asn, L-Glu, D-Glu, L-Gln, D-Gln
Cysteine	D-Cys, L-S-Me-Cys, Seleno-Cys (Sec), L-Met, D-Met, L-Thr, D-Thr, L-Ser, D-Ser
Glutamine	D-Gln, L-Asn, D-Asn, L-Glu, D-Glu, L-Asp, D-Asp
Glutamic Acid	D-Glu, D-Asp, L-Asp, L-Asn, D-Asn, L-Gln, D-Gln
Glycine	L-Ala, D-Ala, L-Pro, D-Pro, Aib, β-Ala
Isoleucine	D-Ile, L-Val, D-Val, L-Leu, D-Leu, L-Met, D-Met
Leucine	L-Val, D-Val, L-Met, D-Met, D-Ile, D-Leu, L-Ile
Lysine	D-Lys, L-Arg, D-Arg, L-Orn, D-Orn
Methionine	D-Met, L-S-Me-Cys, L-Ile, D-Ile, L-Leu, D-Leu, L-Val, D-Val
Phenylalanine	D-Phe, L-Tyr, D-Tyr, L-His, D-His, L-Trp, D-Trp
Proline	D-Pro
Serine	D-Ser, L-Thr, D-Thr, allo-Thr, L-Cys, D-Cys, Seleno-Cys (Sec)
Threonine	D-Thr, L-Ser, D-Ser, allo-Thr, L-Met, D-Met, L-Val, D-Val
Tyrosine	D-Tyr, L-Phe, D-Phe, L-His, D-His, L-Trp, D-Trp

Valine	D-Val, L-Leu, D-Leu, L-Ile, D-Ile, L-Met, D-Met

Specific examples of CDRs (from F3131, #1 in Table B) with suitable substitutions are provided in the table below.

Table B1. Substitutions of CDR Residues

CDR	No.*	Residue	Can be substituted with
CDRL1	27	Q	N, D, E, S, T, Y, W, H, K, R
	28	S	N, D, E, Q, T, Y, W, H, K, R
	29	V	A, I, L, M, P, F
	36	S	N, D, E, Q, T, Y, W, H, K, R
	37	S	N, D, E, Q, T, Y, W, H, K, R
	38	A	V, I, L, M, P, F
CDRL2	56	S	N, D, E, Q, T, Y, W, H, K, R
	57	A	V, I, L, M, P, F
	65	S	N, D, E, Q, T, Y, W, H, K, R
CDRL3	105	Q	N, D, E, S, T, Y, W, H, K, R
	106	Q	N, D, E, S, T, Y, W, H, K, R
	107	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	108	G	N, D, E, S, T, Q, W, H, K, R
	109	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	110	H	N, D, E, S, T, Y, W, Q, K, R
	112	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	113	A	V, I, L, M, P, F
	114	G	V, I, L, M, P, F
	115	L	V, I, A, M, P, F
	116	I	V, L, A, M, P, F
	117	T	N, D, E, Q, S, Y, W, H, K, R
CDRH1	27	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	28	F	A, I, L, M, P, V
	29	N	Q, D, E, S, T, Y, W, H, K, R
	30	L	V, I, A, M, P, F
	35	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	36	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	37	S	N, D, E, Q, T, Y, W, H, K, R
	38	S	N, D, E, Q, T, Y, W, H, K, R
	39	M	V, L, A, I, P, F
CDRH2	55	S	N, D, E, Q, T, Y, W, H, K, R
	56	I	V, L, A, M, P, F
	57	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	58	S	N, D, E, Q, T, Y, W, H, K, R
	59	S	N, D, E, Q, T, Y, W, H, K, R

	62	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	63	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	64	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	65	T	N, D, E, Q, S, Y, W, H, K, R
	66	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
CDRH3	105	A	V, I, L, M, P, F
	106	R	N, D, E, Q, T, Y, W, H, K, S
	107	S	N, D, E, Q, T, Y, W, H, K, R
	108	S	N, D, E, Q, T, Y, W, H, K, R
	109	F	A, I, L, M, P, V
	110	S	N, D, E, Q, T, Y, W, H, K, R
	111	H	N, D, E, S, T, Y, W, Q, K, R
	111.1	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	112.2	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	112.1	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	112	W	A, I, L, M, P, V, F
	113	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	114	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	115	L	V, I, A, M, P, F
	116	D	N, Q, E, S, T, Y, W, H, K, R
	117	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A

* IMGT numbering system

Specific example antibodies include those that have a heavy chain sequence of SEQ ID NO:2, 6, 10, 14, 18, 22, 26, 30, 34, or 38 and/or a light chain sequence of SEQ ID NO:4, 8, 12, 16, 20, 24, 28, 32, 36, and 40, and their respective biological variants.

Antibody 3131 (with a heavy chain variable region of SEQ ID NO:2, and a light chain variable region of SEQ ID NO:4) went through a few rounds of affinity maturations, resulting in the generation of 3131 AM1-1 and AM1-2 (see **Table 2**), and those provided in **Table 8**. Each of these affinity maturated antibodies, their Fab fragments, variable regions and CDRs are also within the scope of the present disclosure.

In some embodiments, an antibody or fragment of the present disclosure includes CDRL3, CDRH1, CDRH2, and CDRH3 of 3131 or each of its affinity maturated variants (e.g., **Table 9**). In some embodiments, an antibody or fragment of the present disclosure includes CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 of 3131 or each of its affinity maturated variants (e.g., **Table 9**).

In some embodiments, an antibody or fragment of the present disclosure includes a heavy chain variable region and a light chain variable region of an affinity maturated variant of

Table 8, such as AM2-1, AM2-1, AM2-2, AM2-2, AM2-3, AM2-3, AM2-4, AM2-4, AM2-5, AM2-5, AM2-6, AM2-6, AM2-7, AM2-7, AM2-8, AM2-8, AM2-9, AM2-9, AM2-10, AM2-10, AM2-11, AM2-11, AM2-13, AM2-13, AM2-14, AM2-14, AM2-15, AM2-15, AM2-16, AM2-16, AM2-17, AM2-17, AM2-18, AM2-18, AM2-21, AM2-21, AM2-24, AM2-24, AM2-25, AM2-25, AM2-26, AM2-26, AM2-28, AM2-28, AM2-29, AM2-29, AM2-30, AM2-30, AM2-31, AM2-31, AM2-32, AM2-32, AM2-33, AM2-33, AM2-35, AM2-35, AM2-36, AM2-36, AM2-37, AM2-37, AM2-S-G, AM2-S-G, AM2-S-T, AM2-S-T, AM2-S-H, AM2-S-H, AM2-S-Y, AM2-S-T, AM2-O-01, AM2-O-01, AM2-O-02, AM2-O-02, AM2-O-03, AM2-O-03, AM2-O-04, AM2-O-04, AM2-O-05, AM2-O-05, AM2-O-06, AM2-O-06, AM2-O-07, AM2-O-07, AM2-O-08, AM2-O-08, AM2-O-09, AM2-O-09, AM2-O-10, AM2-O-10, AM2-O-11, AM2-O-11, AM2-O-12, AM2-O-12, AM2-O-13, AM2-O-13, AM2-O-14, AM2-O-14, AM2-O-15, AM2-O-15, AM2-O-16, AM2-O-16, AM2-O-17, AM2-O-17, AM2-O-18, AM2-O-18, AM2-O-19, AM2-O-19, AM2-O-20, AM2-O-20, AM2-O-21, AM2-O-21, AM2-O-22, AM2-O-22, AM2-O-23, AM2-O-23, AM2-O-24, AM2-O-24, AM2-O-25, AM2-O-25, AM2-O-26, AM2-O-26, AM2-O-27, AM2-O-27, AM2-O-28, AM2-O-28, AM2-O-29, AM2-O-29, AM2-O-30, AM2-O-30, AM2-O-31, AM2-O-31, AM2-O-32, AM2-O-32, AM2-O-33, AM2-O-33, AM2-O-34, AM2-O-34, AM2-O-35, AM2-O-35, AM2-O-36, AM2-O-36, AM2-O-37, AM2-O-37, AM2-O-38, AM2-O-38, AM2-O-39, AM2-O-39, AM2-O-40, AM2-O-40, AM2-O-41, AM2-O-41, AM2-O-42, AM2-O-42, AM2-O-43, AM2-O-43, AM2-O-44, AM2-O-44, AM2-O-45, AM2-O-45, AM2-O-46, and AM2-O-46.

In some embodiments, an antibody or fragment of the present disclosure includes the CDRs of an affinity maturated variant of **Table 8**, such as AM2-1, AM2-1, AM2-2, AM2-2, AM2-3, AM2-3, AM2-4, AM2-4, AM2-5, AM2-5, AM2-6, AM2-6, AM2-7, AM2-7, AM2-8, AM2-8, AM2-9, AM2-9, AM2-10, AM2-10, AM2-11, AM2-11, AM2-13, AM2-13, AM2-14, AM2-14, AM2-15, AM2-15, AM2-16, AM2-16, AM2-17, AM2-17, AM2-18, AM2-18, AM2-21, AM2-21, AM2-24, AM2-24, AM2-25, AM2-25, AM2-26, AM2-26, AM2-28, AM2-28, AM2-29, AM2-29, AM2-30, AM2-30, AM2-31, AM2-31, AM2-32, AM2-32, AM2-33, AM2-33, AM2-35, AM2-35, AM2-36, AM2-36, AM2-37, AM2-37, AM2-S-G, AM2-S-G, AM2-S-T, AM2-S-T, AM2-S-H, AM2-S-H, AM2-S-Y, AM2-S-T, AM2-O-01, AM2-O-01, AM2-O-02, AM2-O-02, AM2-O-03, AM2-O-03, AM2-O-04, AM2-O-04, AM2-O-05, AM2-O-05, AM2-O-06, AM2-O-06, AM2-O-07, AM2-O-07, AM2-O-08, AM2-O-08, AM2-O-09, AM2-O-09, AM2-O-10, AM2-O-10, AM2-O-11, AM2-O-11, AM2-O-12, AM2-O-12, AM2-O-13, AM2-O-13, AM2-O-14, AM2-O-14, AM2-O-15, AM2-O-15, AM2-O-16, AM2-O-16,

AM2-O-17, AM2-O-17, AM2-O-18, AM2-O-18, AM2-O-19, AM2-O-19, AM2-O-20, AM2-O-20, AM2-O-21, AM2-O-21, AM2-O-22, AM2-O-22, AM2-O-23, AM2-O-23, AM2-O-24, AM2-O-24, AM2-O-25, AM2-O-25, AM2-O-26, AM2-O-26, AM2-O-27, AM2-O-27, AM2-O-28, AM2-O-28, AM2-O-29, AM2-O-29, AM2-O-30, AM2-O-30, AM2-O-31, AM2-O-31, AM2-O-32, AM2-O-32, AM2-O-33, AM2-O-33, AM2-O-34, AM2-O-34, AM2-O-35, AM2-O-35, AM2-O-36, AM2-O-36, AM2-O-37, AM2-O-37, AM2-O-38, AM2-O-38, AM2-O-39, AM2-O-39, AM2-O-40, AM2-O-40, AM2-O-41, AM2-O-41, AM2-O-42, AM2-O-42, AM2-O-43, AM2-O-43, AM2-O-44, AM2-O-44, AM2-O-45, AM2-O-45, AM2-O-46, and AM2-O-46.

Examples of such CDR combinations include, without limitation, for CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, SEQ ID NO:45, 46, 332, 74, 95, and 117 (AM2-1), SEQ ID NO:45, 46, 47, 74, 340, and 117 (AM2-2), SEQ ID NO:45, 46, 47, 74, 341, and 117 (AM2-3), SEQ ID NO:45, 46, 47, 74, 342, and 117 (AM2-4), SEQ ID NO:45, 46, 47, 74, 343, and 117 (AM2-5), SEQ ID NO:45, 46, 47, 74, 344, and 117 (AM2-6), SEQ ID NO:45, 46, 333, 74, 345, and 117 (AM2-7), SEQ ID NO:45, 46, 47, 74, 346, and 117 (AM2-8), SEQ ID NO:45, 46, 334, 74, 95, and 117 (AM2-9), SEQ ID NO:45, 46, 47, 74, 347, and 117 (AM2-10), SEQ ID NO:45, 46, 47, 74, 347, and 117 (AM2-11), SEQ ID NO:45, 46, 333, 74, 95, and 117 (AM2-13), SEQ ID NO:45, 46, 335, 74, 95, and 117 (AM2-14), SEQ ID NO:45, 46, 47, 74, 348, and 117 (AM2-15), SEQ ID NO:45, 322, 47, 74, 95, and 117 (AM2-16), SEQ ID NO:45, 46, 47, 74, 349, and 117 (AM2-17), SEQ ID NO:45, 46, 47, 74, 350, and 117 (AM2-18), SEQ ID NO:45, 323, 47, 74, 95, and 117 (AM2-21), SEQ ID NO:45, 324, 47, 74, 95, and 117 (AM2-24), SEQ ID NO:45, 46, 47, 74, 95, and 117 (AM2-25), SEQ ID NO:45, 325, 47, 74, 95, and 117 (AM2-26), SEQ ID NO:45, 326, 47, 74, 95, and 117 (AM2-28), SEQ ID NO:45, 322, 47, 74, 95, and 117 (AM2-29), SEQ ID NO:45, 46, 47, 74, 95, and 117 (AM2-30), SEQ ID NO:45, 325, 47, 74, 95, and 117 (AM2-31), SEQ ID NO:45, 327, 47, 74, 95, and 117 (AM2-32), SEQ ID NO:45, 46, 47, 74, 351, and 117 (AM2-33), SEQ ID NO:45, 46, 336, 74, 95, and 117 (AM2-35), SEQ ID NO:45, 46, 47, 74, 352, and 117 (AM2-36), SEQ ID NO:45, 46, 336, 74, 352, and 117 (AM2-37), SEQ ID NO:45, 328, 47, 74, 95, and 117 (AM2-S-G), SEQ ID NO:45, 329, 47, 74, 95, and 117 (AM2-S-T), SEQ ID NO:45, 330, 47, 74, 95, and 117 (AM2-S-H), SEQ ID NO:45, 331, 47, 74, 95, and 117 (AM2-S-Y), SEQ ID NO:45, 46, 47, 337, 350, and 117 (AM2-O-01), SEQ ID NO:45, 46, 47, 338, 350, and 117 (AM2-O-02), SEQ ID NO:45, 46, 47, 339, 350, and 117 (AM2-O-03), SEQ ID NO:45, 46, 47, 337, 343, and 117 (AM2-O-04), SEQ ID NO:45, 46, 47, 338, 343, and 117 (AM2-O-05),

SEQ ID NO:45, 46, 47, 339, 343, and 117 (AM2-O-06), SEQ ID NO:45, 328, 47, 74, 350, and 117 (AM2-O-07), SEQ ID NO:45, 328, 47, 337, 350, and 117 (AM2-O-08), SEQ ID NO:45, 328, 47, 338, 350, and 117 (AM2-O-09), SEQ ID NO:45, 328, 47, 339, 350, and 117 (AM2-O-10), SEQ ID NO:45, 328, 47, 74, 343, and 117 (AM2-O-11), SEQ ID NO:45, 328, 47, 337, 343, and 117 (AM2-O-12), SEQ ID NO:45, 328, 47, 338, 343, and 117 (AM2-O-13), SEQ ID NO:45, 328, 47, 339, 343, and 117 (AM2-O-14), SEQ ID NO:45, 46, 333, 74, 350, and 117 (AM2-O-15), SEQ ID NO:45, 46, 333, 337, 350, and 117 (AM2-O-16), SEQ ID NO:45, 46, 333, 338, 350, and 117 (AM2-O-17), SEQ ID NO:45, 46, 333, 339, 350, and 117 (AM2-O-18), SEQ ID NO:45, 46, 333, 74, 343, and 117 (AM2-O-19), SEQ ID NO:45, 46, 333, 337, 343, and 117 (AM2-O-20), SEQ ID NO:45, 46, 333, 338, 343, and 117 (AM2-O-21), SEQ ID NO:45, 46, 333, 339, 343, and 117 (AM2-O-22), SEQ ID NO:45, 328, 333, 74, 350, and 117 (AM2-O-23), SEQ ID NO:45, 328, 333, 337, 350, and 117 (AM2-O-24), SEQ ID NO:45, 328, 333, 338, 350, and 117 (AM2-O-25), SEQ ID NO:45, 328, 333, 339, 350, and 117 (AM2-O-26), SEQ ID NO:45, 328, 333, 74, 343, and 117 (AM2-O-27), SEQ ID NO:45, 328, 333, 337, 343, and 117 (AM2-O-28), SEQ ID NO:45, 328, 333, 338, 343, and 117 (AM2-O-29), SEQ ID NO:45, 328, 333, 339, 343, and 117 (AM2-O-30), SEQ ID NO:45, 46, 335, 74, 350, and 117 (AM2-O-31), SEQ ID NO:45, 46, 335, 337, 350, and 117 (AM2-O-32), SEQ ID NO:45, 46, 335, 338, 350, and 117 (AM2-O-33), SEQ ID NO:45, 46, 335, 339, 350, and 117 (AM2-O-34), SEQ ID NO:45, 46, 335, 74, 343, and 117 (AM2-O-35), SEQ ID NO:45, 46, 335, 337, 343, and 117 (AM2-O-36), SEQ ID NO:45, 46, 335, 338, 343, and 117 (AM2-O-37), SEQ ID NO:45, 46, 335, 339, 343, and 117 (AM2-O-38), SEQ ID NO:45, 328, 335, 74, 350, and 117 (AM2-O-39), SEQ ID NO:45, 328, 335, 337, 350, and 117 (AM2-O-40), SEQ ID NO:45, 328, 335, 338, 350, and 117 (AM2-O-41), SEQ ID NO:45, 328, 335, 339, 350, and 117 (AM2-O-42), SEQ ID NO:45, 328, 335, 74, 343, and 117 (AM2-O-43), SEQ ID NO:45, 328, 335, 337, 343, and 117 (AM2-O-44), SEQ ID NO:45, 328, 335, 338, 343, and 117 (AM2-O-45), and SEQ ID NO:45, 328, 335, 339, 343, and 117 (AM2-O-46).

Non-limiting examples of such antibodies or fragments include those having the heavy chain variable region and light chain variable region of each of the variants in **Table 8**, as well as those having about at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% sequence identity to each of the heavy chain variable region and light chain variable region of each of the variants in **Table 8**, while retaining the respective CDR sequences (see, e.g., **Table 9**).

The present disclosure likewise provides antibodies and fragments thereof that specifically bind to a human interleukin-18 receptor alpha (IL-18Rα) protein. In some embodiments, the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-12 of **Table C**. The antibody or fragment disclosure herein can also include a CDRL1 and a CDRL2. A good variety of CDRL1 and CDRL2 sequences can be employed here. Non-limiting examples include QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively, as well as their biological equivalents as illustrated in **Table C1**.

Table C. CDR sequences for anti-IL-18Rα antibodies

Comb #	Fab ID	CDRL1 (SEQ ID NO:)		CDRL2 (SEQ ID NO:)		CDRL3 (SEQ ID NO:)		CDRH1 (SEQ ID NO:)		CDRH2 (SEQ ID NO:)		CDRH3 (SEQ ID NO:)	
1	F1	QSVSSA	45	SAS	46	QQYYSPFT	137	GFNIYYSSM	83	SISSYYGSTY	150	ARGAFDY	156
2	F2	QSVSSA	45	SAS	46	QQYASPFT	138	GFNIYYSSI	145	SISSSYSSTS	151	ARGAFDY	156
3	F3	QSVSSA	45	SAS	46	QQYASPFT	138	GFNIYYSSM	83	SISSSYGSTY	152	ARGAMDY	157
4	F4	QSVSSA	45	SAS	46	QQYYVPFT	139	GFNISSSSM	146	SISSSYGSTY	152	ARGAMDY	157
5	F6	QSVSSA	45	SAS	46	QQYYHPFT	140	GFNLSSSSI	147	SISSYYGSTY	150	ARGAMDY	157
6	F7	QSVSSA	45	SAS	46	QQYASPFT	138	GFNIYYSSI	145	SISSSYSSTS	151	ARGAFDY	156
7	F8	QSVSSA	45	SAS	46	QQYYHPFT	140	GFNISSSSM	146	SISSYYGSTY	150	ARGAMDY	157
8	F9	QSVSSA	45	SAS	46	QQYASPFT	138	GFNLSSSSI	147	SISSYYGSTY	150	ARGAMDY	157
9	F10	QSVSSA	45	SAS	46	QQYFHPFT	141	GFNLSYSSM	84	SISSSYSSTY	153	ARGALDY	158
10	F11	QSVSSA	45	SAS	46	QQGFFHPIT	142	GFNIYYSSM	83	SIYSYYGSTS	154	ARYYHGYWGSYSAGSSAWGFDY	159
11	F12	QSVSSA	45	SAS	46	QQYWHPFT	143	GFNISSSSI	148	SISSSYSSTY	153	ARGAFDY	156
12	F13	QSVSSA	45	SAS	46	QQAGYSIT	144	GFNFSSSSI	149	YISSYYGSTS	155	ARSVVYGYWYGGWVGFDY	160

It can be readily appreciated that certain modification (e.g., one, two, or three amino acid additions, deletions, conservative amino acid substitutions) to one or more of the CDR sequences can be made while retaining the binding activity of the antibody or fragment. In some embodiments, the modifications are amino acid substitution of one, two, or three residues.

In some embodiments, the modification is substitution at no more than one hot spot position from each of the CDRs. In some embodiments, the modification is substitution at one, two or three such hot spot positions. In one embodiment, the modification is substitution at one of the hot spot positions. Such substitutions, in some embodiments, are conservative substitutions.

Specific examples of CDRs (from CDR Combination #11 in Table C) with suitable substitutions are provided in the table below.

Table C1. Substitutions of CDR Residues

CDR	No.*	Residue	Can be substituted with
CDRL1	27	Q	N, D, E, S, T, Y, W, H, K, R
	28	S	N, D, E, Q, T, Y, W, H, K, R
	29	V	A, I, L, M, P, F
	36	S	N, D, E, Q, T, Y, W, H, K, R
	37	S	N, D, E, Q, T, Y, W, H, K, R
	38	A	V, I, L, M, P, F
CDRL2	56	S	N, D, E, Q, T, Y, W, H, K, R
	57	A	V, I, L, M, P, F
	65	S	N, D, E, Q, T, Y, W, H, K, R
CDRL3	105	Q	N, D, E, S, T, Y, W, H, K, R
	106	Q	N, D, E, S, T, Y, W, H, K, R
	107	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	108	W	A, I, L, M, P, V, F
	114	H	N, D, E, S, T, Y, W, Q, K, R
	115	P	V, I, A, M, L, F
	116	F	A, I, L, M, P, V
	117	T	N, D, E, Q, S, Y, W, H, K, R
CDRH1	27	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	28	F	A, I, L, M, P, V
	29	N	Q, D, E, S, T, Y, W, H, K, R
	30	I	V, L, A, M, P, F
	35	S	N, D, E, Q, T, Y, W, H, K, R
	36	S	N, D, E, Q, T, Y, W, H, K, R
	37	S	N, D, E, Q, T, Y, W, H, K, R
	38	S	N, D, E, Q, T, Y, W, H, K, R
	39	I	V, L, A, M, P, F
CDRH2	55	S	N, D, E, Q, T, Y, W, H, K, R
	56	I	V, L, A, M, P, F

	57	S	N, D, E, Q, T, Y, W, H, K, R
	58	S	N, D, E, Q, T, Y, W, H, K, R
	59	S	N, D, E, Q, T, Y, W, H, K, R
	62	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
	63	S	N, D, E, Q, T, Y, W, H, K, R
	64	S	N, D, E, Q, T, Y, W, H, K, R
	65	T	N, D, E, Q, S, Y, W, H, K, R
	66	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A
CDRH3	105	A	V, I, L, M, P, F
	106	R	N, D, E, Q, T, Y, W, H, K, S
	107	G	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A, Y
	114	A	V, I, L, M, P, F
	115	F	A, I, L, M, P, V
	116	D	N, Q, E, S, T, Y, W, H, K, R
	117	Y	N, D, E, S, T, Q, W, H, K, R, V, I, L, M, P, F, A

* IMGT numbering system

Specific example antibodies include those that have a heavy chain sequence of SEQ ID NO:42, and/or a light chain sequence of SEQ ID NO:44, and their respective biological variants.

It will also be understood by one of ordinary skill in the art that antibodies as disclosed herein may be modified such that they vary in amino acid sequence from the naturally occurring binding polypeptide from which they were derived. For example, a polypeptide or amino acid sequence derived from a designated protein may be similar, *e.g.*, have a certain percent identity to the starting sequence, *e.g.*, it may be 60%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the starting sequence.

In certain embodiments, the antibody comprises an amino acid sequence or one or more moieties not normally associated with an antibody. Exemplary modifications are described in more detail below. For example, an antibody of the disclosure may comprise a flexible linker sequence or may be modified to add a functional moiety (*e.g.*, PEG, a drug, a toxin, or a label).

Antibodies, variants, or derivatives thereof of the disclosure include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to the epitope. For example, but not by way of limitation, the antibodies can be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known

techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the antibodies may contain one or more non-classical amino acids.

In some embodiments, the antibodies may be conjugated to therapeutic agents, prodrugs, peptides, proteins, enzymes, viruses, lipids, biological response modifiers, pharmaceutical agents, or PEG.

The antibodies may be conjugated or fused to a therapeutic agent, which may include detectable labels such as radioactive labels, an immunomodulator, a hormone, an enzyme, an oligonucleotide, a photoactive therapeutic or diagnostic agent, a cytotoxic agent, which may be a drug or a toxin, an ultrasound enhancing agent, a non-radioactive label, a combination thereof and other such agents known in the art.

The antibodies can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antigen-binding polypeptide is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

The antibodies can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA). Techniques for conjugating various moieties to an antibody are well known, *see, e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. (1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.*, (eds.), Marcel Dekker, Inc., pp. 623- 53 (1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), Academic Press pp. 303-16 (1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* (52:119-58 (1982)).

Bi-functional Molecules

IL-18 is a pro-inflammatory, IFN-γ-inducing cytokine. As a member of the IL-1 family of cytokines, it is thought to play a role in early inflammatory responses and is synthesized by a range of both hematopoietic and non-hematopoietic cells (e.g., macrophages, dendritic cells, Kuppfer cells, keratinocytes, osteoblasts, astrocytes, adrenal cortex cells, intestinal epithelial cells, microglial cells, and synovial fibroblasts) both constitutively and in response to lipopolysaccharide and other cytokines such as TNF-α. It is contemplated that bi-functional molecules that combine an anti-IL-18R alpha or beta antibody or fragment with another molecule or fragment that has specificity (second specificity) to a cytokine, an immune checkpoint, or a cancer antigen would have synergistic effect in treatments.

In some embodiments, the second specificity is to a molecule selected from IL-1, CD3, CD16, CD19, CD28, and CD64. Other examples include PD-1, CTLA-4, LAG-3 (also known as CD223), CD28, CD122, 4-1BB (also known as CD137), TIM3, OX-40 or OX40L, CD40 or CD40L, LIGHT, ICOS/ICOSL, GITR/GITRL, TIGIT, CD27, VISTA, B7H3, B7H4, HEVM or BTLA (also known as CD272), killer-cell immunoglobulin-like receptors (KIRs), and CD47.

As an immune checkpoint inhibitor, an antibody or antigen-binding fragment specific to IL-18 receptor can be combined with a second antigen-binding fragment specific to a tumor antigen to generate a bispecific antibody. A "tumor antigen" is an antigenic substance produced in tumor cells, *i.e.*, it triggers an immune response in the host. Tumor antigens are useful in identifying tumor cells and are potential candidates for use in cancer therapy. Normal proteins in the body are not antigenic. Certain proteins, however, are produced or overexpressed during tumorigenesis and thus appear "foreign" to the body. This may include normal proteins that are well sequestered from the immune system, proteins that are normally produced in extremely small quantities, proteins that are normally produced only in certain stages of development, or proteins whose structure is modified due to mutation.

An abundance of tumor antigens are known in the art and new tumor antigens can be readily identified by screening. Non-limiting examples of tumor antigens include EGFR, Her2, EpCAM, CD20, CD30, CD33, CD47, CD52, CD133, CD73, CEA, gpA33, Mucins, TAG-72, CIX, PSMA, folate-binding protein, GD2, GD3, GM2, VEGF, VEGFR, Integrin, αVβ3,

α5β1, ERBB2, ERBB3, MET, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP and Tenascin.

Different formats of bispecific antibodies are also provided. In some embodiments, each of the anti-IL-18 receptor fragment and the second fragment each is independently selected from a Fab fragment, a single-chain variable fragment (scFv), or a single-domain antibody. In some embodiments, the bispecific antibody further includes a Fc fragment.

Bifunctional molecules that include not just antibody or antigen binding fragment are also provided. As a tumor antigen-targeting molecule, an antibody or antigen-binding fragment specific to IL-18R alpha or beta, such as those described here, can be combined with an immune cytokine or ligand optionally through a peptide linker. The linked immune cytokines or ligands include, but not limited to, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, GM-CSF, TNF-α, CD40L, OX40L, CD27L, CD30L, 4-1BBL, LIGHT and GITRL. Such bi-functional molecules can combine the immune checkpoint blocking effect with tumor site local immune modulation.

Polynucleotides Encoding the Antibodies and Methods of Preparing the Antibodies

The present disclosure also provides isolated polynucleotides or nucleic acid molecules (e.g., SEQ ID NO:41 and 43) encoding the antibodies, variants or derivatives thereof of the disclosure. The polynucleotides of the present disclosure may encode the entire heavy and light chain variable regions of the antigen-binding polypeptides, variants or derivatives thereof on the same polynucleotide molecule or on separate polynucleotide molecules. Additionally, the polynucleotides of the present disclosure may encode portions of the heavy and light chain variable regions of the antigen-binding polypeptides, variants or derivatives thereof on the same polynucleotide molecule or on separate polynucleotide molecules.

Methods of making antibodies are well known in the art and described herein. In certain embodiments, both the variable and constant regions of the antigen-binding polypeptides of the present disclosure are fully human. Fully human antibodies can be made using techniques described in the art and as described herein. For example, fully human antibodies against a specific antigen can be prepared by administering the antigen to a transgenic animal which has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled. Exemplary techniques that can be used to make

such antibodies are described in U.S. patents: 6,150,584; 6,458,592; 6,420,140 which are incorporated by reference in their entireties.

Autoimmune and Inflammatory Diseases

As provided, IL-18 has been shown to be upregulated or to be a risk factor for the development of various autoimmune and inflammatory diseases, such as Crohn's disease, rheumatoid arthritis, systemic lupus erythrites, and cardiovascular disease.

Further, increased IL-18 levels have been observed in individuals at risk of developing either Type I (T1D) or Type 2 diabetes (T2D). Elevated IL-18 has also been observed in the serum, urine and islets of juvenile and adult T1D and T2D patients, correlating with the severity of disease, and the development of sequelae such as diabetic nephropathy. Moreover, studies on Alzheimer's patients have revealed expression of IL-18 is increased in the brain and is thought to contribute to immune and inflammatory processes that enhance oxidative stress and alter the expression of proteins that contribute to Aβ formation.

In one embodiment, therefore, provided are methods of using the antibodies and fragments thereof for treating autoimmune and inflammatory diseases. Non-limiting examples include Parkinson's disease, arthritis, rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, lupus, systemic lupus erythematous, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, Grave's disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, dermatomyositis, multiple sclerosis, myasthenia gravis, pernicious anemia, Sjogren syndrome, type I diabetes, type II diabetes, vasculitis, uveitis, sepsis, atherosclerosis and ankylosing spondylitis.

Cancer Treatment

As described above, high IL-18 levels have been observed in numerous cancers either at the tumor site or systemically. Such cancers include breast, esophageal, gastrointestinal, lung, hepatic, and ovarian cancers. It is believed that administration of the presently described antibodies can be useful for treating or inhibit cancer, and studies in pre-clinical models of cancer suggest that anti-tumor activity of IL-18 arises from its ability to potentiate effector cells such as T cells and NK cells.

Accordingly, in some embodiments, provided are methods for treating a cancer in a patient in need thereof. The method, in one embodiment, entails administering to the patient an effective amount of an antibody of the present disclosure. In some embodiments, at least one of the cancer cells (e.g., stromal cells) in the patient expresses, over-express, or is induced to express IL-18 or one of its receptors.

Cancers that can be suitably treated include bladder cancer, non-small cell lung cancer, renal cancer, breast cancer, urethral cancer, colorectal cancer, head and neck cancer, squamous cell cancer, Merkel cell carcinoma, gastrointestinal cancer, stomach cancer, oesophageal cancer, ovarian cancer, renal cancer, and small cell lung cancer. Accordingly, the presently disclosed antibodies can be used for treating any one or more such cancers. In some embodiments, the cancer is selected from breast, esophageal, gastrointestinal, lung, hepatic, and ovarian cancers.

Cellular therapies, such as chimeric antigen receptor (CAR) T-cell therapies, are also provided in the present disclosure. A suitable cell can be used, that is put in contact with an anti-IL-18R alpha or beta antibody of the present disclosure. Upon such contact or engineering, the cell can then be introduced to a cancer patient in need of a treatment. The cancer patient may have a cancer of any of the types as disclosed herein. The cell (e.g., T cell) can be, for instance, a tumor-infiltrating T lymphocyte, a CD4+ T cell, a CD8+ T cell, or the combination thereof, without limitation.

In some embodiments, the cell was isolated from the cancer patient him- or her-self. In some embodiments, the cell was provided by a donor or from a cell bank. When the cell is isolated from the cancer patient, undesired immune reactions can be minimized.

Additional diseases or conditions associated with increased cell survival, that may be treated, prevented, diagnosed and/or prognosed with the antibodies or variants, or derivatives thereof of the disclosure include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (*e.g.*, acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (*e.g.*, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (*e.g.*, Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma,

chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyo sarcoma, colon carcinoma, pancreatic cancer, breast cancer, thyroid cancer, endometrial cancer, melanoma, prostate cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma and retinoblastoma.

Combination Therapies

In a further embodiment, the compositions of the disclosure are administered in combination with an antineoplastic agent, an antiviral agent, antibacterial or antibiotic agent or antifungal agents. Any of these agents known in the art may be administered in the compositions of the current disclosure. Such combinations can be useful for treating various cancers.

In another embodiment, compositions of the disclosure are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the compositions of the disclosure include, but are not limited to, antibiotic derivatives (*e.g.*, doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (*e.g.*, tamoxifen); antimetabolites (*e.g.*, fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (*e.g.*, carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (*e.g.*, medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (*e.g.*, mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (*e.g.*, bethamethasone sodium phosphate); and others (*e.g.*, dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In an additional embodiment, the compositions of the disclosure are administered in combination with cytokines. Cytokines that may be administered with the compositions of the disclosure include, but are not limited to, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, anti-CD40, CD40L, and TNF-α.

In additional embodiments, the compositions of the disclosure are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Diagnostic Methods

Over-expression of IL-18 or its receptors is observed in certain tumor samples, and such patients are likely responsive to treatments with the anti-IL-18 receptor antibodies of the present disclosure. Accordingly, the antibodies of the present disclosure can also be used for diagnostic and prognostic purposes.

A sample that preferably includes a cell can be obtained from a patient, which can be a cancer patient or a patient desiring diagnosis. The cell be a cell of a tumor tissue or a tumor block, a blood sample, a urine sample or any sample from the patient. Upon optional pre-treatment of the sample, the sample can be incubated with an antibody of the present disclosure under conditions allowing the antibody to interact with an IL-18 receptor protein potentially present in the sample. Methods such as ELISA can be used, taking advantage of the anti-IL-18 receptor antibody, to detect the presence of the IL-18 receptor protein in the sample.

Presence of the IL-18 receptor protein in the sample (optionally with the amount or concentration) can be used for diagnosis of cancer, as an indication that the patient is suitable for a treatment with the antibody, or as an indication that the patient has (or has not) responded to a cancer treatment. For a prognostic method, the detection can be done at once, twice or more, at certain stages, upon initiation of a cancer treatment to indicate the progress of the treatment.

Compositions

The present disclosure also provides pharmaceutical compositions. Such compositions comprise an effective amount of an antibody, and an acceptable carrier. In some

embodiments, the composition further includes a second anticancer agent (e.g., an immune checkpoint inhibitor).

In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. Further, a "pharmaceutically acceptable carrier" will generally be a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents such as acetates, citrates or phosphates. Antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; and agents for the adjustment of tonicity such as sodium chloride or dextrose are also envisioned. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences by E. W. Martin, incorporated herein by reference. Such compositions will contain a therapeutically effective amount of the antigen-binding polypeptide, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. The parental preparation

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

In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the disclosure can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

EXAMPLES

Example 1: Selection, characterization and optimization of Il-18R alpha and beta antibodies

By panning against purified, Fc-tagged versions of either the human IL-18Rα or Rβ receptors (R&D) *in vitro*, this example isolated high affinity antibody binders to each receptor. Specifically, receptor-binding Fab-phage clones to each were sequenced, converted to IgG and evaluated for apparent affinity, cell binding and ability to inhibit functional IL-18 signaling.

Selections against the human IL-18Rα ECD Fc fusion (816-LR-100; R&D Systems) yielded 12 unique receptor-binding Fab sequences (**Table 1**), whereas selections against the IL-18Rβ

ECD Fc fusion (118-AP-100, R&D Systems) yielded 21 unique sequences (**Table 2**). The CDR-encoding regions of Fab-phage clones were sub-cloned into expression constructs for expression and purification of Fab protein.

Table 1. CDRs in IL-18Rα-binding Fab sequences

Fab ID	CDRL3	CDRH1	CDRH2	CDRH3
F1	QQYY----SPFT	GFNIYYSSSM	SISSYYGSTY	ARG----------A FDY
F2	QQYA----SPFT	GFNIYYSSSI	SISPSYSSTS	ARG----------A FDY
F3	QQYA----SPFT	GFNIYYSSSM	SISPSYGSTY	ARG----------A MDY
F4	QQYY----VPFT	GFNISSSSSM	SISPSYGSTY	ARG----------A MDY
F6	QQYY----HPFT	GFNLSSSSSI	SISPYYGSTY	ARG----------A MDY
F7	QQYA----SPFT	GFNIYYSSSI	SISPSYSSTS	ARG----------A FDY
F8	QQYY----HPFT	GFNISSSSSM	SISPYYGSTY	ARG----------A MDY
F9	QQYA----SPFT	GFNLSSSSSI	SISPYYGSTY	ARG----------A MDY
F10	QQYF----HPFT	GFNLSYSSSM	SISPSYSSTY	ARG----------G LDY
F11	QQGFF---HPIT	GFNIYYSSSM	SIYSYYGSTS	ARYYHGYWGSYSAGSSAWGFDY
F12	QQYW----HPFT	GFNISSSSSI	SISPSYSSTY	ARG----------A FDY
F13	QQAG----YSIT	GFNFSSSSSI	YISSYYGSTS	ARSVVYGYW----YGGWVGFDY

Table 2. CDRs in IL-18Rβ-binding Fab sequences

Fab ID	CDRL3	CDRH1	CDRH2	CDRH3
F3131	QQYGYHYAGLIT	GFNLYYSSSM	SIYSSYGYTY	ARSSFSHG--YGWYGLDY
F3132	QQHWWASVPPFT	GFNISYYYSI	SIYSYSGYTS	ARAS----------AMDY
F3133	QQHYW---GYLIT	GFNLSYYYSI	SIYSSYGYTS	ARSY----------GLDY
F3134	QQHHW---SYPIT	GFNISYSYSI	SIYPSYGYTS	ARSF----------GLDY
F3135	QQHHH-WAVLIT	GFNFYSYSSM	YIYPYSGYTS	ARSF----------AMDY
F3136	QQHYW---GGPIT	GFNISSYSSM	SIYSYYSYTS	ARSY----------AMDY
F3137	QQSWG-WSWLIT	GFNLSSYSSI	YIYPSYGSTY	ARSY----------ALDY
F3138	QQHSF-HSGLIT	GFNLYSYSSM	YIYSYSGYTS	ARGF----------ALDY
F3139	QQSHGWWGFPFT	GFNISSYSSI	SIYPYYGYTY	ARSW----------AMDY
F3140	QQYYW-ASYPFT	GFNFYSYSSM	SIYPSYGYTS	ARSF----------GFDY
F3141	QQYYY-SAALIT	GFNIYYSSSM	YIYPYSGYTS	ARYF----------AMDY
F3142	QQWWGGPYVLIT	GFNLSYSSSM	SIYPSSSSTY	ARSSHSHG--YYFYGIDY
F3143	QQYHWGSYYPFT	GFNLSSYYYM	SIYPYYGYTY	ARSS----------AMDY
F3144	QQHWW-GYPLIT	GFNLSYYYSI	SIYSYSGYTS	ARSS----------AMDY
F3145	QQHYYGSFPPIT	GFNFYSYSSM	SIYSYYGYTS	ARSF----------GMDY
F3147	QQHWW---AALIT	GFNLSSYSSI	YIYSSYGYTS	ARSF----------GMDY
F3148	QQHYY---SSLIT	GFNIYSYSSM	SIYPYYSSTY	ARSS----------AMDY
F3150	QQHSW---AVPIT	GFNLSSYSSM	SIYPYYGYTS	ARSS----------AFDY
F3152	QQHSY-SAPLIT	GFNIYSYSSM	SIYPSYSYTS	ARSY----------AMDY
FA3	QQSY----FLIT	GFNLYSSSYI	SIYSSSGYTY	ARSVHSYYSSAAYYAMDY
FE60	QQYPSASHYLIT	GFNLYYYYYM	SIYSYYGYTS	ARSYPSS--SWGSVALDY
3131 AM1-1	QQYAYHEPGLLT	GFNPYYSSSI	SISPSYSSTY	ARSSCSHS--CRFYGLDY
3131-AM1-2	QQWGYRYAPLVT	GFNFYYSSSI	SISSATGNTS	ARSSYSHG--HSWYGLDY
3144-AM1-3	QQHSWA-YPMIT	GFNLTWWSSI	TIFSGFSYTS	ARSS----------AMDY
3144-AM1-4	QQHWFG-YPAVT	GFNISQYTSI	SIYARSRFTS	ARSS----------RMDY
3144-AM1-5	QQHWWG-YPMIT	GFNISYYTSI	SIYSYSLYTS	ARSS----------AMDY
3144-AM1-6	QQHSWR-YPLIT	GFNLSSYSSI	AIYAGFGSTT	ARSS----------AMDY

The amino acid and nucleotide sequences of representative Fab fragments are provided in **Tables 3 and 4** below.

Table 3. IL-18Rα-binding Fab sequences

Name (SEQ ID NO:)	Sequence
Fab 12 Heavy chain nucleotide sequence (SEQ ID NO:41)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACATCTCTTCTTCTTCTATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTCTCCTTCTTATAGCTCTACTTATTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCGGTGCT TTTGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAGGGTCCA TCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGC TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGC AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACT CACACATAA
Fab 12 Heavy chain amino acid sequence (SEQ ID NO:42)	EVQLVESGGGLVQPGGSLRLSCAASGFNISSSSIHWVRQAPGKGLEWVASISPSYSSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGAFDYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab 12 Light chain nucleotide sequence (SEQ ID NO:43)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAATACTGGCATCCGTTCACGTTCGGACAGGGT ACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT GATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAG AGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG AGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGATTACAAAGAT GACGATGACAAATAA
Fab 12 Light chain amino acid sequence (SEQ ID NO:44)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSR FSGSRSGTDFTLTISSLQPEDFATYYCQQYWHPFTFGQGTKVEIKRTVAAPSVFIFPPSDS QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK

Table 4. IL-18Rβ-binding Fab sequences

Name (SEQ ID NO:)	Sequence
Fab 3131 Heavy chain nucleotide sequence (SEQ ID NO:1)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCTCTATTATTCTTCTATGCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTATTCTTCTTATGGCTATACTTATTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCTTCT TTCTCTCATGGTTACGGTTGGTACGGTTTGGACTACTGGGGTCAAGGAACCCTGGTCACC GTCTCCTCGGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAA GTTGAGCCCAAATCTTGTGACAAAACTCACACATAA
Fab 3131 Heavy chain amino acid sequence (SEQ ID NO:2)	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVASIYSSYGYTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSFSHGYGWYGLDYWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab 3131 Light chain	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA

nucleotide sequence (SEQ ID NO:3)	GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAATACGGTTACCATTACGCTGGTCTGATCACG TTCGGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAAT AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGT AACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACC CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCT GATTACAAAGATGACGATGACAAATAA
Fab 3131 Light chain amino acid sequence (SEQ ID NO:4)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGLITFGQGTKVEIKRTVAAPSVFI FPPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab 3132 Heavy chain nucleotide sequence (SEQ ID NO:5)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACATCTCTTATTATTATATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTATTCTTATTCTGGCTATACTTCTTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCGCTTCT GCTATGGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAGGGT CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA ACTCACACATAA
Fab 3132 Heavy chain amino acid sequence (SEQ ID NO:6)	EVQLVESGGGLVQPGGSLRLSCAASGFNISYYYIHWVRQAPGKGLEWVASIYSYSGYTSY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARASAMDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab 3132 Light chain nucleotide sequence (SEQ ID NO:7)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTGGTGGGCTTCTGTTCCGCCGTTCACG TTCGGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAAT AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGT AACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACC CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCT GATTACAAAGATGACGATGACAAATAA
Fab 3132 Light chain amino acid sequence (SEQ ID NO:8)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHWWASVPPFTFGQGTKVEIKRTVAAPSVFI FPPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab 3144 Heavy chain nucleotide sequence (SEQ ID NO:9)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCTCTCTTATTATTCTATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTATTCTTATTCTGGCTATACTTCTTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCTTCT GCTATGGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAGGGT CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA ACTCACACATAA
Fab 3144 Heavy chain amino acid sequence	EVQLVESGGGLVQPGGSLRLSCAASGFNLSYYSIHWVRQAPGKGLEWVASIYSYSGYTSY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSAMDYWGQGTLVTVSSASTKG

(SEQ ID NO:10)	PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab 3144 Light chain nucleotide sequence (SEQ ID NO:11)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTGGTGGGGTTACCCGCTGATCACGTTC GGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAAC TTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC CTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGAT TACAAAGATGACGATGACAAATAA
Fab 3144 Light chain amino acid sequence (SEQ ID NO:12)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHWWGYPLITFGQGTKVEIKRTVAAPSVFIF PPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab A3 Heavy chain nucleotide sequence (SEQ ID NO:13)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCTCTATTCTTCTTATATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTATTCTTCTTCTGGCTATACTTATTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCTGTT CATTCTTACTACTCTTCTGCTGCTTACTACGCTATGGACTACTGGGGTCAAGGAACCCTG GTCACCGTCTCCTCGGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCC AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTCGAC AAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATAA
Fab A3 Heavy chain amino acid sequence (SEQ ID NO:14)	EVQLVESGGGLVQPGGSLRLSCAASGFNLYSSYIHWVRQAPGKGLEWVASIYSSSGYTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSVHSYYSSAAYYAMDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab A3 Light chain nucleotide sequence (SEQ ID NO:15)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAATCTTACTTCCTGATCACGTTCGGACAGGGT ACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT GATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAG AGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG AGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGATTACAAAGAT GACGATGACAAATAA
Fab A3 Light chain amino acid sequence (SEQ ID NO:16)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQSYFLITFGQGTRVEIKRTVAAPSVFIFPPS DSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-1 Heavy chain nucleotide sequence (SEQ ID NO: 17)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCCCTATTATTCTTCCATTCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTATTTCTCCTTCTTATAGCTCTACTTATTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCTTCT TGCTCTCATAGTTGCCGTTTTTTACGGTTTGGACTACTGGGGTCAAGGAACCCTGGTCACC GTCTCCTCGGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC

	ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAA GTTGAGCCCAAATCTTGTGACAAAACTCACACATAA
Fab AM1-1 Heavy chain amino acid sequence (SEQ ID NO:18)	EVQLVESGGGLVQPGGSLRLSCAASGFNPYYSSIHWVRQAPGKGLEWVASISPSYSSTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSCSHSCRFYGLDYWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-1 Light chain nucleotide sequence (SEQ ID NO:19)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAATACGCTTACCATGAGCCCGGTTTGCTCTCT TCTTATTCTCTGATCACGTTCGGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCT GCACCATCTGTCTTCATCTTCCCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCT GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTC TACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGG GGAGAGTGTGGTGGTTCTGATTACAAAGATGACGATGACAAATAA
Fab AM1-1 Light chain amino acid sequence (SEQ ID NO:20)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQYAYHEPGLLTFGQGTKVEIKRTVAAPSVFI FPPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-2 Heavy chain nucleotide sequence (SEQ ID NO:21)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACTTCTATTATTCTTCGATTCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTTCGATTTCTTCGGCTACTGGAAATACTTCT TATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCC TACCTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCT TCTTACTCTCATGGTCATAGTTGGTACGGTTTGGACTACTGGGGTCAAGGAACCCTGGTC ACCGTCTCCTCGGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTCGACAAG AAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATAA
Fab AM1-2 Heavy chain amino acid sequence (SEQ ID NO:22)	EVQLVESGGGLVQPGGSLRLSCAASGFNFYYSSIHWVRQAPGKGLEWVASSISSATGNTS YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSYSHGHSWYGLDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-2 Light chain nucleotide sequence (SEQ ID NO:23)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCCGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAATGGGGTTACCGGTACGCACCCCTGGTCACG TTCGGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAAT AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGT AACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACC CATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCT GATTACAAAGATGACGATGACAAATAA
Fab AM1-2 Light chain amino acid sequence (SEQ ID NO:24)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQWGYRYAPLVTFGQGTKVEIKRTVAAPSVFI FPPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-3 Heavy chain nucleotide sequence (SEQ ID	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCTCACTTGGTGGTCTATCCTCCACTTGGGTGGTCTA TCCACTGGGTGCGTCAGGCCCCGGGTAAGGGCCTGGAATGGGTTGCATCTACTATTTTTT CTGGTTTTTCCTATACTTCTTATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAG

NO:25)	ACACATCCAAAAACACAGCCTACCTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCG TCTATTATTGTGCTCGCTCTTCTGCTATGGACTACTGGGGTCAAGGAACCCTGGTCACCG TCTCCTCGGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCA CCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTAC AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA CCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAG TTGAGCCCAAATCTTGTGACAAAACTCACACATAA
Fab AM1-3 Heavy chain amino acid sequence (SEQ ID NO:26)	EVQLVESGGGLVQPGGSLRLSCAASGFNLTWWSIHWVRQAPGKGLEWVASTIFSGFSYTS YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-3 Light chain nucleotide sequence (SEQ ID NO:27)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTCATGGGCATACCCGATGATAACGTTC GGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAAC TTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC CTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGAT TACAAAGATGACGATGACAAATAA
Fab AM1-3 Light chain amino acid sequence (SEQ ID NO:28)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHSWAYPMITFGQGTKVEIKRTVAAPSVFIF PPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-4 Heavy chain nucleotide sequence (SEQ ID NO:29)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACATCTCTCAGTATACTATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGTTGCATCTATTTATGCTCGTTCTAGGTTTACTTCTTAT GCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCCTAC CTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCTTCT CGTATGGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAGGGT CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA ACTCACACATAA
Fab AM1-4 Heavy chain amino acid sequence (SEQ ID NO:30)	EVQLVESGGGLVQPGGSLRLSCAASGFNISQYTIHWVRQAPGKGLEWVASIYARSRFTSY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSRMDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-4 Light chain nucleotide sequence (SEQ ID NO:31)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTGGTTTGGATACCCAGCGGTATCTTCT TATTCTCTGATCACGTTCGGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTT GTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACC TACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTAC GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA GAGTGTGGTGGTTCTGATTACAAAGATGACGATGACAAATAA
Fab AM1-4 Light chain amino acid	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHWFGYPAVTFGQGTKVEIKRTVAAPSVFIF PPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST

sequence (SEQ ID NO:32)	LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-5 Heavy chain nucleotide sequence (SEQ ID NO:33)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACATCTCTTATTATACTATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCCTCTATTTATTCTTATTCTCTCTATACTTCT TATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCC TACCTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCT TCTGCTATGGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAG GGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCC CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCC CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGAC AAAACTCACACATAA
Fab AM1-5 Heavy chain amino acid sequence (SEQ ID NO:34)	EVQLVESGGGLVQPGGSLRLSCAASGFNISYYTIHWVRQAPGKGLEWVASSIYSYSLYTS YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-5 Light chain nucleotide sequence (SEQ ID NO:35)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTGGTGGGGTTACCCTATGATCACGTTC GGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAAC TTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC CTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGAT TACAAAGATGACGATGACAAATAA
Fab AM1-5 Light chain amino acid sequence (SEQ ID NO:36)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHWWGYPMITFGQGTKVEIKRTVAAPSVFIF PPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK
Fab AM1-6 Heavy chain nucleotide sequence (SEQ ID NO:37)	GAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCTGGTGCAGCCAGGGGGCTCACTCCGTTTG TCCTGTGCAGCTTCTGGCTTCAACCTCTCTTCTTATTCTATCCACTGGGTGCGTCAGGCC CCGGGTAAGGGCCTGGAATGGGTTGCATCTGCAATTTATGCTGGTTTCGGCTCAACTACG TATGCCGATAGCGTCAAGGGCCGTTTCACTATAAGCGCAGACACATCCAAAAACACAGCC TACCTACAAATGAACAGCTTAAGAGCTGAGGACACTGCCGTCTATTATTGTGCTCGCTCT TCAGCTATGGACTACTGGGGTCAAGGAACCCTGGTCACCGTCTCCTCGGCCTCCACCAAG GGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCC CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCC CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCCCAAATCTTGTGAC AAAACTCACACATAA
Fab AM1-6 Heavy chain amino acid sequence (SEQ ID NO:38)	EVQLVESGGGLVQPGGSLRLSCAASGFNLSSYSIHWVRQAPGKGLEWVASAIYAGFGSTT YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARSSAMDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
Fab AM1-6 Light chain nucleotide sequence (SEQ ID NO:39)	GATATCCAGATGACCCAGTCCCCGAGCTCCCTGTCCGCCTCTGTGGGCGATAGGGTCACC ATCACCTGCCGTGCCAGTCAGTCCGTGTCCAGCGCTGTAGCCTGGTATCAACAGAAACCA GGAAAAGCTCCGAAGCTTCTGATTTACTCGGCATCCAGCCTCTACTCTGGAGTCCCTTCT CGCTTCTCTGGTAGCGGTTCCGGGACGGATTTCACTCTGACCATCAGCAGTCTGCAGCCG GAAGACTTCGCAACTTATTACTGTCAGCAACATTCTTGGCGGTACCCGCTGATTACGTTC GGACAGGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATTCACAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAAC TTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC

	CTGACGCTGAGCAAAGCAGACTACGAAAAACATAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTGGTGGTTCTGAT TACAAAGATGACGATGACAAATAA
Fab AM1-6 Light chain amino acid sequence (SEQ ID NO:40)	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHSWRYPLITFGQGTKVEIKRTVAAPSVFIF PPSDSQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGSDYKDDDDK

Example 2. Functional characterization of IL-18R-binding antibodies

Evaluation of expressed and purified Fab protein in an IL-18-dependent NF-κB cellular luciferase reporter assay inhibition of IL-18 induced luciferase signals > 60% 2 anti-IL-18Rα Fabs (Fab 9 and 12) (**FIG. 1A**) and > 80 % by 7 anti-IL-18Rβ Fabs (**FIG. 1B**). In light of the sequence identity and high likelihood of similar epitopes, Fab CDR regions for five Fabs (1 anti-IL-18Rα and 4 anti-IL-18Rβ) were sub-cloned in to IgG expression constructs, transfected and expressed in 293F cells and then purified from the media to homogeneity over a Sepharose A column. *In vitro* binding of each IgG to receptor was then evaluated over a range of concentrations revealing in all cases, EC_{50} values in the low double-digit nanomolar binding to IL-18Rβ with virtually no binding to either negative control protein (F_c, BSA) at all concentrations tested (**FIG. 2, panel A**). Additional estimation of binding affinity by multi-point competitive ELISA revealed affinities in the 100 nM and sub-100 nM range (**FIG. 2, panel B**). SPR analysis of the same Fabs confirmed these estimates and enabled the determined of kinetics constants and equilibrium binding affinity (**Table 5**).

Table 5. Fab kinetics of binding versus mouse and human IL-18R by surface plasmon resonance (SPR)

		Human receptor			Mouse receptor		
Fab ID	Target Receptor	k_a ($10^4 M^{-1}s^{-1}$)	k_d ($10^{-4}s^{-1}$)	K_D (nM)	k_a ($10^4 M^{-1}s^{-1}$)	k_d ($10^{-4}s^{-1}$)	K_D (nM)
3131	IL-18Rβ	21 ± 0.1	12.7 ± 0.1	6.2 ±	12 ± 0.1	8.2 ± 0.5	5.2 ±
3132	IL-18Rβ						
3144	IL-18Rβ	32 ± 0.1	5.8 ± 0.2	1.8 ±	9.3 ± 0.1	12 ± 0.4	12.9 ±
A3	IL-18Rβ	2 ± 0.1	16.0 ± 0.2	78 ±	ND	ND	ND
12	IL-18Rα	11 ± 0.1	2.0 ± 0.2	1.9 ±	ND	ND	ND

To determine whether IgGs bound unique or overlapping epitopes, binding experiments were conducted using by pre-incubating IgGs with immobilized receptor to block epitopes, the

testing Fab binding by co-incubation with IgG-blocked receptor. Results showed that Fab clone FA3 was blocked only by its corresponding IgG (suggesting a unique epitope), whereas the remaining three Fabs (F3131, F3132, F3144) could be blocked by any of the IgG molecules (I3131, I3132, I3144) except the IA3 clone (corresponding to Fab FA3) (**FIG. 2, panel D**), suggesting a shared or overlapping epitope.

Example 3. Cell binding of IL-18R-binding antibodies by fluorescence microscopy and flow cytometry

To assess IgG binding to its target cellular receptor, HEK293 cells were transiently transfected with a construct encoding either full length IL-18Rα or IL-18Rβ and cultivated for 24 hrs prior to IgG labeling. Both untransfected cells and cells transiently transfected with the receptor-GFP fusion were incubated with saturating concentrations of IL-18R-binding IgG (or an isotype control) before washing and fluorostaining with a Cy3-labeled secondary antibody. After removal of the secondary antibody and fixation, cells were imaged by fluorescence microscopy (**FIG 3, panels A and B**). Images obtained by staining with each IgG of the anti-IL-18R antibodies revealed co-incident GFP expression (taken as confirmation of receptor expression) and antibody staining that was not apparent in the control IgG-stained cells. Similar analysis of GFP-expressing cells by flow cytometry revealed a distinct population of IL-18R-expressing (based on GFP expression) cells that stained positively with each of the IgGs and a positive commercially-sourced control.

HEK293 cells transfected in the same manner for expression of individual receptors were used to further test binding by flow cytometry. Cells expressing IL-18R-GFP fusions were stained with saturating IgG concentrations (red histograms) and compared to receptor-expressing cells stained with a non-receptor binding isotype control IgG (dark grey histograms) or anti-human Alexa 488-labeled secondary antibody alone (blue histograms) (**FIG. 3, panels C and D**). These results confirmed a significant shift in receptor-expressing cells that was not apparent with either secondary antibody alone or with the isotype control. Though controls IgGs targeting IL-18Rα and IL-18Rβ, also exhibited respective binding to cells expressing their cognate receptor, they also showed some binding to non-expressing HEK293 cells (pink histograms), despite the absence of binding of secondary alone controls (green histogram). Since these cells are not expected to express either of the IL-18 receptors,

this may simply represent a stickiness to non-expressing cells evident in only one of our antibodies to IL-18Rβ (IgG 3132) and the single antibody to IL-18Rα (IgG A3).

To test cell binding to endogenously expressed IL-18Rβ, macrophage-derived KG-1 myeloblast cells, known to express both IL-18Rs, were similarly immuno-stained with each IgG over a range of concentrations in comparison to a non-binding isotype control antibody (this needs to be added in). Plots of the median fluorescence intensity of staining versus a range of antibody concentrations revealed clear and saturable binding that enabled the fitting of the various binding curves and estimation of EC_{50}s for cell binding (**FIG. 4**).

Example 4. Functional consequence of IL-18R IgG binding by phospho-western analysis and IFN-γ ELISA

To evaluate the functional consequences of anti-IL18Rβ binding by IgG, IL-18-induced phospho-signaling was first assessed in KG-1 cells for several downstream effectors of IL-18R activation including IKKα/IKKβ, p38 MAPK and SAPK/JNK using phosphospecific antibodies in Western blots that quantify phosphorylation of specific residues within each protein. Antibodies specific for their respective non-phosphorylated parent proteins were also used to probe blots prepared from the same lysates for comparison as load controls (**FIG. 4, panel A).** Initially, KG-1 cells were incubated with saturating concentrations of IL-18R-binding antibodies for 1 hr prior to stimulation. Cells were then stimulated with IL-18 (10ng/mL, R&D Systems) for 24 hrs in the presence of antibody prior to collection of cell lysates for Western blot analysis and compared with cells in the absence of antibody and cells incubated with antibody but not stimulated with IL-18. Following stimulation, cell lysates were collected on ice and separated by SDS-PAGE before transfer to a solid PVDF support. Transferred proteins were probed separately with antibodies to rabbit anti-human p-IKKα/β (Ser176/180)(#2078; Cell Signaling), p-p38 MAPK (Thr180/Tyr182) (#4631; Cell Signaling), or phospho p44/42 MAPK (Thr202/Tyr204) (#4370; Cell Signaling) monoclonal antibodies developing with an anti-rabbit-HRP fusion secondary antibody (#7074; Cell Signaling) and enhanced chemi-luminescence reagent (ECL; #34095, Thermo).

Intensity results from both were quantified by densitometry to calculate the ratio of phosphorylated to non-phosphorylated protein, normalized to no antibody, no-IL-18 controls and ratios plotted versus the antibody treatment with or without IL-18 stimulation. Results

show IL-18-induced phosphorylation of IKKα/β, p38 MAPK and SAPK/JNK that could be inhibited by pre-incubation with any of the four anti-IL-18Rβ antibodies such that phospho-signal were virtually indistinguishable from no IL-18 controls, suggesting potent inhibition (**FIG. 4, panels B-D**).

To corroborate these results, secretion of IFN-γ was additionally used as a phenotypic readout to assess activity and quantified from cell supernatants by ELISA. KG-1 cells or isolated PBMCs were incubated with a range of concentrations of anti-IL-18Rβ IgG, then stimulated with 10 ng/mL IL-18 for 24 hours. Quantification of secreted IFN-γ revealed for each antibody tested revealed a similar dose-dependent reduction in secreted IFN-γ in both KG-1 cells and isolated PBMCs to approximately 50% of maximal at a range of ~0.5-2 μM for IgGs 3131, 3132 and 3144 and ~4-6 μM IgG A3 (lesser activity corresponding to its lesser affinity), in KG-1 cells (**FIG. 4, panel E**). Similar results were obtained in PBMCs, in which IgGs 3131, 3132 and 3144 inhibited ~50% of maximal signals at ~0.5-2 μM with substantially higher levels of IgG A3 required for similar inhibition (**FIG. 4, panel F**). Additionally, anti-IL-18Rα-binding IgG 12 was shown to possess similar potency to the Il-18Rβ-binding antibodies, inhibiting ~50% of IFN-γ secreted at ~1 μM IgG in PBMCs.

Example 5. Structural characterization of the anti-IL-18Rα/IL-18Rβ complex

To glean additional insight into how the anti-IL-18Rβ-binding Fab 3131 inhibited the non-ligand-binding receptor component of the IL-18R, crystallographic studies were undertaken to structurally characterize the interactions between the scFv format of Fab 3131 and the extracellular domain (ECD) of receptor IL-18Rβ. IL-18Rβ was expressed as an N-terminal HisX6 tag fusion from baculovirus expression vector pFastBac Dual in High Five insect cells. scFv format of 3131 was constructed from Fab 3131 by fusion of VH and VL with a linker of 17 amino acids. scFv 3131 was expressed in *E. coli* as an N-terminal HisX6 tag fusion protein and purified to homogeneity using a TALON® Metal Affinity Resin. The ECD of IL-18Rβ receptor was purified to homogeneity using a TALON® Metal Affinity Resin and mixed 1:2 molar ratio with purified scFv 3131; the mixture was then loaded onto size exclusion chromatography column for purification of complex (**FIG. 5**). The complex was concentrated to 10 mg/mL before screening for crystals with a battery of crystallization suites. Ultimately crystals were generated from a buffer comprised of 0.2 M Ammonium iodide and

20% (w/v) PEG 3350 and isolated crystals were stored in cryosolution in liquid N_2 prior to X-ray diffraction.

X-ray diffraction data were collected at the Shanghai Synchrotron Radiation Facility (SSRF) with a resolution of 3.3 Å. The crystal belonged to $P3_1$ with the unit cell a=163.160, b=163.160, c= 64.145, α= 90°, β=90°, γ=120°.

A refined model revealed a novel mode of non-competitive antagonism in which the antibody binds to the face opposite the ligand binding site, locking the receptor into a non-functional conformation in which the geometry of the ligand-biding site is disrupted (**FIG. 6**). These results provide mechanistic insight into the mode of antagonism of signaling via the non-ligand binding component of the receptor that suggests that antagonism arises from locking the receptor into a confirmation that impeded interaction with the IL-18Rα-ligand complex.

Example 6. Characterization of IgG 3131 binding to monkey IL-18Rβ

This example tested the binding of antibody 313 to monkey IL-18Rβ.

EC_{50} value of IgG 3131 binding to rhesus IL-18Rβ was determined by multipoint direct binding ELISA. The kinetics of IgG 3131 binding was determined to rhesus IL-18 receptor beta by Surface Plasmon Resonance (SPR) to confirm EC_{50} estimates. The cellular effects of IgG 3131 pre-incubation on rhesus IL-18 (50 ng/ml) plus rhesus IL-12 (5 ng/ml) induced stimulation of IFN-γ secretion was assessed over a range of IgG concentrations on isolated fresh cynomolgus monkey PBMCs. The mean and the standard deviation (SD) were calculated from three different monkeys. IC_{50} values were estimated from the dose response curves by curve fitting in GraphPad Prism (Version5.0). The summary results are shown below and the dose-dependency is plotted in **FIG. 7**.

IgG ID	Target	EC_{50} (nM)	k_a (10^4 M^{-1} s^{-1})	k_d (10^{-4} s^{-1})	K_D (nM)
3131	Rhesus IL-18Rβ	11.5±0.4	3.8±0.1	1.5±0.1	3.9±0.1

IgG 3131 serum concentration from individual monkeys. Following intravenous administration of IgG 3131 at a dose of 30 mg/kg (group 1, or G1) or 10 mg/kg (group 2, or G2), 2 ml whole blood were collected at pre-dose, 0.5, 1, 3, 6, 24, 48 h, 3 d, 4 d, 144h (6 d),

192 h (8 d), 240 h (10 d) and 336h (14d). After serum isolation, analysis of sample IgG was conducted by ELISA. The results are shown in **Table 6** and **FIG. 8**.

Table 6. IgG 3131 serum concentration from individual male monkeys.

	G1 30 mg/kg		G2 10 mg/kg	
Time points(hr)	Mean Single Conc.(ng/mL)	CV%	Mean Single Conc.(ng/mL)	CV%
predose	BQL	NA	BQL	NA
0.5 hr	621501.346	8.2	203564.463	4.4
1 hr	532472.449	6.6	196796.426	5.2
3 hr	470342.688	5.1	189477.094	4.8
6 hr	359419.118	5.7	150558.530	2.4
24 hr	237529.252	5.1	89643.134	0.5
48 hr	172548.375	10.6	51125.427	17.1
Day3	76872.242	0.1	37305.556	25.4
Day4	62353.833	4.5	29332.824	13.3
Day6	39732.496	2.4	22742.962	23.8
Day8	32240.520	1.5	18363.603	17.4
Day10	31031.273	1.0	13901.55	14.6
Day14	22526.709	0.9	9022.943	7.7
DAY21	15808.016	1.7	2641.525	1.2
Day 28	9866.219	0.4	1705.89	1.5

BLQ: below the limit of quantitation; N/A: not available

Table 7 shows selected pharmacokinetics parameters of IgG 3131 in male monkeys.

Table 7. Pharmacokinetics parameters of IgG 3131 in rhesus

Group	G1	G2
Dose (mg/kg)	30	10
λ_z (1/day)	0.0613	0.127
$T_{1/2}$ (day)	11.3	5.46
T_{max} (day)	0.0208333	0.0208333
C_{max} (ng/mL)	621501.35	203564.46
AUC_{0-t} (day*ng/mL)	1311391.3	511163.9
$AUC_{0-\infty}$ (day*ng/mL)	1472301.3	524605.3
AUC_% Extrap_obs ({%})	10.93	2.56
Vz_obs (mL/kg)	332.32	150.2
MRTlast (day)	6.22	5.33
Vss_obs (mL/kg)	211.51	116.43

Example 7. Further affinity maturation of IgG 3131

This example presents antibody Fab sequences derived from affinity maturation of antibody 3131. Affinity maturation libraries were subject to rounds of affinity-based solution-phase

phage display selection with decreasing concentration of antigen at each round. Antibodies with improved affinity are listed in Table 8.

Table 8. Affinity matured sequences

Seq ID	Sequence	Name	VH/VL
162	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHHAGL ITFGQGTKVEIK	3131 AM2-1	VL
163	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-1	VH
164	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSRDSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-2	VL
165	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSHGRTGYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-2	VH
166	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-3	VL
167	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGYTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-3	VH
168	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-4	VL
169	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGSTCYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-4	VH
170	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-5	VL
171	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-5	VH
172	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-6	VL
173	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSHGGTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-6	VH
174	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-7	VL
175	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSHGGTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-7	VH
176	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-8	VL
177	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSNGRTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR	3131 AM2-8	VH

	SSFSHGYGWYGLDYWGQGTLVTVSS		
178	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHNAGL ITFGQGTKVEIK	3131 AM2-9	VL
179	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-9	VH
180	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-10	VL
181	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSNGNTGYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-10	VH
182	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-11	VL
183	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSNGNTGYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-11	VH
184	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-13	VL
185	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-13	VH
186	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-14	VL
187	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-14	VH
188	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-15	VL
189	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTGYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-15	VH
190	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY STSSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-16	VL
191	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-16	VH
192	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-17	VL
193	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSHGNTDYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-17	VH
194	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-18	VL
195	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-18	VH

196	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SGSSGRSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-21	VL
197	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-21	VH
198	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SDSSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-24	VL
199	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-24	VH
200	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSRDSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-25	VL
201	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-25	VH
202	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SESSLSSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-26	VL
203	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-26	VH
204	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SRSSDSSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-28	VL
205	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-28	VH
206	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY STSSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-29	VL
207	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-29	VH
208	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSERSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-30	VL
209	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-30	VH
210	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SESSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-31	VL
211	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-31	VH
212	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SSSSVYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-32	VL
213	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-32	VH
214	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY	3131 AM2-33	VL

	SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK		
215	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGHTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-33	VH
216	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHSAGL ITFGQGTKVEIK	3131 AM2-35	VL
217	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-35	VH
218	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-36	VL
219	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-36	VH
220	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHSAGL ITFGQGTKVEIK	3131 AM2-37	VL
221	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-37	VH
222	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-S-G	VL
223	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-S-G	VH
224	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY TASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-S-T	VL
225	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-S-T	VH
226	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY HASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-S-H	VL
227	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-S-H	VH
228	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIY YASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-S-Y	VL
229	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSYGYTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-S-T	VH
230	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-01	VL
231	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-01	VH
232	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL	3131 AM2-O-02	VL

	ITFGQGTKVEIK		
233	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-02	VH
234	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-03	VL
235	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-03	VH
236	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-04	VL
237	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-04	VH
238	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-05	VL
239	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-05	VH
240	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-06	VL
241	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-06	VH
242	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-07	VL
243	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-07	VH
244	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-08	VL
245	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-08	VH
246	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-09	VL
247	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-09	VH
248	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-10	VL
249	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-10	VH
250	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-11	VL

251	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-11	VH
252	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-12	VL
253	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-12	VH
254	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-13	VL
255	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-13	VH
256	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHYAGL ITFGQGTKVEIK	3131 AM2-O-14	VL
257	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-14	VH
258	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-15	VL
259	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-15	VH
260	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-16	VL
261	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-16	VH
262	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-17	VL
263	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-17	VH
264	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-18	VL
265	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-18	VH
266	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-19	VL
267	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-19	VH
268	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-20	VL
269	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA	3131 AM2-O-	VH

	SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	20	
270	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-21	VL
271	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-21	VH
272	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-22	VL
273	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-22	VH
274	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-23	VL
275	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-23	VH
276	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-24	VL
277	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-24	VH
278	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-25	VL
279	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-25	VH
280	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-26	VL
281	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-26	VH
282	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-27	VL
283	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-27	VH
284	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-28	VL
285	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-28	VH
286	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-29	VL
287	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR	3131 AM2-O-29	VH

	SSFSHGYGWYGLDYWGQGTLVTVSS		
288	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHDAGL ITFGQGTKVEIK	3131 AM2-O-30	VL
289	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-30	VH
290	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-31	VL
291	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-31	VH
292	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-32	VL
293	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-32	VH
294	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-33	VL
295	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-33	VH
296	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-34	VL
297	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-34	VH
298	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-35	VL
299	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-35	VH
300	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-36	VL
301	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-36	VH
302	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-37	VL
303	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-37	VH
304	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY SASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-38	VL
305	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-38	VH

306	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-39	VL
307	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-39	VH
308	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-40	VL
309	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-40	VH
310	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-41	VL
311	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-41	VH
312	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-42	VL
313	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSGGSTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-42	VH
314	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-43	VL
315	EVQLVESGGGLVQPGGSLRLSCAASGFNLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-43	VH
316	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-44	VL
317	EVQLVESGGGLVQPGGSLRLSCAASGFTLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-44	VH
318	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-45	VL
319	EVQLVESGGGLVQPGGSLRLSCAASGFDLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-45	VH
320	DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPRLLIY GASSLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQYGYHGAGL ITFGQGTKVEIK	3131 AM2-O-46	VL
321	EVQLVESGGGLVQPGGSLRLSCAASGFSLYYSSMHWVRQAPGKGLEWVA SIYSSSGDTHYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCAR SSFSHGYGWYGLDYWGQGTLVTVSS	3131 AM2-O-46	VH

The CDRs are summarized in Table 9 below.

Table 9. CDRs of the affinity matured variants

Name	CDRL1 (SEQ ID NO:)		CDRL2 (SEQ ID NO:)		CDRL3 (SEQ ID NO:)		CDRH1 (SEQ ID NO:)		CDRH2 (SEQ ID NO:)		CDRH3 (SEQ ID NO:)	
AM2-1	QSVSSA	45	SAS	46	QQYGYHHAGLIT	332	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-2	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSHGRTG	340	ARSSFSHGYGWYGLDY	117
AM2-3	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGYTS	341	ARSSFSHGYGWYGLDY	117
AM2-4	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGSTC	342	ARSSFSHGYGWYGLDY	117
AM2-5	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-6	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSHGGTN	344	ARSSFSHGYGWYGLDY	117
AM2-7	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSHGGTY	345	ARSSFSHGYGWYGLDY	117
AM2-8	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSNGRTY	346	ARSSFSHGYGWYGLDY	117
AM2-9	QSVSSA	45	SAS	46	QQYGYHNAGLIT	334	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-10	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSNGNTG	347	ARSSFSHGYGWYGLDY	117
AM2-11	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSNGNTG	347	ARSSFSHGYGWYGLDY	117
AM2-13	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-14	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-15	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGDTG	348	ARSSFSHGYGWYGLDY	117
AM2-16	QSVSSA	45	STS	322	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-17	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSHGNTD	349	ARSSFSHGYGWYGLDY	117
AM2-18	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-21	QSVSSA	45	SGS	323	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-24	QSVSSA	45	SDS	324	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-25	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-26	QSVSSA	45	SES	325	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-28	QSVSSA	45	SRS	326	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-29	QSVSSA	45	STS	322	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117

AM2-30	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-31	QSVSSA	45	SES	325	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-32	QSVSSA	45	SSS	327	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-33	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGHTS	351	ARSSFSHGYGWYGLDY	117
AM2-35	QSVSSA	45	SAS	46	QQYGYHSAGLIT	336	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-36	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGSTS	352	ARSSFSHGYGWYGLDY	117
AM2-37	QSVSSA	45	SAS	46	QQYGYHSAGLIT	336	GFNLYYSSM	74	SIYSSSGSTS	352	ARSSFSHGYGWYGLDY	117
AM2-S-G	QSVSSA	45	GAS	328	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-S-T	QSVSSA	45	TAS	329	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-S-H	QSVSSA	45	HAS	330	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-S-Y	QSVSSA	45	YAS	331	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSYGYTY	95	ARSSFSHGYGWYGLDY	117
AM2-O-01	QSVSSA	45	SAS	46	CQYGYHYAGLIT	47	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-02	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-03	QSVSSA	45	SAS	46	CQYGYHYAGLIT	47	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-04	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFTLYYSSM	337	SIYSSGGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-05	QSVSSA	45	SAS	46	QQYGYHYAGLIT	47	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-06	QSVSSA	45	SAS	46	CQYGYHYAGLIT	47	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-07	QSVSSA	45	GAS	328	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-08	QSVSSA	45	GAS	328	CQYGYHYAGLIT	47	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-09	QSVSSA	45	GAS	328	QQYGYHYAGLIT	47	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-10	QSVSSA	45	GAS	328	CQYGYHYAGLIT	47	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-11	QSVSSA	45	GAS	328	QQYGYHYAGLIT	47	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-12	QSVSSA	45	GAS	328	CQYGYHYAGLIT	47	GFTLYYSSM	337	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-13	QSVSSA	45	GAS	328	QQYGYHYAGLIT	47	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-14	QSVSSA	45	GAS	328	CQYGYHYAGLIT	47	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-15	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-16	QSVSSA	45	SAS	46	CQYGYHDAGLIT	333	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117

AM2-O-17	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-18	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-19	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-20	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFTLYYSSM	337	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-21	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-22	QSVSSA	45	SAS	46	QQYGYHDAGLIT	333	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-23	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-24	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-25	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-26	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-27	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-28	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFTLYYSSM	337	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-29	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-30	QSVSSA	45	GAS	328	QQYGYHDAGLIT	333	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-31	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-32	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-33	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-34	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-35	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-36	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFTLYYSSM	337	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-37	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-38	QSVSSA	45	SAS	46	QQYGYHGAGLIT	335	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-39	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFNLYYSSM	74	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-40	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFTLYYSSM	337	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-41	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFDLYYSSM	338	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-42	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFSLYYSSM	339	SIYSSGGSTS	350	ARSSFSHGYGWYGLDY	117
AM2-O-43	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFNLYYSSM	74	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117

AM2-O-44	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFTLYYSSM	337	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-45	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFDLYYSSM	338	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117
AM2-O-46	QSVSSA	45	GAS	328	QQYGYHGAGLIT	335	GFSLYYSSM	339	SIYSSSGDTH	343	ARSSFSHGYGWYGLDY	117

Example 8. Binding competition assay of the affinity maturated antibodies

This example assessed the epitopes of the affinity matured antibody variants of Example 7 (AM2) relative to the parent 3131 antibody.

The results are presented in **FIG. 9**, in which the binding signals for purified AM2 Fab clones (white bars) to recombinant human IL-18Rb were evaluated by ELISA and compared to those obtained in the presence of saturating IgG 3131 (black bars). Fab 3131 was used as a positive control, to observe self-blocking by IgG 3131 (top plot, far left). Error bars represent standard deviation of replicate measurements. The results demonstrate that these affinity matured antibody variants bind to the same epitope as the parent 3131 antibody.

* * *

The present disclosure is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the disclosure, and any compositions or methods which are functionally equivalent are within the scope of this disclosure. It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference

CLAIMS

What is claimed is:

1. An antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor beta (IL-18Rβ) protein having the amino acid sequence of SEQ ID NO:1, wherein the binding comprises at least:

an amino acid residue selected from the group consisting of L167, D213 and T242,

an amino acid residue selected from the group consisting of V244, G245 and D246, and

an amino acid residue selected from the group consisting of G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1.

2. The antibody or fragment thereof of claim 1, wherein the binding comprises at least:

an amino acid residue selected from the group consisting of D213 and T242,

an amino acid residue selected from the group consisting of V244, G245 and D246, and

an amino acid residue selected from the group consisting of G278, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1.

3. The antibody or fragment thereof of claim 1, wherein the binding comprises at least:

an amino acid residue selected from the group consisting of D213 and T242,

the amino acid residue V244, and

an amino acid residue selected from the group consisting of G278, R281, V282, F283, N284, P285, S310, E315 and I317, of SEQ ID NO:1.

4. The antibody or fragment thereof of claim 1, wherein the binding comprises at least the amino acid residues D213, T242, V244, G278, R281, V282, F283, N284, P285, S310, E315 and I317 of SEQ ID NO:1.

5. The antibody or fragment thereof of claim 1, wherein the binding comprises at least the amino acid residues L167, D213, T242, V244, G278, F279, R281, V282, F283, N284, P285, S310, E315 and I317 of SEQ ID NO:1.

6. The antibody or fragment thereof of any preceding claim, which further is capable of binding to a mouse IL-18Rβ protein.

7. An antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor beta (IL-18Rβ) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-27 of **Table B** or each of the combinations 1-27 in which each of the CDRL3, CDRH1, CDRH2, and CDRH3 includes one, two, or three amino acid addition, deletion, conservative amino acid substitution or the combinations thereof.

8. The antibody or fragment thereof of claim 7, wherein the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combination 1 of **Table B** or have one amino acid substitution.

9. The antibody or fragment thereof of claim 8, wherein the substitutions are selected from **Table B1**.

10. The antibody or fragment thereof of claim 7, wherein the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combinations 1-27 of **Table B** or any row of **Table 9**.

11. The antibody or fragment thereof of any one of claims 7-10, wherein the CDRL1 and CDRL2 have sequences of QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively.

12. The antibody or fragment thereof of claim 7, wherein the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2 and CDRH3 are selected from the group consisting of:

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 68, 90, 111, and 134, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 69, 91, 112, and 135, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 332, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 340, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 341, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 342, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 344, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 74, 345, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 346, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 334, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 347, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 347, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 348, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 322, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 349, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 323, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 324, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 325, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 326, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 322, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 325, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 327, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 351, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 336, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 74, 352, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 336, 74, 352, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 329, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 330, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 331, 47, 74, 95, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 339, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 337, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 338, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 47, 339, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 339, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 74, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 337, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 338, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 47, 339, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 339, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 74, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 337, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 338, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 333, 339, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 339, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 74, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 337, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 338, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 333, 339, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 339, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 74, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 337, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 338, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 46, 335, 339, 343, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 335, 74, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 335, 337, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 335, 338, 350, and 117, respectively,

the amino acid sequences of SEQ ID NO:45, 328, 335, 339, 350, and 117, respectively, the amino acid sequences of SEQ ID NO:45, 328, 335, 74, 343, and 117, respectively, the amino acid sequences of SEQ ID NO:45, 328, 335, 337, 343, and 117, respectively, the amino acid sequences of SEQ ID NO:45, 328, 335, 338, 343, and 117, respectively, and the amino acid sequences of SEQ ID NO:45, 328, 335, 339, 343, and 117, respectively.

13. An antibody or fragment thereof, wherein the antibody or fragment thereof has binding specificity to a human interleukin-18 receptor alpha (IL-18Rα) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL3, CDRH1, CDRH2, and CDRH3, are selected from combinations 1-12 of **Table C** or each of the combinations 1-12 in which each of the CDRL3, CDRH1, CDRH2, and CDRH3 includes one, two, or three amino acid addition, deletion, conservative amino acid substitution or the combinations thereof.

14. The antibody or fragment thereof of claim 13, wherein the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combination 11 of **Table C** or have one amino acid substitution.

15. The antibody or fragment thereof of claim 14, wherein the substitutions are selected from **Table C1**.

16. The antibody or fragment thereof of claim 13, wherein the CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combinations 1-12 of **Table C**.

17. The antibody or fragment thereof of any one of claims 13-16, wherein the CDRL1 and CDRL2 have sequences of QSVSSA (SEQ ID NO:45) and SAS (SEQ ID NO:46), respectively.

18. The antibody or fragment thereof of claim 1 or 7, comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, and 321 or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, and 321.

19. The antibody or fragment thereof of claim 1, 7 or 18, comprising a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216,

218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320.

20. The antibody or fragment thereof of claim 13, comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:42, or a peptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:42.

21. The antibody or fragment thereof of claim 13 or 20, comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:44, or a peptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:44.

22. The antibody or fragment thereof of any one of claims 1-21, which can combine with other antibodies against second target protein.

23. The antibody or fragment thereof of claim 22, wherein the second target protein can be other pro-inflammatory cytokines, including but not limited to, IL-1, IL-4, IL-5, IL-6, IL13, IL-17 and IL36. Other examples include but not limited to CD3, CD16, CD19, CD20, CD28, CD64, PD-1, CTLA-4, LAG-3 (also known as CD223), CD28, CD122, 4-1BB (also known as CD137), TIM3, OX-40 or OX40L, CD40 or CD40L, LIGHT, ICOS/ICOSL, GITR/GITRL, TIGIT, CD27, VISTA, B7H3, B7H4, HEVM or BTLA (also known as CD272), killer-cell immunoglobulin-like receptors (KIRs), and CD47.

24. A composition comprising the antibody or fragment thereof of any one of claims 1-23 and a pharmaceutically acceptable carrier.

25. An isolated cell comprising one or more polynucleotide encoding the antibody or fragment thereof of any one of claims 1-23.

26. A method of treating an autoimmune or inflammatory disease in a patient in need thereof, comprising administering to the patient the antibody or fragment thereof of any one of claims 1-23.

27. The method of claim 26, wherein said autoimmune or inflammatory disease is selected from the group consisting of a Parkinson's disease, arthritis, rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, lupus, systemic lupus erythematous, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, Grave's disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, dermatomyositis, multiple sclerosis, myasthenia gravis, pernicious anemia, Sjogren syndrome, type I diabetes, type II diabetes, vasculitis, uveitis, sepsis, atherosclerosis and ankylosing spondylitis.

28. A method of treating cancer in a patient in need thereof, comprising administering to the patient the antibody or fragment thereof of any one of claims 1-23.

29. The method of claim 28, wherein the cancer is selected from the group consisting of bladder cancer, liver cancer, colon cancer, rectal cancer, endometrial cancer, leukemia, lymphoma, pancreatic cancer, small cell lung cancer, non-small cell lung cancer, breast cancer, urethral cancer, head and neck cancer, gastrointestinal cancer, stomach cancer, oesophageal cancer, ovarian cancer, renal cancer, melanoma, prostate cancer and thyroid cancer.

30. A method of detecting expression of IL-18 receptor in a sample, comprising contacting the sample with an antibody or fragment thereof of any one of claims 1-23 under conditions for the antibody or fragment thereof to bind to the IL-18 receptor, and detecting the binding which indicates expression of IL-18 receptor in the sample.

31. The method of claim 30, wherein the sample is isolated from a human patient.

32. The method of claim 30, wherein the detection indicates a disease associated with abnormal expression of the IL-18 receptor.

33. The method of claim 32, wherein the disease is selected from the group consisting of infection, an autoimmune or inflammatory disease, or cancer.

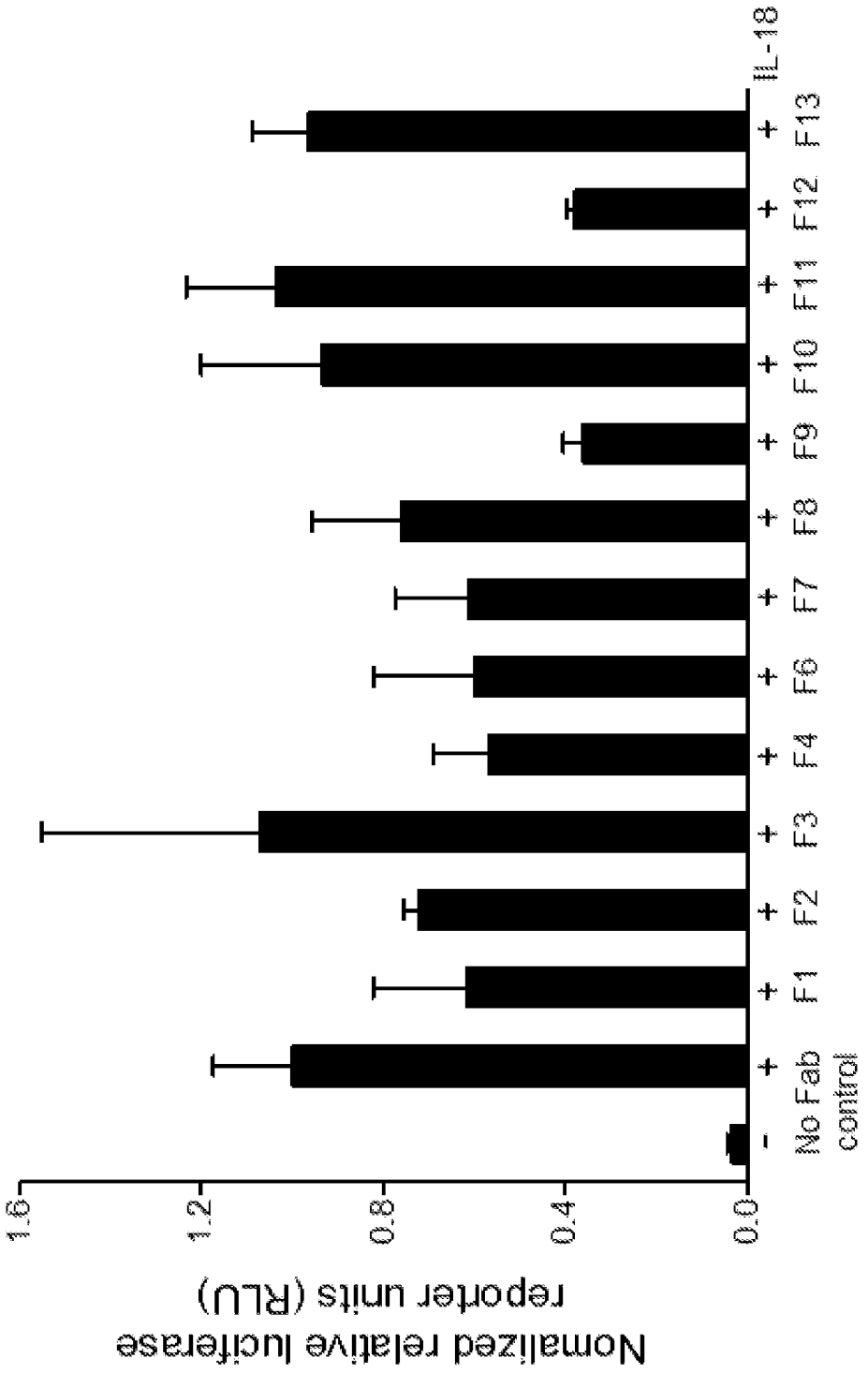

Normalized relative luciferase reporter units (RLU)
1.6
1.2
0.8
0.4
0.0
-
+
+
+
+
+
+
+
+
+
+
+
+
No Fab control
F1
F2
F3
F4
F6
F7
F8
F9
F10
F11
F12
F13
IL-18

FIG. 1A

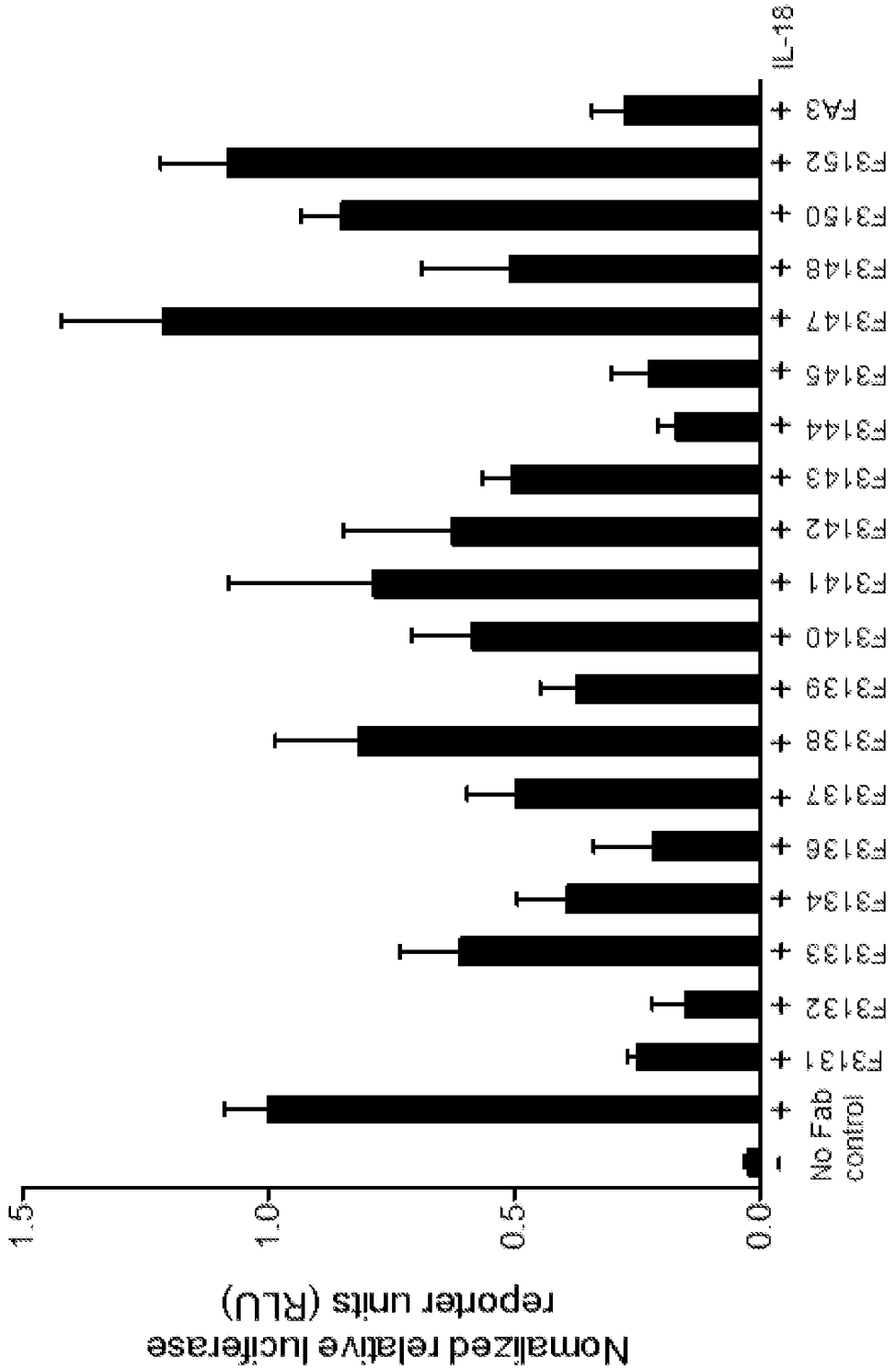

Normalized relative luciferase reporter units (RLU)
1.5
1.0
0.5
0.0
IL-18
-
+
FA3 +
F3152 +
F3150 +
F3148 +
F3147 +
F3145 +
F3144 +
F3143 +
F3142 +
F3141 +
F3140 +
F3139 +
F3138 +
F3137 +
F3136 +
F3134 +
F3133 +
F3132 +
F3131 +
No Fab control

FIG. 1B

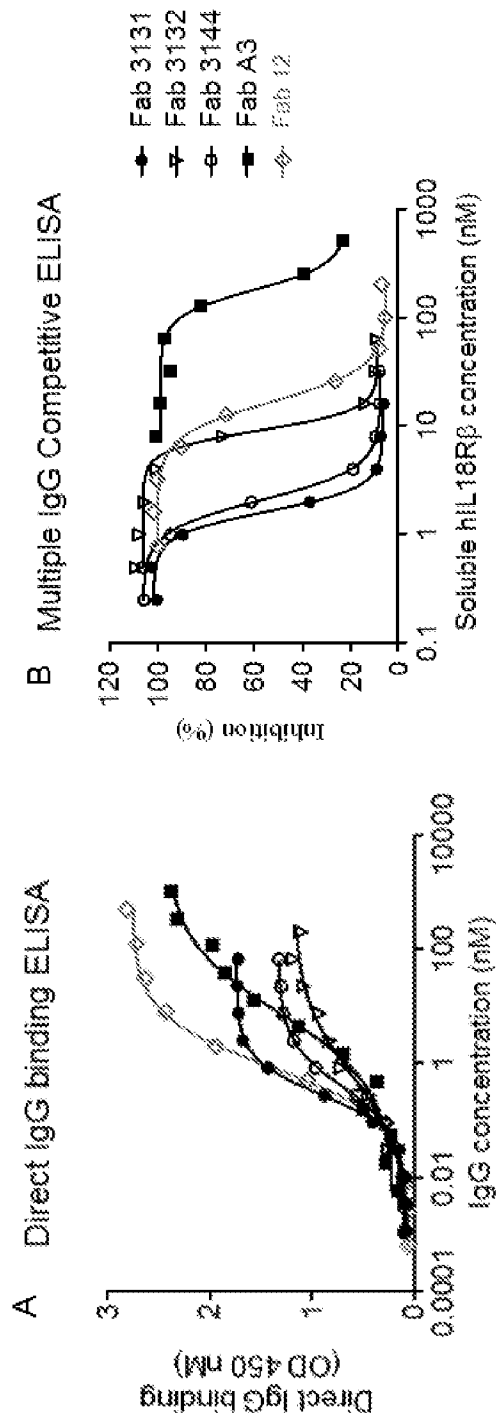

A
Direct IgG binding ELISA
Direct IgG binding (OD 450 nM)
IgG concentration (nM)
B
Multiple IgG Competitive ELISA
Inhibition (%)
Soluble hIL18Rβ concentration (nM)
Fab 3131
Fab 3132
Fab 3144
Fab A3
Fab 12

FIG. 2A-B

C

Fab ID	Target	EC_{50} (nM)	IC_{50} (nM)	Human receptor k_a (10^{-4} M^{-1} s^{-1})	Human receptor k_d (10^{-4} s^{-1})	Human receptor K_D (nM)
3131	IL-18Rβ	16 ± 0.1	82 ± 2.0	21 ± 0.1	13 ± 0.1	6.1 ± 0.1
3132		33 ± 0.1	74 ± 2.3	1.0 ± 0.1	13 ± 1.0	133 ± 1.8
3144		16 ± 0.1	19 ± 4.1	17 ± 0.1	11 ± 0.1	6.4 ± 0.1
A3		86 ± 0.1	105 ± 7.2	5.1 ± 0.1	15 ± 0.1	30 ± 0.1
12	IL-18Rα	86 ± 0.1	105 ± 7.2	11 ± 0.1	2.0 ± 0.2	1.9 ± 0.1

D

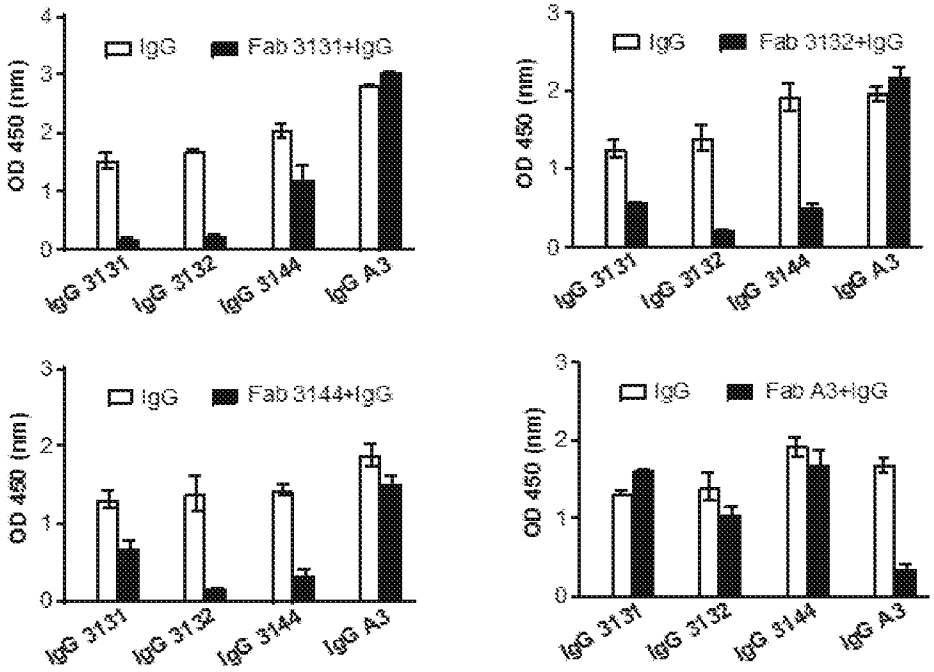
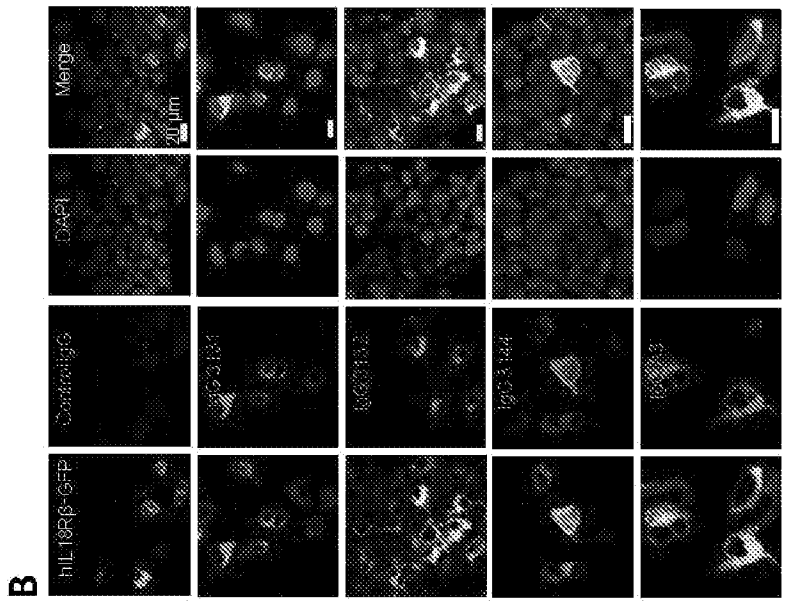


FIG. 2C-D


B
hIL18Rβ-GFP
Control IgG
DAPI
Merge
20 μm

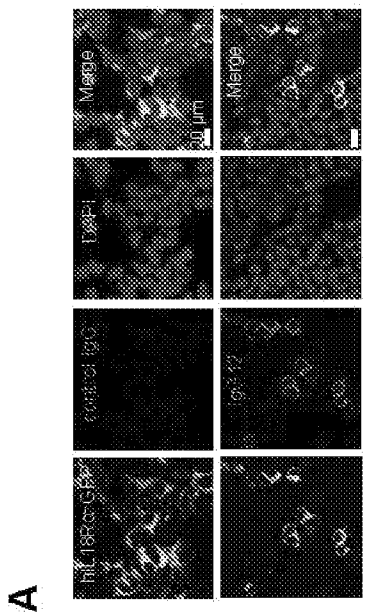

A
hIL18Rβ-GFP
control IgG
DAPI
Merge
20 μm

FIG. 3A-B

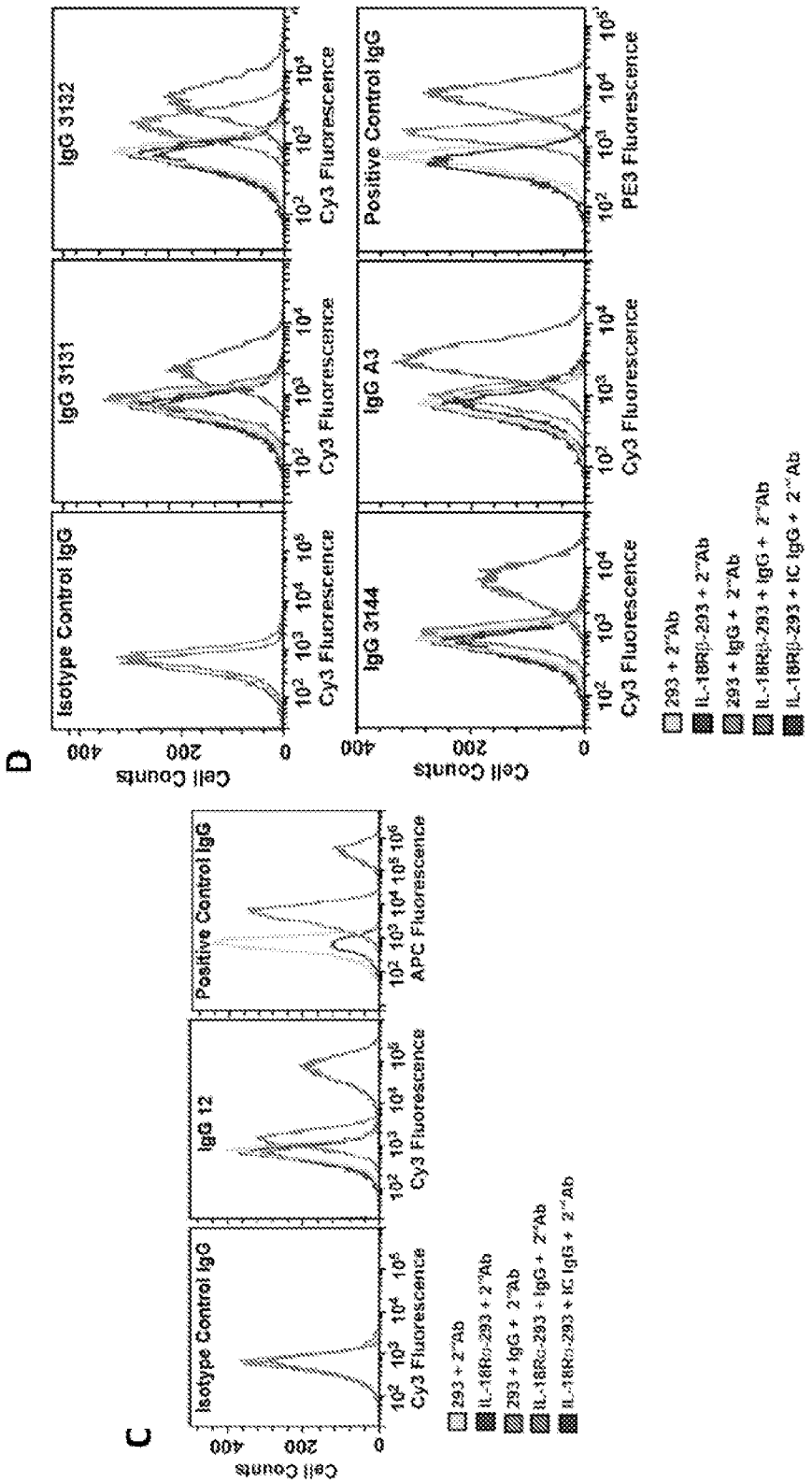

C
Isotype Control IgG
IgG 12
Positive Control IgG
Cell Counts
Cy3 Fluorescence
APC Fluorescence
293 + 2°Ab
IL-18Rβ-293 + 2°Ab
293 + IgG + 2°Ab
IL-18Rβ-293 + IgG + 2°Ab
IL-18Rβ-293 + IC IgG + 2°Ab
D
Isotype Control IgG
IgG 3131
IgG 3132
IgG 3144
IgG A3
Positive Control IgG
Cell Counts
Cy3 Fluorescence
PE3 Fluorescence
293 + 2°Ab
IL-18Rβ-293 + 2°Ab
293 + IgG + 2°Ab
IL-18Rβ-293 + IgG + 2°Ab
IL-18Rβ-293 + IC IgG + 2°Ab

FIG. 3C-D

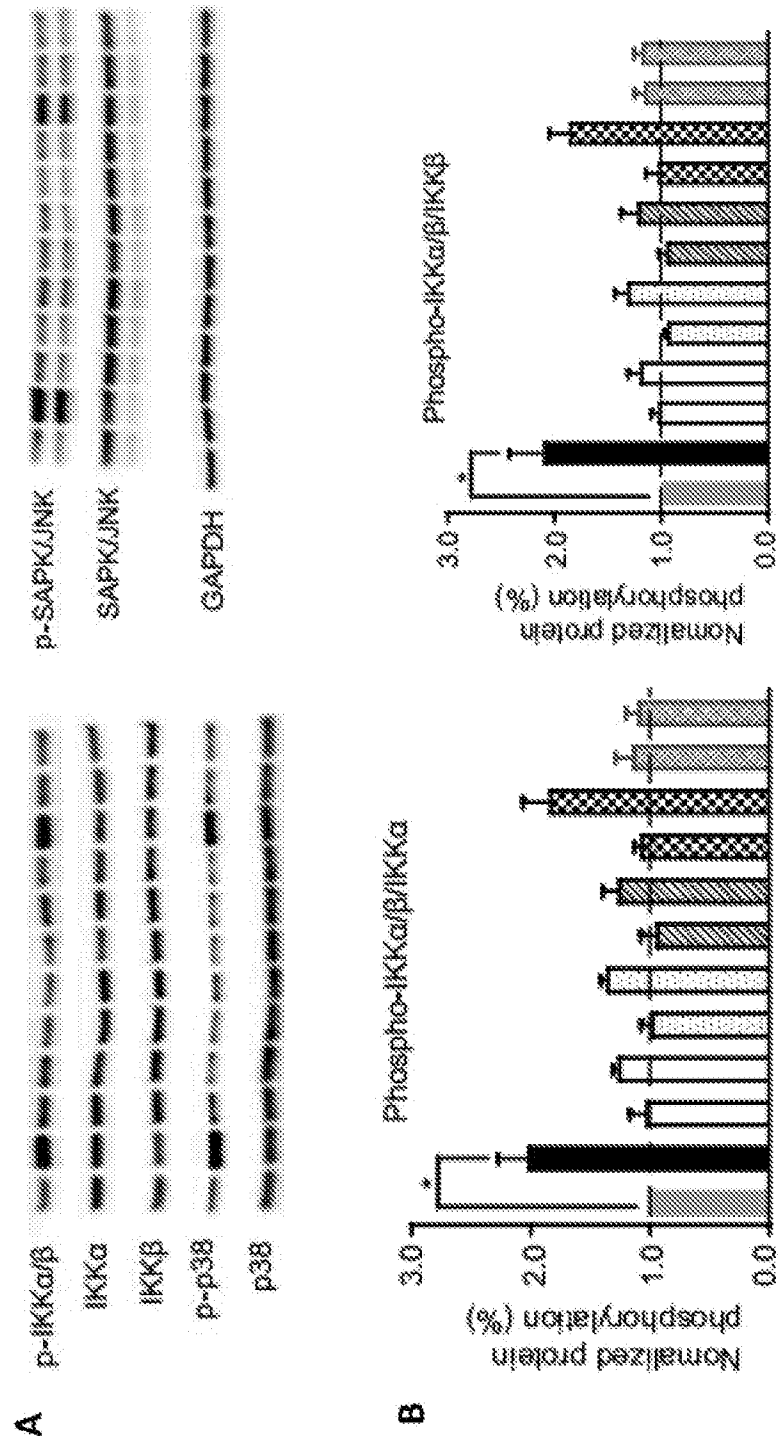

A
p-IKKα/β
IKKα
IKKβ
p-p38
p38
p-SAPK/JNK
SAPK/JNK
GAPDH
B
Phospho-IKKα/β/IKKα
Normalized protein phosphorylation (%)
3.0
2.0
1.0
0.0
Phospho-IKKα/β/IKKβ
Normalized protein phosphorylation (%)
3.0
2.0
1.0
0.0

FIG. 4A-B

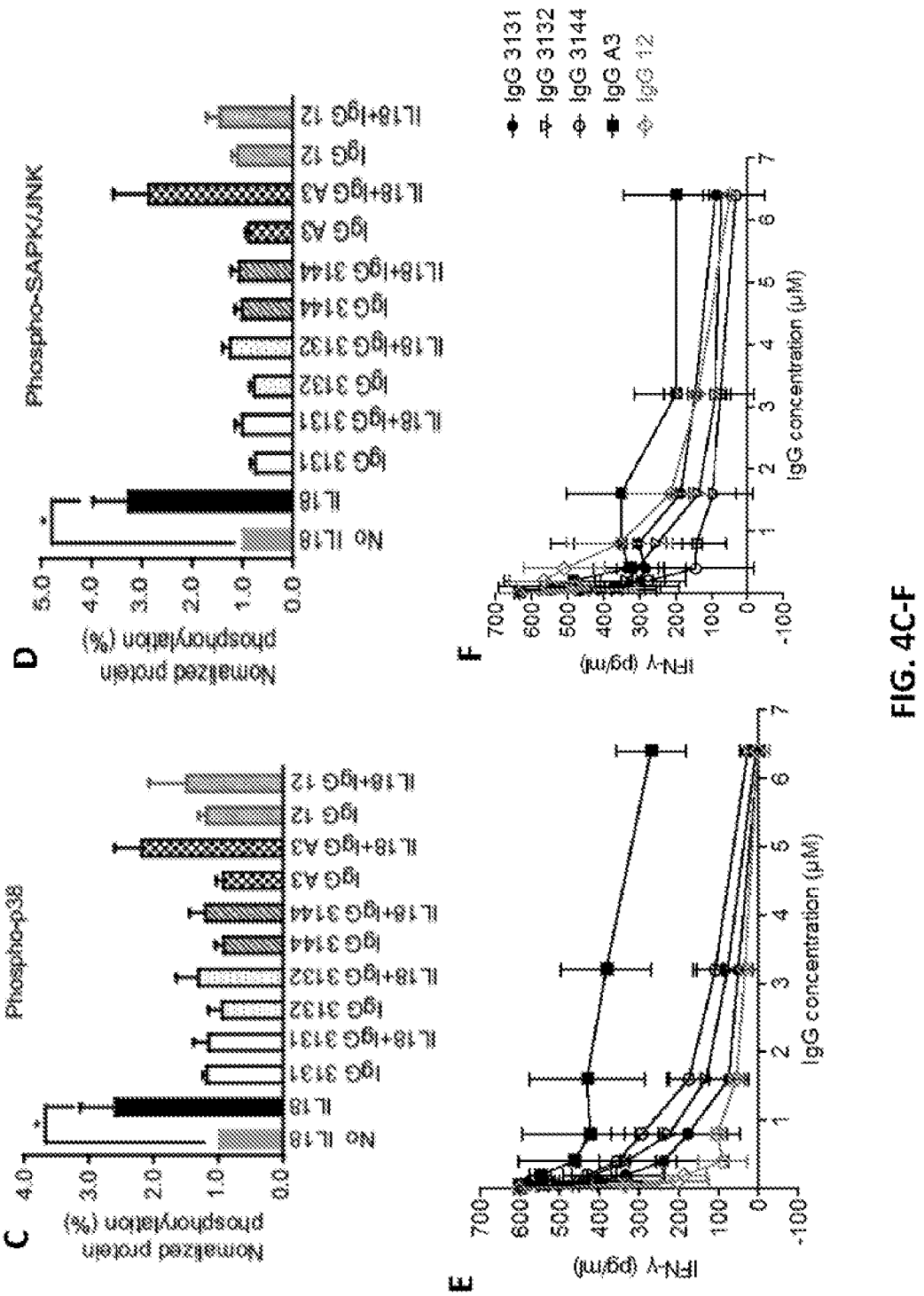

C
Phospho-p38
Normalized protein phosphorylation (%)
4.0
3.0
2.0
1.0
0.0
*
No IL18
IL18
IgG 3131
IL18+IgG 3131
IgG 3132
IL18+IgG 3132
IgG 3144
IL18+IgG 3144
IgG A3
IL18+IgG A3
IgG 12
IL18+IgG 12
D
Phospho-SAPK/JNK
Normalized protein phosphorylation (%)
5.0
4.0
3.0
2.0
1.0
0.0
*
No IL18
IL18
IgG 3131
IL18+IgG 3131
IgG 3132
IL18+IgG 3132
IgG 3144
IL18+IgG 3144
IgG A3
IL18+IgG A3
IgG 12
IL18+IgG 12
E
IFN-γ (pg/ml)
700
600
500
400
300
200
100
0
-100
IgG concentration (μM)
1
2
3
4
5
6
7
F
IgG 3131
IgG 3132
IgG 3144
IgG A3
IgG 12
IFN-γ (pg/ml)
700
600
500
400
300
200
100
0
-100
IgG concentration (μM)
1
2
3
4
5
6
7

FIG. 4C-F

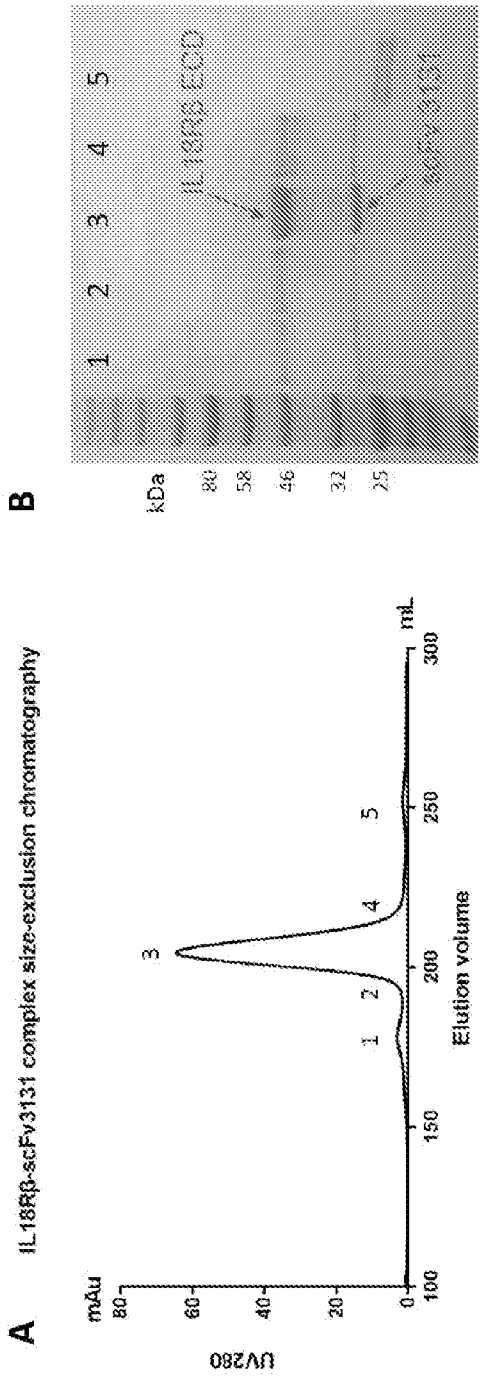

A
IL18Rβ-scFv3131 complex size-exclusion chromatography
mAu
80
60
40
20
0
UV280
100
150
200
250
300
mL
Elution volume
1
2
3
4
5
B
kDa
80
58
46
32
25
1
2
3
4
5

FIG. 5

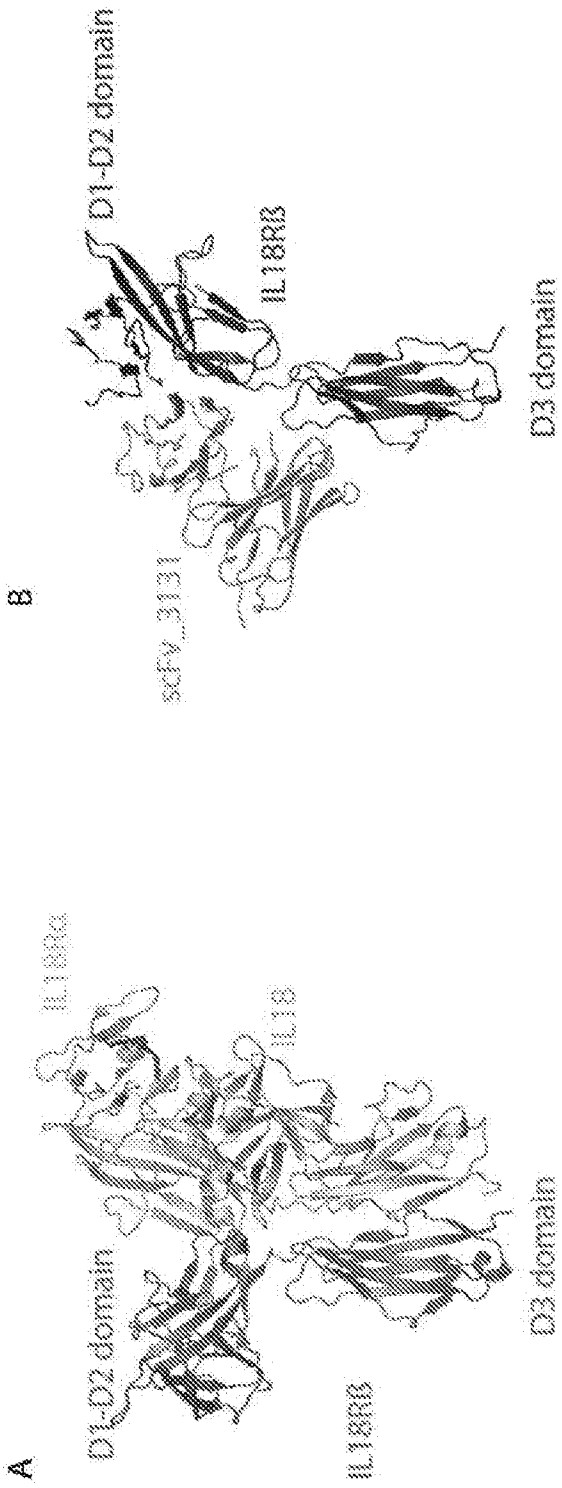

A
IL18Rα
D1-D2 domain
IL18
IL18Rβ
D3 domain
B
D1-D2 domain
IL18Rβ
scFv_3131
D3 domain

FIG. 6

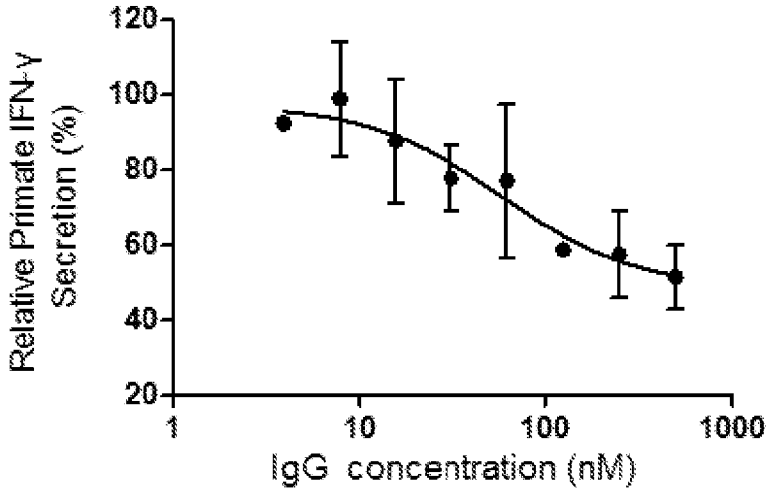

Relative Primate IFN-γ Secretion (%)
120
100
80
60
40
20
1
10
100
1000
IgG concentration (nM)

FIG. 7

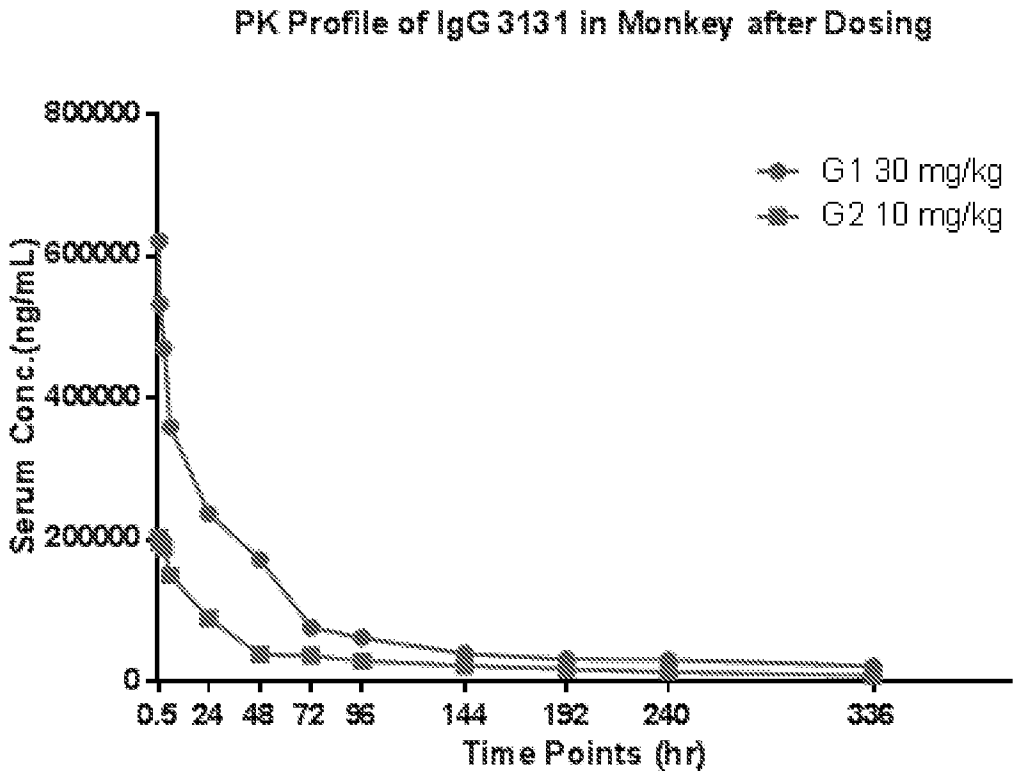

PK Profile of IgG 3131 in Monkey after Dosing
G1 30 mg/kg
G2 10 mg/kg
Serum Conc.(ng/mL)
800000
600000
400000
200000
0
0.5
24
48
72
96
144
192
240
336
Time Points (hr)

FIG. 8

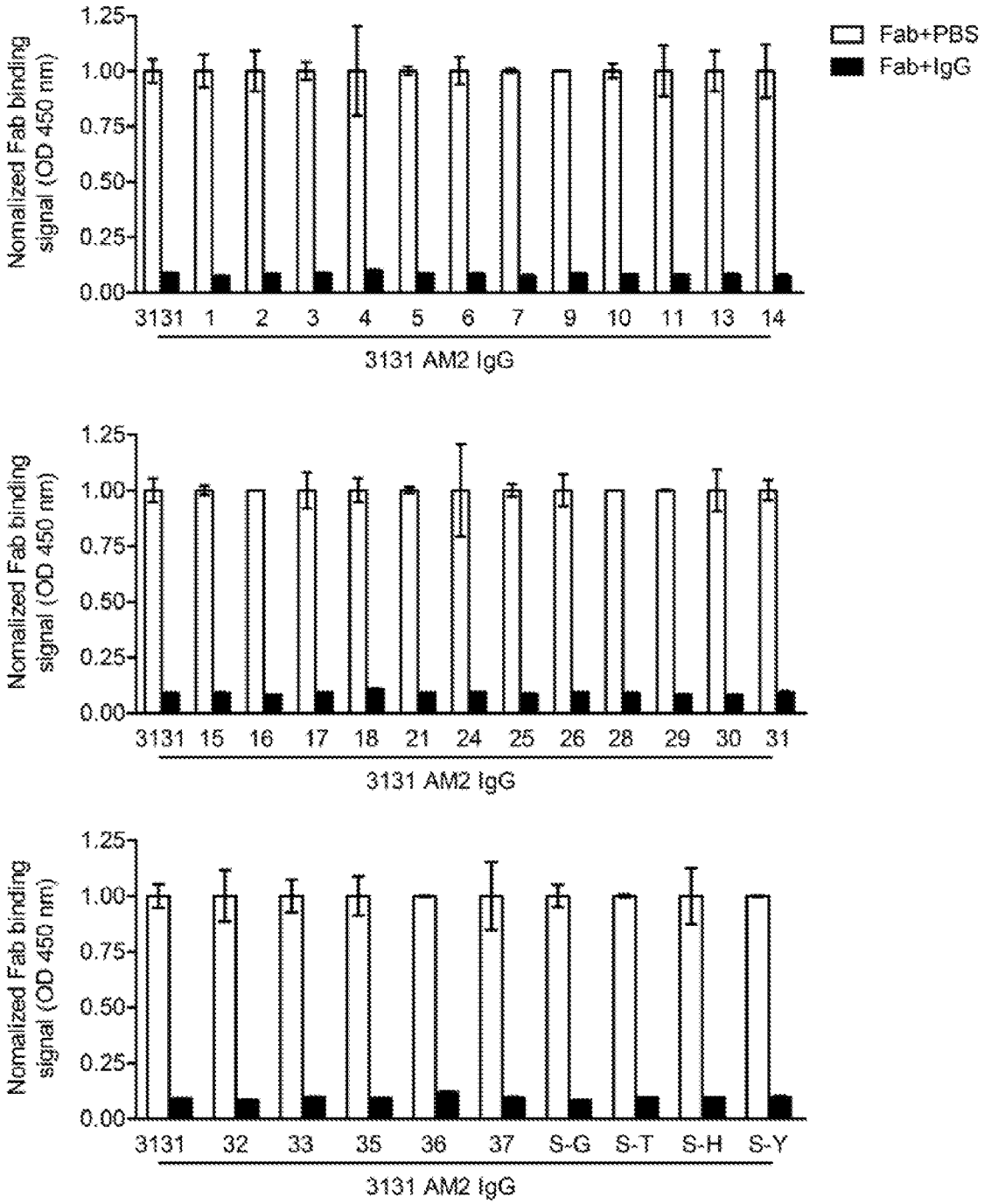

Nomalized Fab binding signal (OD 450 nm)
1.25
1.00
0.75
0.50
0.25
0.00
Fab+PBS
Fab+IgG
3131 1 2 3 4 5 6 7 9 10 11 13 14
3131 AM2 IgG
Nomalized Fab binding signal (OD 450 nm)
3131 15 16 17 18 21 24 25 26 28 29 30 31
3131 AM2 IgG
Nomalized Fab binding signal (OD 450 nm)
3131 32 33 35 36 37 S-G S-T S-H S-Y
3131 AM2 IgG

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/091936

A. CLASSIFICATION OF SUBJECT MATTER

C07K 16/28(2006.01)i; C07K 16/46(2006.01)i; A61K 39/395(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, SIPOABS, CNABS, CNKI, PubMed, ISI web of Knowledge, GenBank, STN, EBI, antibody, antigen binding fragment, CDR, heavy chain variable region, light chain variable region, IL-18R, IL-18Rβ,CD218b,interleukin-18 receptor beta, tumor, cancer, SEQ ID NOs:1-161

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DESROCHES, C.V. et al. "Monoclonal antibodies specific for the IL-18 receptor." *CELLULAR IMMUNOLOGY.*, Vol. 236, 12 September 2005 (2005-09-12), abstract, page 102, right column, paragraph 2	1-33
A	WO 2009/015284 A2 (AMGEN, INC. ET AL.) 29 January 2009 (2009-01-29) the whole document	1-33
A	"UniProtKB - O95256 (I18RA_HUMAN)" *UNIPROT.*, 01 May 1999 (1999-05-01), the whole document	1-33
A	WO 2015/032932 A1 (AB2 BIO SA) 12 March 2015 (2015-03-12) the whole document	1-33
A	US 2002/0068060 A1 (ABRAMS, J. S. ET AL) 06 June 2002 (2002-06-06) the whole document	1-33
A	WO 2012/015662 A1 (BAYLOR RESEARCH INSTITUTE ET AL.) 02 February 2012 (2012-02-02) the whole document	1-33

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2019	**27 September 2019**

Name and mailing address of the ISA/CN	Authorized officer
National Intellectual Property Administration, PRC **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088** **China**	**JIN,Chunpeng**
Facsimile No. **(86-10)62019451**	Telephone No. **86-（10）-53961947**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/091936

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/025536 A1 (F.HOFFMANN-LA ROCHE AG ET AL.) 01 March 2012 (2012-03-01) the whole document	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/091936

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed:
      ☑ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/091936

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **26-29**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 26-29 relate to a method of treating an autoimmune or inflammatory or cancer disease in a patient in need thereof. Therefore claims 26-29 relate to the treatment of diseases, and do not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). An international search is still carried out on the basis of the use of the antibody or antigen-binding fragment in the manufacture of a medicament for treating a disease.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/091936

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2009/015284	A2	29 January 2009	EA	016783	B1	30 July 2012
				CN	101835489	B	16 October 2013
				US	8540993	B2	24 September 2013
				CA	2693503	A1	29 January 2009
				PE	05182009	A1	25 April 2009
				AU	2008279127	B2	27 March 2014
				CN	101835489	A	15 September 2010
				EP	2178917	A2	28 April 2010
				US	2013034569	A1	07 February 2013
				EP	2178917	A4	28 March 2012
				KR	20100049535	A	12 May 2010
				BR	PI0813016	A2	15 December 2015
				JP	2010534478	A	11 November 2010
				TW	I436778	B	11 May 2014
				US	2011014201	A1	20 January 2011
				AU	2008279127	A1	29 January 2009
				WO	2009015284	A8	02 July 2009
				US	8257707	B2	04 September 2012
				SG	183070	A1	30 August 2012
				JP	2015015957	A	29 January 2015
				ZA	201001140	B	30 March 2011
				AR	067666	A1	21 October 2009
				US	2014093915	A1	03 April 2014
				WO	2009015284	A3	01 October 2009
				EA	201000238	A1	30 August 2010
				TW	200927167	A	01 July 2009
				IL	202833	D0	01 August 2011
WO	2015/032932	A1	12 March 2015	MX	2016002719	A	06 September 2016
				EP	3041864	A1	13 July 2016
				CL	2016000506	A1	23 September 2016
				SG	11201601717V	A	28 April 2016
				RU	2016112596	A	09 October 2017
				CN	105722858	A	29 June 2016
				JP	2016536332	A	24 November 2016
				RU	2016112596	A3	18 July 2018
				HK	1221726	A1	09 June 2017
				US	2016215048	A1	28 July 2016
				IL	244169	D0	21 April 2016
				PH	12016500425	A1	23 May 2016
				AU	2014317035	A1	10 March 2016
				CA	2922498	A1	12 March 2015
				KR	20160044045	A	22 April 2016
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