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(54) Title: ANTI-IL-1R3 ANTIBODIES FOR USE IN INFLAMMATORY CONDITIONS

(57) Abstract: The present invention relates to methods for treating medical conditions and/or disorders characterized by uncontrolled or abnormal expression of members of the IL1R3 signaling pathway such as IL-lα, IL-Iβ, IL-33, IL-36, IL1RA and/or IL1R3, as well as variants thereof. More specifically, the present invention relates to anti-IL1R3 antibodies for use in the treatment of an IL1R3-mediated inflammatory condition and/or disorder in a subject. Such conditions and disorders include but are not limited to inflammatory diseases, immune disorders, fibrotic disorders, eosinophilic disorders, infection, pain, a central nervous system disorder, an ophthalmologic disorder, Hereditary Systemic Inflammatory Diseases, and Systemic and Local Inflammatory Diseases and cancer associated chronic inflammation.

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Anti-IL-1R3 Antibodies for use in inflammatory conditions

Field of invention

The invention pertains to methods for treating medical conditions and/or disorders characterized by uncontrolled or abnormal expression of members of the IL1R3 signaling pathway such as IL-1α, IL-1ß, IL-33, IL-36, IL1RA and/or IL1R3. More specifically, the present invention relates to methods and uses of anti-IL-1R3 antibodies in inflammatory conditions and/or disorders.

Background

The interleukin 1 receptor accessory protein (IL1RAP), also called IL1R3, is a coreceptor of type 1 interleukin 1 receptor (IL1R1) and is indispensable for transmission of IL-1 signaling. Upon binding of IL-1, IL-1R1 associates with IL-1RAcP forming a functional signaling receptor complex, which stimulates NFkB activity.

IL-33, its receptor ST2, and IL-1RAcP form also a complex (IL-33/ST2/IL-1RAcP) with a similar activity in regard to NFkB activation as the IL-1β/IL-1R1/IL-1RAcP complex. IL-36 (IL-36α (IL-1F6), IL-36β (IL-1F8), and IL-36γ (IL-1F9)), their receptor IL-36R, and IL-1RAcP form also a complex (IL-36/Il-36R/IL-1RAcP) with a similar activity in regard to NFkB activation as the IL-1β/IL-1R1/IL-1RAcP complex.

The Interleukin-1 (IL-1) pathway is a cellular signaling pathway that plays a crucial role in the mammalian

inflammatory response and is associated with a wide range of immunologic, metabolic, physiological and hematopoietic activities. The IL-1 family includes three structurally related cytokines: IL-1 alpha, IL-1 beta and IL-1 receptor antagonist (IL-1 ra). Of the three, IL-1 alpha and IL-1 beta are proinflammatory agonists while IL-1 receptor antagonist (IL-1ra) functions to block IL-1 alpha and IL-1 beta activity. All known biological functions of IL-1 are mediated through the type I IL-1 R. IL-1 alpha, IL-1 beta and IL-1 ra bind the type I IL-1 R with high affinity. In contrast, IL-1 beta binds the type II IL-1R with high affinity and IL-1 alpha and IL-lra bind the type II IL-1 R with a low affinity. The type II IL-1 R has a severely truncated cytoplasmic domain and upon binding to

IL-1 does not transduce signal to a cell, but instead is involved in regulating an IL-1-mediated response by acting as a decoy receptor.

IL-1 production is triggered by infections, microbial toxins, inflammatory agents and allergic reactions. Overall
the main functions of IL-1 is to regulate the amplitude and duration of the immune and inflammatory response at the sites of inflammation or allergic immune reaction. When excess IL-1 is produced or IL-1 expression is not appropriately regulated disease states can develop. Accordingly, IL-1 has been implicated in a variety of inflammatory and immunoregulatory diseases and conditions. It has been proposed that a systemic or localized excess of IL-1 contributes to the incidence of numerous medical disorders. Further to this proposal, it has been shown that IL-1ra, which blocks IL-1 alpha and IL-1 beta activity, has varying degrees of efficacy in treating some diseases thought to be mediated by IL-1 signaling.

It has been suggested that the suppression of IL-1 might be beneficial in patients suffering from various disorders
characterized by abnormal or excessive IL-1 expression or IL-1 activity. The IL-1ra and ICE inhibitors have met with limited degrees of success as therapeutics for diseases associated with IL-1 activity. Although progress has been made in devising effective treatment for such diseases, improved medicaments and methods of treatment are needed.

Unfortunately, existing IL-1 pathway inhibitors such as Kineret, ilaris or Arcalyst have certain disadvantages which impede their therapeutic use. For example, Kineret (IL-1Ra) has a short half-life and therefore needs very frequent treatment intervals (daily). Antibodies targeting single cytokines (e.g. Ilaris) allow redundant signaling/activities of other IL-1 family cytokines to occur. In addition, IL-1 family cytokines are known to elicit both pro-inflammatory and IL-1R3-independent anti-inflammatory signaling, both of which are interfered with when targeting the cytokines or their alpha-chain receptors. In contrast, the antibodies of the present invention combine the advantages of infrequent treatment intervals, concomitant inhibition of different IL-1 family cytokine mediated signaling and specificity with regard to blocking pro-inflammatory signaling pathways.

Therefore, the present invention provides for novel and improved methods for treating conditions associated with an uncontrolled expression of members of the IL1R3 signaling pathway with the favorable features described in the following.

Summary of invention

The present invention relates to methods for treating medical conditions and/or disorders characterized by uncontrolled or abnormal expression of members of the IL1R3 signaling pathway such as IL-1α, IL-1ß, IL-33, IL-36, IL1RA and/or IL1R3, as well as variants thereof.

More specifically, the present invention relates anti-IL1R3 antibodies for use in the treatment of an IL1R3-mediated inflammatory condition and/or disorder in a subject.

Such conditions and disorders include but are not limited to inflammatory diseases, immune disorders, fibrotic disorders, eosinophilic disorders, infection, pain, a central nervous system disorder, an ophthalmologic disorder, Hereditary Systemic Inflammatory Diseases, and Systemic and Local Inflammatory Diseases and cancer associated chronic inflammation.

Definitions

The term "rabbit" according to the invention means an animal of the members of the taxonomic order Lagomorpha, which includes the families (hares and rabbits) and Ochotonidae (pikas), preferably of genus Oryctolagus.

The term "antibody" encompasses the various forms of antibody structures including, but not being limited to, whole antibodies and antibody fragments as long as it shows the properties according to the invention.

The term "rabbit monoclonal antibody "according to the invention means a monoclonal antibody produced by immunizing a rabbit and isolated from a antigen producing cell of said rabbit as well as such an antibody which is further modified, preferably a humanized antibody, a chimeric antibody, a fragment thereof, or a further genetically engineered and recombinant produced

antibody as long as the characteristic properties according to the invention are retained. Preferably the antibody is from a B cell or a rabbit hybridoma cell of said rabbit.

The term "antibody producing cell" according to the invention means a rabbit B cell which produce antibodies, preferably a B cell or rabbit hybridoma cell.

"Native antibodies" are usually heterotetrameric glycoproteins composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

"Percent (%) amino acid sequence identity" with respect to a peptide or polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software.

The term "VL (or VH) region" has the same meaning as VL (or VH) domain.

The terms "Fc receptor" or "FcR" according to the invention refers to a human receptor that binds to the Fc region of an antibody. FcRs bind IgG antibodies and include receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic

domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain (see review M. in Daeron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRIIIA (CD16a) mediaties ADCC. FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991); Capel et al, Immunomethods 4:25-34 (1994); and de Haas et al, J. Lab. CHn. Med. 126:330-41 (1995). These and all other FcRs are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al, J. Immunol. 117:587 (1976) and Kim et al, J. Immunol. 24:249 (1994)) and mediates slower catabolism, thus longer half-life.

The term "antibody effector function(s)," or "effector function" as used herein refers to a function contributed by an Fc effector domain(s) of an IgG (e.g., the Fc region of an immunoglobulin). Such function can be effected by, for example, binding of an Fc effector domain(s) to an Fc receptor on an immune cell with phagocytic or lytic activity or by binding of an Fc effector domain(s) to components of the complement system. Typical effector functions are ADCC, ADCP and CDC.

An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')2; diabodies; linear antibodies; single-chain antibody molecules (e.g. scFv); and multispecific antibodies formed from antibody fragments.

An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

"Antibody-dependent cell-mediated cytotoxicity" and "ADCC" refer to a cell- mediated reaction in which nonspecific cytotoxic cells that express FcRs (e.g. Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FCYRIII.

The term "Antibody-dependent cellular phagocytosis" and "ADCP" refer to a process by which antibody-coated cells are internalized, either in whole or in part, by phagocytic immune cells (e.g., macrophages, neutrophils and dendritic cells) that bind to an immunoglobulin Fc region.

C1q" is a polypeptide that includes a binding site for the Fc region of an immunoglobulin. C1q together with two serine proteases, C1r and C1s, forms the complex C1, the first component of the complement dependent cytotoxicity (CDC) pathway. Human C1q can be purchased commercially from, e.g. Quidel, San Diego, Calif .

The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called a, δ, ε, γ, and μ, respectively.

An "effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat, et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991).

A "variant Fc region" comprises an amino acid sequence which differs from that of a "native" or "wildtype" sequence Fc region by virtue of at least one "amino acid modification" as herein defined. The term "Fc-variant" as used herein refers to a polypeptide comprising a modification in an Fc domain. The Fc variants of the present invention are defined according to the amino acid modifications that compose them. Thus, for example, P329G is an Fc variant with the substitution of proline with glycine at position 329 relative to the parent Fc polypeptide, wherein the

numbering is according to the EU index. The identity of the wildtype amino acid may be unspecified, in which case the aforementioned variant is referred to as P329G. For all positions discussed in the present invention, numbering is according to the EU index. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody (Edelman, et al., Proc Natl Acad Sci USA 63 (1969) 78-85, hereby entirely incorporated by reference.) The modification can be an addition, deletion, or substitution. Substitutions can include naturally occurring amino acids and non- naturally occurring amino acids. Variants may comprise non-natural amino acids. Examples include U.S. Pat. No. 6,586,207; WO 98/48032; WO 03/073238; US 2004/0214988 Al; WO 05/35727 A2; WO 05/74524 A2; Chin, J.W., et al., Journal of the American Chemical Society 124 (2002) 9026-9027; Chin, J.W., and Schultz, P.G., ChemBioChem 11 (2002) 1135-1137; Chin, J.W., et al., PICAS United States of America 99 (2002) 11020-11024; and, Wang, L., and Schultz, P.G., Chem. (2002) 1-10, all entirely incorporated by reference.

The term "Fc region-containing polypeptide" refers to a polypeptide, such as an antibody or immunoadhesin (see definitions below), which comprises an Fc region.

The terms "Fc receptor" or "FcR" are used to describe a receptor that binds to the Fc region of an antibody. A FcR which binds an IgG antibody (a gamma receptor) includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain, (see review in Daeron, M., Annu. Rev. Immunol. 15 (1997) 203-234). FcRs are reviewed in Ravetch, and Kinet, Annu. Rev. Immunol 9 (1991) 457-492; Capel, et al., Immunomethods 4 (1994) 25-34; and de Haas, et al., J. Lab. Clin. Med. 126 (1995) 330-41. Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer, et al., J. Immunol. 117 (1976) 587 and Kim, et al., J. Immunol. 24 (1994) 249).

By "IgG Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an IgG antibody to form an Fc/Fc ligand complex. Fc

ligands include but are not limited to FcγRs, FcγRs, FcγRs, FcRn, Clq, C3, mannan binding lectin, mannose receptor, staphylococcal protein A, streptococcal protein G, and viral FcγR. Fc ligands also include Fc receptor homologs (FcRH), which are a family of Fc receptors that are homologous to the FcγRs (Davis, et al., Immunological Reviews 190 (2002) 123-136, entirely incorporated by reference). Fc ligands may include undiscovered molecules that bind Fc. Particular IgG Fc ligands are FcRn and Fc gamma receptors. By "Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an antibody to form an Fc/Fc ligand complex.

By "Fc gamma receptor", "FcγR" or "FcgammaR" as used herein is meant any member of the family of proteins that bind the IgG antibody Fc region and is encoded by an FcγR gene. In humans, this family includes but is not limited to FcγRI (CD64), including isoforms FcγRIA, FcγRIB, and FcγRIC; FcγRII (CD32), including isoforms FcγRIIA (including allotypes H131 and R131), FcγRIIB (including FcγRIIB-l and FcγRIIB-2), and FcγRIIc; and FcγRIII (CD 16), including isoforms FcγRIIIA (including allotypes VI 58 and F158) and FcγRIIIb (including allotypes FcγRIIB-NAl and FcγRIIB-NA2) (Jefferis, et al., Immunol Lett 82
(2002) 57-65, entirely incorporated by reference), as well as any undiscovered human FcγRs or FcγR isoforms or allotypes. An FcγR may be from any organism, including but not limited to humans, mice, rats, rabbits, and monkeys. Mouse FcγRs include but are not limited to FcγRI (CD64), FcγRII (CD32), FcγRIII (CD 16), and FCYRIII-2 (CD 16-2), as well as any undiscovered mouse FcγRs or FcγR isoforms or allotypes.

By "FcRn" or "neonatal Fc Receptor" as used herein is meant a protein that binds the IgG antibody Fc region and is encoded at least in part by an FcRn gene. The FcRn may be from any organism, including but not limited to humans, mice, rats, rabbits, and monkeys. As is known in the art, the functional FcRn protein comprises two polypeptides, often referred to as the heavy chain and light chain. The light chain is beta-2-microglobulin and the heavy chain is encoded by the FcRn gene. Unless otherwise noted herein, FcRn or an FcRn protein refers to the complex of FcRn heavy chain with beta-2-microglobulin.

An "immunoconjugate" means an antibody conjugated to one or more cytotoxic agents, such as a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin, another antibody or a radioactive isotope.

"Antibody fragments" comprise a portion of a full-length antibody, preferably the variable regions thereof, or at least the antigen binding site thereof. Examples of antibody fragments include diabodies, Fab fragments, and single-chain antibody molecules. scFv antibodies are, e.g., described in Huston, J.S., Methods in Enzymol. 203 (1991) 46-88.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of a single amino acid composition.

The term "humanized antibody" or "humanized version of an antibody" also refers to antibodies for which both heavy and light chains are humanized as a result of antibody engineering. A humanized chain is typically a chain in which the V-region amino acid sequence has been changed so that, analyzed as a whole, is closer in homology to a human germline sequence than to the germline sequence of the species of origin. Humanization assessment is based on the resulting amino acid sequence and not on the methodology per se.

The terms "specifically binding, against target, or anti-target antibody ", as used herein, refer to binding of the antibody to the respective antigen (target), measured by ELISA, wherein said ELISA preferably comprises coating the respective antigen to a solid support, adding said antibody under conditions to allow the formation of an immune complex with the respective antigen or protein, detecting said immune complex by measuring the Optical Density values (OD) using a secondary antibody binding to an antibody according to the invention and using a peroxidase-mediated color development.

The term "antigen" according to the invention refers to the antigen used for immunization or a protein comprising said antigen as part of its protein sequence. For example, for immunization a fragment of the extracellular domain of a protein (e.g. the first 20 amino acids) can be used and for detection/assay and the like the extracellular domain of the protein or the full-length protein can be used.

The term "specifically binding" or "specifically recognized" herein means that an antibody exhibits appreciable affinity for an antigen and, preferably, does not exhibit significant cross-reactivity.

"Appreciable" binding affinity includes binding with an affinity of at least 10^{-7}M, specifically at least 10^{-8}M, more specifically at least 10^{-9}M, or even more specifically at least 10^{-10}M.

An antibody that "does not exhibit significant cross-reactivity" is one that will not appreciably bind to an undesirable other protein. An antibody specific for an epitope according to the invention will, for example, not significantly cross-react with other epitopes on IL-1R3. Specific binding can be determined according to any art-recognized means for determining such binding, e.g. by competitive binding assays (e.g. ELISA).

All protein terms as used herein refers to the human proteins. If a protein from another species is meant, this is explicitly mentioned.

The term "IL-1alpha"", as used herein, refers to human IL-1 (UniProtKB P01583). The term "IL-1beta"", as used herein, refer to human IL-1beta (UniProtKB P01584). IL-1 stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity. IL-1 proteins are involved in the inflammatory response, being identified as endogenous pyrogens (UniProtKB).
The term "IL-33"", as used herein, refers to human IL-33 (UniProtKB O95760), a cytokine that binds to and signals through the IL1RL1/ST2 receptor which in turn activates NF-kappa-B and MAPK signaling pathways in target cells (UniProtKB).

The term "IL-36"", as used herein, refers to human IL-36alpha (UniProtKB Q9UHA7, IL-36beta (UniProtKB Q9NZH7) and or IL-36gamma (UniProtKB Q9NZH8). IL-36 are cytokines that bind to and signal through the IL1RL2/IL-36R receptor which in turn activates NF-kappa-B and MAPK signaling pathways in target cells linked to a pro-inflammatory response. IL-36 seems to be involved in skin inflammatory response by acting on keratinocytes, dendritic cells and indirectly on T cells to drive tissue infiltration, cell maturation and cell proliferation (UniProtKB).

The term "NFkB" as used herein, refer to human nuclear factor NF-kappa-B, which consists of p105 subunit (P19838) and p100 subunit (Q00653).

"Inhibition of NFkB" is measured according to the invention as inhibition of NFkB dependent luciferase gene expression in human cells. Such methods are e.g. described in Windheim M. et al.,

Mol. Cell. Biol. 28 (2008) 1783-1791; Huang J. et al. PNAS USA 94 (1997) 12829-12832; Xiaoxia L. et al., Mol. Cell, Biol. 19 (1999) 4643-4652. If murine NFkB is meant herein it is explicitly mentioned.

The "variable region (or domain) of an antibody according to the invention" (variable region of a light chain (VL), variable region of a heavy chain (VH)) as used herein denotes each of the pair of light and heavy chain regions which are involved directly in binding the antibody to the antigen. The variable light and heavy chain regions have the same general structure and each region comprises four framework (FR) regions whose sequences are widely conserved, connected by three complementary determining regions, CDRs. The antibody according to the invention comprises a VH region and a VL region or parts thereof, which are both together sufficient for the specific binding to the respective antigen.

The term "antigen-binding portion of an antibody" when used herein refer to the amino acid residues of an antibody which are responsible for antigen-binding. The antigen-binding portion of an antibody comprises preferably amino acid residues from the "complementary determining regions" or "CDRs". The CDR sequences are defined, and their residues are numbered, according to Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991). Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or CDR of the variable region. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

The term "cancer" as used herein may be, for example, lung cancer, non-small cell lung (NSCL) cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of

the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers.

Detailed description of the invention

As outlined in the introduction of this application, there are several difficulties in providing for suitable methods to treat inflammatory conditions that are mediated through an uncontrolled expression of members of the IL1R3 pathway. The present invention is meeting this need and provides for methods of treating, inhibiting, or ameliorating inflammatory conditions and/or disorders, including an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an ophthalmologic disorder, Hereditary Systemic Inflammatory Diseases, and Systemic and Local Inflammatory Diseases.

The present invention relates to a method of treating, inhibiting or ameliorating an inflammatory condition and/or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an antagonistic IL1R3 antibody.

In particular, the invention encompasses anti-IL1R3 antibody for use in the treatment of an IL1R3-mediated inflammatory condition and/or disorder in a subject.
Such inflammatory condition and/or disorder may be selected from the group consisting of an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an

infection, pain, a central nervous system disorder, an ophthalmologic disorder, Hereditary Systemic Inflammatory Diseases, and Systemic and Local Inflammatory Diseases.

In one aspect of the invention, the inflammatory disorder treated is an IL-1 dependent diseases. The disease can be a Systemic and Local Inflammatory Diseases such as Schnitzler Syndrome, Behçet Disease, secondary amyloidosis, Henoch-Schonlein purpura, Idiopathic recurrent pericarditis, Systemic-onset Juvenile Idiopathic Arthritis, Adult Onset Still Disease, Macrophage Activation Syndrome, Sweet's Syndrome/neutrophilic dermatoses, neutrophilic panniculitis, Erdheim-Chester/histiocytoses, SAPHO, PFAPA, Multicentric Castleman Disease, Jessner-Kanof Disease, Primary Sjoegren Syndrome Fatigue, Kawasaki Disease, Colitis in Chronic Granulomatous Disease, Hidradenitis Suppurativa, Autoimmune Inner Ear Disease, Severe Traumatic Brain Injury), or a Hereditary Systemic Inflammatory Diseases such as Familial Mediterranean fever (FMF), CAPS , TRAPSa, HIDS, PAPA, PASH, DIRA, Blau syndrome/granulomatous arthritis, mevalonate kinase deficiency, Majeed Syndrome, NLRP12 Autoinflammatory Syndrome.

In preferred aspects of the invention, the inflammatory condition is selected from the group of COPD, inflammatory skin diseases, psoriasis, generalized pustular psoriasis (GPP), Inflammatory bowel disease (IBD), asthma, atopic dermatitis, Idiopathic pulmonary fibrosis, peritonitis, rheumatoid arthritis (RA), or a metabolic rheumatic disorder associated with hyperuricemia.

In one preferred embodiment, the inflammatory condition is a metabolic rheumatic disorder associated with hyperuricemia. The metabolic rheumatic disorder can be selected from the group of gout, pseudogout, drug-induced gout and chronic active (refractory) gout.

For the treatment of said metabolic rheumatic disorders in accordance with one aspect of the invention, an IL1R3 antagonistic antibody is administered. Said IL1R3 antagonistic antibody can be administered in combination with a therapeutic agent for the treatment of gout.

It can be administered simultaneously with a therapeutic agent for the treatment of gout. But it can also be administered sequentially with a therapeutic agent for the treatment of gout.

Another aspect of the invention encompasses methods for treatment of an inflammatory condition and/or disorder, wherein the inflammatory condition is a cancer associated chronic inflammation.

The invention also relates to anti-IL1R3 antibodies for the treatment of an inflammatory condition and/or disorder, wherein the inflammatory condition is a cancer associated chronic inflammation.

The term "cancer" as used herein may be, for example, lung cancer, non-small cell lung (NSCL) cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers.

Preferably, the antibody according to the invention is used for the treatment of a cancer associated chronic inflammation wherein the cancer is selected from the group consisting of pancreatic cancer, liver cancer, lung cancer (associated with inflammation caused by asbestos, infections, smoking, silica), non-small-cell-lung cancer, colorectal cancer/colitis-associated cancer (associated with Inflammatory bowel disease), stomach cancer, gastric cancer, chronic gastritis associated gastric cancer, estrogen-receptor-positive breast cancer, head and neck squamous cell carcinoma, Mesothelioma, Gall bladder cancer (chronic cholecystitis associated), ovarian cancer, bladder cancer, prostate cancer, E.coli-infection associated prostate cancer, Thyroid cancer, Hodgkin disease, MALT lymphoma, salivary gland cancer, melanoma, endometriosis associated endometrial carcinoma, Barrett's esophagitis associated Esophageal cancer.

Preferably, the cancer is breast cancer, colon cancer, lung cancer, pancreatic cancer, liver cancer, non-small-cell-lung cancer, colorectal cancer, stomach cancer, gastric cancer, estrogen-receptor-positive breast cancer, head and neck squamous cell carcinoma, Mesothelioma, Gall bladder cancer, ovarian cancer, bladder cancer, prostate cancer, Thyroid cancer, Hodgkin disease, MALT lymphoma, salivary gland cancer, or melanoma.

The antibodies of the invention can be used for treating a cancer associated chronic inflammation as some tumors are caused or promoted by tumor micro-environment cells secreting inflammatory cytokines such as IL-1α, IL-1ß, IL-33, IL-36. In some instances, expression of such cytokines results in the formation of tumor resistance.

Therefore, in one aspect of the invention, the antibody is used for the treatment of subjects, wherein the subjects comprise a tumor, such as a solid tumor, and show tumor resistance or insufficient response to cytotoxic, cytostatic or targeted/immunotherapy. Preferably, the subjects are human subjects, e.g. cancer patients.

A concomitant or sequential use of cytokine inhibitors and anti-cancer compounds significantly improves the response rate of such treatments or can break tumor resistance.

The present invention therefore also encompasses a method for the treatment of a subject, wherein the subject is characterized in being resistant or showing insufficient response to treatment with one or more cytotoxic, cytostatic or targeted anti-cancer agents.

In one aspect of this invention, said IL1R3 antibody is administered in combination with one or more cytotoxic, cytostatic or targeted anti-cancer agents.

In one aspect of the invention, said IL1R3 antagonistic antibody is administered simultaneously with one or more cytotoxic, cytostatic or targeted anti-cancer agents. In another aspect, the IL1R3 antagonistic antibody is administered sequentially with one or more cytotoxic, cytostatic or targeted anti-cancer agents.

In the latter case, it is preferred that the antibody is administered after treatment with one or more cytotoxic, cytostatic or targeted anti-cancer agents.

The cytotoxic or cytostatic anti-cancer agents according to the invention can be taxanes, anthracyclins, alkylating agents, Histone Deacetylase Inhibitors, Topoisomerase inhibitors, kinase inhibitors, nucleotide analogs, peptide antibiotics, and platinum-based agents.

Preferably the targeted anti-cancer agents are used in targeted therapy and selected from one of the following, or combinations thereof: anti-EGFR compounds such as cetuximab, gefitinib, erlotinib, lapatinib, panitumumab, and anti-HER2 compounds such as trastuzumab, ado-trastuzumab emtansine, pertuzumab.

It is further preferred that the targeted anti-cancer agents are targeted checkpoint inhibitors. These can be but are not limited to: anti-PD1 compounds such as pembrolizumab, and nivolumab, and anti-PDL1 compounds such as atezolizumab, Avelumab, and Durvalumab, and anti-CTLA-4 compounds such as Ipilimumab and Tremelimumab.

The present invention provides for a significantly improved response rate to targeted cancer therapy as a broad spectrum of the inhibition of cytokine induced signaling is achieved. Such an activity in cancer indications is not achieved through a direct depletion activity of cancer cells (as done by several compounds of prior art) but through the inhibition of the cancer associated inflammation by modulating IL1R3 signaling pathways.

The antibodies of the present invention provide for a very advantageous activity profile because they enable the effective inhibition of cancer associated chronic inflammation and, at the same time, avoid undesired side effects, because they do not affect the viability of targeted cells that express IL-1R3.

The present invention therefore provides for several advantages over other IL-1 family targeting therapies. The commercially compound Kineret (IL-1Ra) has a short half-life and very frequent treatment intervals (daily). Antibodies targeting single cytokines (e.g. Ilaris) allow redundant signaling/activities of other IL-1 family cytokines to occur. In addition, IL-1 family cytokines are known to elicit both pro-inflammatory and IL-1R3-independent anti-inflammatory signaling, both

of which are interfered with when targeting the cytokines or their alpha-chain receptors. In contrast, the antibodies of the present invention combine the advantages of infrequent treatment intervals, concomitant inhibition of different IL-1 family cytokine mediated signaling and specificity with regard to blocking pro-inflammatory signaling pathways.
The antibodies as described herein are preferably monoclonal antibodies with high affinity, high specificity, and potent neutralizing activity against IL-1R3. The present invention therefore also encompasses IL-1R3 antibody, with high affinity and specificity for IL-1R 3, with potent IL-1R3 neutralizing activity, and improved stability.

In one preferred embodiment of the invention, the antibodies have reduced effector functions. Preferably, the antibodies according to the invention show reduced or no Fcγ-receptor signaling. Further preferred, the antibody does not induce ADCC.

It is another aspect of the invention that the anti-IL1R3 antibodies according comprises at least amino acid substitutions L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region or a corresponding functional mutation in another organism.

In one embodiment of the invention, the anti-IL1R3 antibody comprises

a) a heavy chain variable region (VH) comprising the complementary determining regions comprising CDR-H1, CDR-H2, and CDR-H3

   wherein the CDR-H1 region comprises an amino acid sequence selected from the group of SEQ ID NO: 69 - 85, and 178

   wherein the CDR-H2 region comprises an amino acid sequence selected from the group of SEQ ID NO: 86 - 102, and 179

   and wherein the CDR-H3 region comprises an amino acid sequence selected from the group of SEQ ID NO: 103 – 119 and 180; and

b) a light chain variable region (VL) comprising the complementary determining regions comprising CDR-L1, CDR-L2, and CDR-L3

   wherein the CDR-L1 region comprises an amino acid sequence selected from the group of SEQ ID NO: 120-136 and 181,

wherein the CDR-L2 region comprises an amino acid sequence selected from the group of SEQ ID NO: 137-153 and 182, and

wherein the CDR-L3 region comprises an amino acid sequence selected from the group of SEQ ID NO: 154-170, and SEQ ID NO: 175 and 183.

In one embodiment, said antibody of the invention comprises a substitution at position 2 of CDR-L3. Said substitution may be a cysteine to serine substitution.

In one aspect of the invention, the subject is a human subject and the antibody comprises

a) a heavy chain variable region (VH) comprising the complementary determining regions comprising CDR-H1, CDR-H2, and CDR-H3

wherein the CDR-H1 region comprises an amino acid sequence selected from the group of SEQ ID NO: 69 – 85,

wherein the CDR-H2 region comprises an amino acid sequence selected from the group of SEQ ID NO: 86 – 102,

and wherein the CDR-H3 region comprises an amino acid sequence selected from the group of SEQ ID NO: 103 – 119; and

b) a light chain variable region (VL) comprising the complementary determining regions comprising CDR-L1, CDR-L2, and CDR-L3

wherein the CDR-L1 region comprises an amino acid sequence selected from the group of SEQ ID NO: 120-136,

wherein the CDR-L2 region comprises an amino acid sequence selected from the group of SEQ ID NO: 137-153, and

wherein the CDR-L3 region comprises an amino acid sequence selected from the group of SEQ ID NO: 154-170, and SEQ ID NO: 175.

In another aspect of the invention, the subject is a mouse and the antibody comprises

a) a heavy chain variable region (VH) comprising the complementary determining regions comprising CDR-H1, CDR-H2, and CDR-H3

wherein the CDR-H1 region comprises the amino acid sequence of SEQ ID NO: 178,

wherein the CDR-H2 region comprises the amino acid sequence of SEQ ID NO: 179,

and wherein the CDR-H3 region comprises the amino acid sequence of SEQ ID NO: 180; and

b) a light chain variable region (VL) comprising the complementary determining regions comprising CDR-L1, CDR-L2, and CDR-L3

wherein the CDR-L1 region comprises the amino acid sequence of SEQ ID NO: 181,

wherein the CDR-L2 region comprises the amino acid sequence of SEQ ID NO: 182, and

wherein the CDR-L3 region comprises an amino acid sequence of SEQ ID NO: 183.

In other embodiments of the invention, the antibody comprises a heavy chain variable (VH) region that is at least 90 % identical to a VH region selected from the group consisting of VH regions of SEQ ID NO: 1 to 34 and 173 and 176, and a light chain variable (VL) region that is at least 90% identical to a VL region selected from the group consisting of VL regions of SEQ ID NO: 35 to 68 and 174 and 177.

In one embodiment to the invention, the antibody is a humanized antibody.
In such embodiments, the subject is a human subject and the antibody comprises a heavy chain variable (VH) region that is at least 90 % identical to a VH region selected from the group consisting of VH regions of SEQ ID NO: 1 to 34 and 173, and a light chain variable (VL) region that is at least 90% identical to a VL region selected from the group consisting of VL regions of SEQ ID NO: 35 to 68 and 174.

In another embodiment, the subject is a mouse and the antibody comprises a heavy chain variable (VH) region that is at least 90 % identical to the VH region of SEQ ID NO: 176, and a light chain variable (VL) region that is at least 90% identical to the VL region of SEQ ID NO: 177.

The antibodies according to the invention are in one embodiment, antibodies that bind specifically to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, and may comprise a heavy chain variable (VH) region that is at least 60% identical, preferably at least 70% identical, more preferably at least 80% identical, more preferably at least 90 % identical to a VH region selected from the group consisting of VH regions of SEQ ID NO: 1 to 34 and 173 and 176.

In one embodiment, said antibodies comprise a heavy chain variable region (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from the group of VH sequences according to the invention.

In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, whereby the antibody retains the ability to bind specifically according to the invention to the respective antigen.

The present invention also relates to an antibody that specifically binds to IL-1R3 or a fragment or derivative thereof and contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, and comprises a light chain variable (VL) region that is least 60% identical, preferably at least 70% identical, more preferably at least 80% identical, more preferably at least 90% identical to a VL region selected from the group consisting of VL regions of SEQ ID NO: 35 to 68 and 174 and 177.

Said antibody may comprise a light chain variable region (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of the VL sequences according to the invention.

In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, whereby the antibody retains the ability to bind specifically to the respective antigen.

In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in said VL sequences. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs). The invention also comprises affinity matured antibodies which can be produced according to methods known in the art. Marks et al. Bio/Technology 10:779-783 (1992) describes affinity maturation by VH and VL domain shuffling. Random mutagenesis of CDR and/or framework residues is described by: Barbas et al., Proc Nat. Acad. Sci, USA 91: 3809-3813 (1994); Schier et al., Gene 169: 147-155 (1995); Yelton et al., J.

Immunol. 1 55:1994-2004 (1995); Jackson et al., J. Immunol. 1 54(7):3310-9 (1995); and Hawkins et al., J. Mol. Biol. 226:889-896 (1992) and WO2010108127.

In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in each of said VH or VL sequences. In one embodiment, the antibody of the invention comprises a substitution at position 90 of the VH or VL sequence. It is preferred that the amino acid at position 90 is substituted by a serine. This substitution is preferably at position 90 of the light chain variable region (VL). In a preferred embodiment, the cysteine at position 90 of SEQ ID. NO: 62 is substituted by a serine. However, the antibodies of this invention are not limited to an amino acid substitution at position 90 but may comprise any substitution, deletion or insertion that leads to a functional antibody possessing the properties of the antibodies of this invention. Therefore, the VL and VH sequences of the antibodies of this invention may also comprise further mutations at different positions.
In certain embodiments, substitutions, insertions, or deletions occur in regions outside the CDRs (i.e., in the FRs).

In other embodiments, the substitutions, insertions, or deletions occur in regions inside the CDRs. In one preferred embodiment, the antibody of the invention comprises a substitution at position 2 of CDR-L3. It is preferred that this substitution is cysteine to serine. In one embodiment, said substitution is in SEQ ID NO: 164.

The present invention also encompasses an antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence selected from the group of SEQ ID NO: 1 to 34 and 173 and 176.

Preferably, the heavy chain variable region (VH) sequence is SEQ ID NO:1, alternatively SEQ ID NO:2, or SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28,

or SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33,or alternatively SEQ ID NO:34 or 173 and 176.

Furthermore, the invention relates to methods in which said antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, comprises a light chain variable region (VL) comprising an amino acid sequence selected from the group of SEQ ID NO: 35 to 68 and 174 and 177.

Even more preferred, the light chain variable region (VL) sequence is SEQ ID NO:35, or SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67 , or alternatively SEQ ID NO:68 or 174 or 177.

A antibody according to the invention that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, also comprises a VH region and a VL region comprising the respective CDR1, CDR2 and CDR3 regions of an antibody selected from the group consisting of MAB-15-0139, MAB-15-0106MAB-15-0108, MAB-15-0110, MAB-15-0117, MAB-15-0121, MAB-15-0140, MAB-15-0115, MAB-15-0125, MAB-15-0119, MAB-15-0109, MAB-15-0097, MAB-15-0135, MAB-15-0133, MAB-15-0107, MAB-15-0128, MAB-15-0116, MAB-16-0004, MAB-16-0009, MAB-16-0028, MAB-16-0031, MAB-16-0043, MAB-16-0049, MAB-16-0045, MAB-16-0040, MAB-16-0036, MAB-16-0046, MAB-16-0030, MAB-16-0021, MAB-16-0019, MAB-16-0015, MAB-16-0027, MAB-16-0048, MAB-16-0041, MAB-16-0149, MAB-16-0150, MAB-16-0531.

In one embodiment, the antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, comprises SEQ ID NO.: 1 and 35, or SEQ ID NO.: 2 and 36. An antibody according to the invention may also comprise SEQ ID NO.: 3 and 37, or SEQ ID NO.: 4 and 38, or SEQ ID NO.: 5 and 39., or SEQ ID NO.: 6 and 40., or SEQ ID NO.: 7 and 41., or SEQ ID NO.: 8 and 42, or SEQ ID NO.: 9

and 43, or SEQ ID NO.: 10 and 44, or SEQ ID NO.: 11 and 45, or SEQ ID NO.: 12 and 46. Alternatively, an antibody according to the invention comprises SEQ ID NO.: 13 and 47, or SEQ ID NO.: 14 and 48, or SEQ ID NO.: 15 and 49, or SEQ ID NO.: 16 and 50, or SEQ ID NO.: 17 and 51, or SEQ ID NO.: 18 and 52, or SEQ ID NO.: 19 and 53, or SEQ ID NO.: 20 and 54, or SEQ ID NO.: 21 and 55, or SEQ ID NO.: 22 and 56, or SEQ ID NO.: 23 and 57, or SEQ ID NO.: 24 and 58, or SEQ ID NO.: 25 and 59, or SEQ ID NO.: 26 and 60, or SEQ ID NO.: 27 and 61.

Alternatively, an antibody according to the invention comprises SEQ ID NO.: 28 and 62, or SEQ ID NO.: 29 and 63, or SEQ ID NO.: 30 and 64, or SEQ ID NO.: 31 and 65, or SEQ ID NO.: 32 and 66, or SEQ ID NO.: 33 and 67, or SEQ ID NO.: 34 and 68, or SEQ ID NO.: 173 and 54, or SEQ ID NO.: 28 and 174, or SEQ ID NO.: 176 and 177.

Most preferably, the antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity comprises the constant region sequences CR-H (SEQ ID NO. 172) and CR-L (SEQ ID NO. 171) and a VH region selected from the group of SEQ ID NO: 1 to 34 and 173 and 176 and a VL region selected from the group of SEQ ID NO: 35 to 68 and 174 and 177.

The antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, also comprises the constant region sequences CR-H (SEQ ID NO. 172) and CR-L (SEQ ID NO. 171) and a VH region and a VL region comprising the respective CDR1, CDR2 and CDR3 regions of an antibody selected from the group consisting of MAB-15-0139, MAB-15-0106, MAB-15-0108, MAB-15-0110, MAB-15-0117, MAB-15-0121, MAB-15-0140, MAB-15-0115, MAB-15-0125, MAB-15-0119, MAB-15-0109, MAB-15-0097, MAB-15-0135, MAB-15-0133, MAB-15-0107, MAB-15-0128, MAB-15-0116, MAB-16-0004, MAB-16-0009, MAB-16-0028, MAB-16-0031, MAB-16-0043, MAB-16-0049, MAB-16-0045, MAB-16-0040, MAB-16-0036, MAB-16-0046, MAB-16-0030, MAB-16-0021, MAB-16-0019, MAB-16-0015, MAB-16-0027, MAB-16-0048, MAB-16-0041, MAB-16-0149 and MAB-16-150, and MAB-16-0531.

According to the preferred therapeutic application of the antibodies according to the invention, the effector functions (such as ADCC) of the antibodies of the invention are reduced or lacking. In

contrast to other antibodies of prior art, such as CAN04 (e.g. WO 2015/132602 A1), the antibodies of the invention avoid unwanted depletion of immune cells.

Preferably, the antibodies according to the invention show reduced or no Fcγ-receptor signaling.

Therefore, the invention also relates to an antibody, wherein said antibody comprises at least amino acid substitutions at L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region, or a functional equivalent mutation.

In one embodiment according to the invention, the antibody is a humanized $IgG1_{LALA}$ antibody.
In another embodiment, the antibody is a mouse-$IgG2a_{LALA}$ antibody.

In one embodiment according to the invention, the antibody inhibits IL-1R3 induced NFkB activity.

In another embodiment, the antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, binds to the same epitope as an antibody selected from the group of antibodies MAB-15-0139, MAB-15-0106, MAB-15-0108, MAB-15-0110, MAB-15-0117, MAB-15-0121, MAB-15-0140, MAB-15-0115, MAB-15-0125, MAB-15-0119, MAB-15-0109, MAB-15-0097, MAB-15-0135, MAB-15-0133, MAB-15-0107, MAB-15-0128, MAB-15-0116, MAB-16-0004, MAB-16-0009, MAB-16-0028, MAB-16-0031, MAB-16-0043, MAB-16-0049, MAB-16-0045, MAB-16-0040, MAB-16-0036, MAB-16-0046, MAB-16-0030, MAB-16-0021, MAB-16-0019, MAB-16-0015, MAB-16-0027, MAB-16-0048, MAB-16-0041, MAB-16-0149, MAB-16-150 and MAB-16-0531.

The antibodies according to the invention have the advantage to be very potent when it comes to binding to their target. They exhibit a strong binding capacity to their antigen, IL1R3, but not to other receptors. The binding properties of the antibodies were studied in biochemical enzyme-linked immunosorbent assays (ELISA) and cell binding analysis (flow cytometry) and are exemplified in Figures 2, 6 and 7.

Preferred antibodies according to the invention, show a half maximal effective concentration (EC50) of less than 30ng/ml, preferably of less than 20ng/ml. In other embodiments, they show an

EC50 of less than 15ng/ml, 10ng/ml or of less than 5ng/ml. A preferred antibody according to the invention shows an EC50 of 16.3ng/ml in a biochemical ELISA experiment (cf. Figure 7).

The antibodies according to the invention also show a very strong binding to their antigen in experiments in which human IL1R3 is expressed in different cell lines while the antibodies do not bind cell lines not expressing human IL1R3 (e.g. NIH-3T3, cf. Figure 5).

In the IL1R3 high-expressing cell line SK-MEL-30 (cf. Fig. 6, Example 4) the antibodies exhibit an EC50 of preferably less than 400 ng/ml, more preferably less than 350 ng/ml, or less than 310 ng/ml.

In one preferred embodiment encompassed by the invention, the antibody according to the invention inhibits IL-1alpha and/or IL-1beta stimulated NFkB activity. Figures 3, 4 and 8 exemplify the strong inhibitory activity of the antibodies according to the invention.

In one embodiment, the antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, inhibits IL-1alpha stimulated NFkB activity.

In another embodiment, the antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity inhibits IL-1beta stimulated NFkB activity.

It is preferred that an antibody according to the invention inhibits IL-1beta stimulated NFkB activity in HEK293T/17-FR cells with an EC50 of less than 100 ng/ml, preferably of less than 95 ng/ml, 85 ng/ml, 75 ng/ml, 65 ng/ml, 55ng/ml, 45 ng/ml, 35 ng/ml, 25 ng/ml, 20ng/ml and most preferred of less than 15 ng/ml (e.g. cf. Fig. 3).

It is further preferred that an antibody according to the invention inhibits IL-1alpha stimulated NFkB activity with an EC50 of less than 1000 ng/ml, preferably of less than 500 ng/ml, 300 ng/ml, 200 ng/ml, and most preferred of less than 100 ng/ml (e.g. cf. Fig.8) in A549-NFkB-RE-Luc cells.

It is further preferred that an antibody according to the invention inhibits IL-1beta stimulated NFkB activity with an EC50 of less than 700 ng/ml, preferably of less than 600 ng/ml, 300 ng/ml, 200 ng/ml, 100 ng/ml and most preferred of less than 50 ng/ml in A549-NFkB-RE-Luc cells (e.g. cf. Fig.8).

The invention also encompasses a antibody, wherein said antibody inhibits NFkB activity stimulated by a complex selected from the group consisting of IL-1β/IL-1R1/IL-1RAcP, IL-1α/IL-1R1/IL-1RAcP IL-33/ST2/IL-1RAcP, and/or IL-36/Il-36R/IL-1RAcP.

Moreover, an antibody according to invention inhibits in a concentration of 10 µg/ml (rabbit IgG isotype has a molecular weight of 150 KD) NFkB expression in A549-NFkB-RE-Luc cell lysates (Steady-Glo™ Luciferase Assay System; Promega; Cat. No. E2510) stimulated with 0.1 ng/ml human IL-1alpha, human IL-1beta, IL-33 and/or IL-36 (molecular weight see UniProtKB/Swiss-Prot), for 50% or more, preferably for 70% or more, preferably for 80% or more preferably for 90% and more, and more preferably for 95% or more, related to the same assay without said antibody according to the invention.

In one embodiment, the antibody according to the invention inhibits IL-1alpha, IL-1beta, IL-33, and/or IL-36, respectively, stimulated luciferase activity in HEK 293T/17 cells (HEK 293T/17-FR cells transfected with luciferase under control of NF-kB reporter gene)), HEK-Blue-IL33™ cells (Invivogen) or HEK-293/17-IF cells.

Preferably, said IL-1alpha, stimulated luciferase activity is inhibited by 50% or more, preferably by 70% or more, preferably by 80% or more, preferably by 90% and more, and more preferably by 95% or more. Preferably, said IL-1alpha, stimulated luciferase activity is inhibited by 95%.

Preferably, said IL-1beta, stimulated luciferase activity is inhibited by 50% or more, preferably by 70% or more, preferably by 80% or more, preferably by 90% and more, and more preferably by 95% or more. Preferably, said IL-1beta, stimulated luciferase activity is inhibited by 95%.

Preferably, said IL-33, stimulated luciferase activity is inhibited by 50% or more, preferably by 70% or more, preferably by 80% or more, preferably by 90% and more, and more preferably by 95% or more. Preferably, said IL-33, stimulated luciferase activity is inhibited by 95%.

Preferably, said IL-36, stimulated luciferase activity is inhibited by 50% or more, preferably by 70% or more, preferably by 80% or more, preferably by 90% and more, and more preferably by 95% or more. Preferably, said IL-36, stimulated luciferase activity is inhibited by 95%.

Furthermore, the antibodies according to the invention inhibit human IL-1a and IL-1b mediated IL-6 release and are superior to polyclonal antibodies. This potent inhibitory activity is shown and exemplified in Fig. 9. In these experiments, the EC50 values demonstrate that humanized anti-IL-1R3 IgG1-LALA antibodies are superior to that of goat-anti-human-IL1-R3 polyclonal antibody AF676 (R&D Systems). In preferred embodiments of the invention, the antibodies inhibit human IL-a mediated IL-6 release with an EC50 of less than 2500 ng/ml, preferably of less than 1500 ng/ml, less than 1000 ng/ml, less than 600 ng/ml, less than 400 ng/ml, or less than 300 ng/ml. It is also preferred that the antibodies of the invention inhibit human IL-b mediated IL-6 release with an EC50 of less than 500 ng/ml, preferably of less than 400 ng/ml, less than 300 ng/ml, less than 200 ng/ml, or less than 150 ng/ml.

In another embodiment according to the invention, the antibodies inhibit human IL-33 mediated NfkB-signaling. Fig. 10 exemplifies the inhibitory activity of selected antibodies according to the invention in HEK-Blue-IL33™ cells and demonstrates the superiority over polyclonal antibodies. In preferred embodiments of the invention, the antibodies inhibit human IL-33 mediated NfkB-signaling with an EC50 of less than 20000 ng/ml, preferably of less than 18000 ng/ml, less than 3000 ng/ml, less than 1000 ng/ml, less than 500 ng/ml, or less than 400 ng/ml.

The antibodies of the invention may also inhibit human IL-36 mediated NfkB-signaling (Fig. 11). Preferably, they inhibit human IL-36 mediated NfkB-signaling at an EC50 of less than 100 ng/ml, preferably at less than 50 ng/ml, less than 40 ng/ml, less than 30 ng/ml, less than 20 ng/ml, or less than 15 ng/ml.

Strikingly, the inventors found that the antibodies according to the invention inhibit cytokine release mediated by various different stimuli. For example, the antibodies inhibit cytokine release mediated by IL-1a, IL-33 and IL-36a. Results of a selected antibody are shown in Fig. 12. For example, the antibody MAB-16-0030 inhibits cytokine release mediated by all three stimuli, while IL-1Ra affects only IL-1a mediated cytokine release.

Diseases associated with acute or chronic inflammation are maintained or establish by the action of multiple cytokines either at the same time or consecutively. Early "alarmins" such as IL-1a and IL-33 may trigger other cytokines including IL-1b and IL-36 to establish a strong inflammatory environment. Therefore, the concomitant inhibition of signaling mediated by multiple cytokines exerts efficacious control of inflammatory processes. It is a key aspect of the antibodies of the invention that they inhibit multi-cytokine signaling via the blockage of the IL1R3 receptor.

Binding of antibodies to immune cells may result in cell depleting and deleterious effects, e.g. by direct induction of apoptotic signaling pathways, stimulation of excessive cytokine release or antibody-dependent cellular cytotoxicity (ADCC).

Importantly, the antibodies according to the invention do not affect the viability of immune cells. For example, they do not affect the viability of human peripheral blood mononuclear cells (PBMCs) and they do not induce IL-6 release in PBMCs (cf. Fig. 13).

The antibodies according to the invention, do not only inhibit the functional activation of cytokine release in different cell lines as described above, but also in PMBCs or whole blood cells from donors. They inhibit cytokine release mediated by different specific or complex stimuli. For example, they inhibit activation of PBMCs stimulated with LPS, heat-inactivated *Candida albicans*, IL-12/IL-33 or anti-CD3/CD28 antibodies (cf. Fig. 14 and 15).

Also, in one embodiment, the anti-IL-1R3 IgG1-LALA antibodies according to the invention are able to inhibit release of IFNg, IL-6, TNF-a, IL-13, IL-17 and IL-10 in mixed lymphocyte reactions (cf. Fig. 16).

The method of the present invention also encompasses the administering to a patient a pharmaceutically effective amount of the antibody, or derivative or fragment thereof according to the invention in form of a pharmaceutical composition.
Such a pharmaceutically composition may comprise a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody that specifically binds to the IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, according to the invention.

As used herein, "pharmaceutical carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g. by injection or infusion).

A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. To administer a compound of the invention by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Pharmaceutical carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin. Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional

methods known to those of skill in the art. Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

In another aspect, the present invention relates to an antibody that specifically binds to the mouse-IL-1R3 receptor or a fragment or derivative thereof, wherein the antibody comprises a heavy chain variable (VH) region that is at least 90 % identical to a VH region of SEQ ID NO: 176, and a light chain variable (VL) region that is at least 90% identical to a VL region of SEQ ID NO: 177.

Preferably, said antibody comprises a heavy chain variable region (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from the group of VH sequences according to the invention.

In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, whereby the antibody retains the ability to bind specifically according to the invention to the respective antigen.

In another aspect of the invention, said antibody comprises a light chain variable region (VL) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from the group of VL sequences according to the invention.

In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, whereby the antibody retains the ability to bind specifically according to the invention to the respective antigen.

It is preferred that said antibody that specifically binds to the mouse-IL-1R3 receptor or a fragment or derivative thereof, has reduced or is lacking its effector functions.

Preferably, the antibodies according to the invention show reduced or no Fcγ-receptor signaling. It is further preferred that they do not induce ADCC.

In one embodiment, the antibody of the invention that specifically binds to the mouse-IL-1R3 receptor or a fragment or derivative thereof, is mouse IgG2a with mutations L234A and L235A in its FC part (amino acid positions according to EU numbering index).

Another aspect of the invention relates to an antibody that specifically binds to the mouse-IL-1R3 receptor or a fragment or derivative thereof, for use in pre-clinical studies. Such studies can be carried out in animal models, preferably in murine disease models. Such model systems include but are not limited to monosodium urate crystal (MSU)-induced mouse peritonitis model, Serum transfer induced rheumatoid arthritis, collagen-induced arthritis, antibody- induced arthritis, collagen antibody-induced arthritis, K/BxN antibody transfer arthritis, imiquimod-induced inflammatory skin disease/psoriasis, Epidermolysis bullosa acquisita model, Thioglycollate induced peritonitis, Immunecomplex induced peritonitis, bleomycin induced lung fibrosis, xenotranplantation psoriasis, tobacco smoke–induced lung inflammation COPD, tracheal instillation of elastase COPD, Fluorescein isothiocyanate (FITC) induced lung injury/fibrosis, Radiation-Induced Fibrosis, Silica induced lung fibrosis, asbestos fibre induced lung fibrosis, DSS induced colitis, Trinitrobenzene Sulfonic Acid induced Colitis, Oxazolone induced Colitis, Adoptive Transfer Colitis, house dust mite (HDM), cockroach, or Alternaria alternate induced asthma, ovalbumin induced asthma, papain-induced lung inflammation, epicutaneous sensitization atopic dermatitis model (ovalbumin, House dust mite (HDM), Hapten, S.aureus), xenograft or patient-derived-xenograft tumor growth models using immunocompromised or humanized mice, grafting of syngeneic tumors, chemical induced skin tumor models, DSS-induced colorectal tumor models.

Preferably, the antibody is used in the monosodium urate crystal (MSU)-induced mouse peritonitis model.

Examples

The following examples are used in conjunction with the figures and tables to illustrate the invention.

Example 1: Human-IL-1R3 biochemical ELISA

Assay Principle:

NUNC Maxisorp 384well microtiter plates are coated with Fc-tagged human IL-1R3. After a blocking process, specific antibodies from B-cell supernatants bind to the antigen and are then detected by a POD-labeled antibody. Samples are tested 1:2 diluted.

Materials:

Plates: 384well NUNC Maxisorp plates; Cat. No. 464718

Proteins: Fc-tagged human IL-1R3 (Conc. 1,5mg/ml; Assay Conc. 0,5µg/ml)

Standard Ab: P013-02 (Conc. 1mg/ml; Start Assay Conc. 2µg/ml)

Detection Ab: Anti-rabbit IgG, peroxidase-linked species-specific whole antibody (from donkey) (ECL); GE; Cat. No. NA9340; assay dilution: 1:5000

PBS: Buffers in a Box, Premixed PBS Buffer, 10x; Roche Applied Sciences; Cat. No. 11666789001

BSA: Bovine Serum Albumin Fraction V from bovine serum; Roche Applied Sciences; Cat. No. 10735086001

Tween 20: Tween 20; Carl Roth; Cat. No. 9127.2

TMB: TMB Solution; Life Technologies; Cat. No. SB02

HCl: 1M Titripur Hydrochloric Acid; Merck; Cat. No. 1090571000

ELISA Buffer: PBS, 0.5% BSA, 0.05% Tween

Wash Buffer: PBS, 0.1% Tween

Block Buffer: PBS, 2% BSA, 0.05% Tween

Procedure:

1. Add 12.5µL Fc-tagged human IL-1R3 (0,5µg/ml) in PBS to a 384well NUNC Maxisorp plate and incubate for 1h at RT.
2. Wash 3x with 90µl Wash Buffer.
3. Add 90µL Blocking buffer to each well and incubate for 1h at RT.
4. Wash 3x with Wash Buffer.
5. Add 12.5µL antibody in Elisa Buffer and incubate for 1h at RT.
6. Wash 3x with Wash Buffer.
7. Add 12.5µL 1:5000 POD-Antibody in Elisa Buffer and incubate for 1h at RT.
8. Wash 6x with Wash Buffer.
9. Add 15µL TMB.
10. Add 15µL HCl after sufficient development.
11. Read absorbance at 450nm/620nm.

Example 2: Characterization of h-IL-1R3-specific antibodies inhibiting hIL-1R3-Receptor by Luciferase Reporter experiment

Assay Principle:

293T/17-FR cells, which express a NF-kB-RE firefly luciferase reporter, are seeded into Poly-D-Lysin-Cell culture plates. After stimulation with IL-1b the 293T/17-FR lysate is tested for activated NF-kB using the Steady-Glo Luciferase Assay Kit. Supernatants with functional antibodies bind to hIL-1R3 and inhibit the NF-kB activation, which is shown in low signal.

Materials:

Plates:	Cell plate: 384well PDL Costar Cell Culture plate; Cat. No. 3844
Assay plate:	384well lumitrac white- plate; Corning; Cat. No. 3572
Cells:	293T/17-FR; assay conc. 250.000cells/ml
Proteins:	IL-1b (Conc. 0,03mg/ml; Assay Conc. 115pg/ml; Working Conc. 230pg/ml)
Standard Ab:	P013_06 (Conc. 0,2mg/ml; Start Working Conc. 6µg/ml)
Kit:	Steady-Glo Luciferase Assay System; Promega; Cat. No. E2510
Cell-Medium:	DMEM Medium; PAN Biotech; Cat. No. P04-04510
FCS:	Fetal Bovine Serum, HyClone; Thermo; Cat. No. St30070.03

293T/17-FR Medium: DMEM Medium, 10% FCS, (+ 20µg/ml Hygromycin-B)

Procedure:

1. Cell Culture Procedure:

   Split confluent 293T/17-FR cells every Monday (seed out: 5x106 cells/T175 flask) and Friday (seed out: 3x106 cells/ T175 flask) using trypsin/EDTA (incubate just for 30sec at RT).
2. Seed cells (0,25x106 cells/ml) in 25µl DMEM + 10% FCS to a 384-well PDL- plate (Corning cat # 3844) and incubate over night at 37°C and 5% CO2.
3. Aspirate media and add 12,5µl antibodies in Conditioned Medium or just Conditioned Medium and incubate for 30min at 37°C and 5% CO2 (program: 3 Aspiration and Sample transfer)
4. Add 12.5µl IL-1b in DMEM + 10%FCS and incubate for 5 hours at 37°C and 5% CO2.
5. Equilibrate cultured cells to RT for 10 min.
6. Add 25µl Steady-Glo Reagent and mix several times with pipette
7. Wait 5 minutes before transfer 45µl supernatant to a 384-well lumitrac white plate (Corning Cat# 3572)
8. Measure luminescence in Tecan Reader: Integration Time: 0,5sec

Example 3: Inhibition of NFκB-expression of A549-NFκB-RE-Luc stable transfected cells after stimulation with IL-1 (α/β)

Assay Principle:

A549-NFκB-RE-Luc stable transfected cells (Signosis) are pipetted to a 384-well plate and incubated overnight. On day 2 anti-IL1R3 antibodies are allowed to bind to A549-NFkB-RE-Luc stable transfected cells, which are then stimulated by addition of IL-1 (α or β). This results in transcription of the luciferase gene due to NFκB signaling pathway activation and can be measured by cell lysis and addition of luciferin.

It is tested whether antibodies can inhibit the activation of NFkB pathway and therefore lower the luminescence signal.

Materials:

Plates:	384-well Low Flange White Flat Bottom Polystyrene TC-Treated Microplates Sterile; Corning; Cat. No. 3570
Proteins:	IL-1 α (P026_09); Recombinant Human IL-1alpha/IL-1F1; 10 µg/mL; R&D Systems; Cat. No. 200-LA-002

IL-1 β (P026_10); Recombinant Human IL-1beta/IL-1F2; 25 µg/mL; R&D Systems; Cat. No. 200-LB-005

Standard Ab: MAB-15-0115; MAB Discovery GmbH; 2,51 mg/ml; working conc. 10 µg/ml

Cells: A549-NFκB-RE-Luc stable transfected cells; Signosis; Cat. No. SL-0014

Medium: DMEM; PAN; Cat. No. P04-04510

FCS: Fetal Bovine Serum South Africa Low IgG; PAN; Cat. No. 1552-P120909

Pen/Strep: 10,000 U Penicillin/ml; 10mg Streptomycin/ml; PAN Biotech; Cat. No. P06-07100

Detaching Agent: Trypsin-EDTA 1x; PAN; Cat. No. P10-023100 (4 mL for T175/2 mL for T75; ~8 min 37°C)

Cell-Medium: DMEM, 10 % FCS, 1 % Pen/Strep

Detection Kit: Steady-Glo™ Luciferase Assay System; Promega; Cat. No. E2510

Procedure:

1. Cultivate A549-NFκB-RE-Luc stable transfected cells (1,7E+04 cells/cm^2 for 3 days; 2,28E+04 cells/cm^2 for 2 days) in Cell-Medium. Do not go beyond 10 passages!
2. Plate out 40,000 A549-NFκB-RE-Luc stable transfected cells in 25 µL medium per well (conc. = 1.6x10^6 cells/mL) to a white cell-culture treated 384 well plate with flat bottom.

Incubate over night at 37°C/5% CO_2.

3. Aspirate medium from plate and add 10 µL sample or standard in medium to plate using CyBio pipetting roboter (Program: "Medium removal and sample transfer" in folder P026/NFκB). Incubate for 1 h at 37°C/5% CO_2.
4. Add 10 µL IL-1 (α or β) in medium to plate using CyBio pipetting roboter (Program: "Transfer from reservoir" in folder P026/NFκB) (working conc.: 0.2 ng/mL; assay conc.: 0.1 ng/mL) and incubate 5 h at 37°C/5% CO_2.

Before performing step 4, dissolve Steady-Glo substrate in Steady-Glo buffer according to Steady-Glo protocol and equilibrate this solution and the assay plate to RT.

5. Add 20 µL Steady-Glo mix, mix thoroughly to guarantee proper cell lysis. Incubate at RT, 10 min.
6. Determine the relative luminescence units of each well, using a microplate reader set to 500 ms integration time (program: Lumineszenz-384).

Example 4: Cell Binding analysis

A549 and NIH-3T3 cells were cultured in DMEM + 10% FCS. HEK-293 cells were cultured in DMEM + 15% FCS and SK-MEL-30 in RPMI + 10% FBS. Cells were harvested using Accumax (Sigma), washed with PBS and resuspended in stain buffer (BD Pharmingen). Anti-IL-1R3 antibodies were incubated with the cells in stain buffer for 30 minutes at 4°C at a concentration of 10 µg/ml. For EC50 SK-MEL-30 cell binding analysis, cells were incubated in a 1:2 dilution series starting with 20 µg/ml. Cells were washed with stain buffer and incubated with Alexa-488 labelled goat-anti-human secondary antibody (Dianova) for 30 minutes at 4°C. Cells were washed with stain buffer and resuspended in buffer containing 1:100 diluted DRAQ7 (Abcam) dead cell stain. Cells were analysed using a BD Accuri C6 Sampler flow cytometer. Fitting curve and EC50 calculation was done using Excel (Microsoft) and XLfit (IDBS).

Example 5: Biochemical human-IL-1R3 ELISA

Nunc 384-well Maxisorp plates were coated with recombinant Fc-tagged hIL-1R3 (Ser21-Glu359) at a concentration of 0,25 µg/ml in PBS for 60 minutes at room temperature. Plates were washed threetimes with wash buffer (PBS 0,1% Tween) and blocked with PBS, 0,2% BSA, 0,05% Tween for 60 minutes at room temperature. After three washes with wash buffer, antibodies were added in ELISA buffer (PBS, 0,5% BSA, 0,05% Tween) at concentrations ranging from 6 to 0,03 µg/ml (1:3 dilution series) and were incubated for 60 min at room temperature. Plates were washed three times with wash buffer, followed by incubation with anti-human-IgG peroxidase-linked, species specific F(ab)2 Fragment (goat, AbD Serotec) at a dilution of 1:5000 in ELISA Buffer for 60 minutes at room temperature. Plates were washed six times with wash buffer before TMB substrate solution (Invitrogen, 15 µl/well) was added. After 5 minutes of incubation, stop solution (1M HCl, 15µl/well) was added and absorbance (450nm/620nm) measured using a Tecan M1000 plate reader. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 6: IL-1α and IL-1β functional neutralization assay

A-549-NFκB-RE-Luc (Signosis) were cultivated in DMEM, 10 % FCS, 1 % Pen/Strep for 5 days before they were seeded out in 384-well white flat bottom polystyrene tissue-culture-treated

microplates (Corning) at a cell density of 40,000 cells/well in 25µl medium. Cells were incubated over night at 37°C/5% CO_2. Medium was removed by aspiration and monoclonal or polyclonal (goat-anti-human-IL-1R3, AF676, R&D Systems) antibodies added at various concentrations in a volume of 10µl medium and incubated for 60 minutes at 37°C/5% CO_2. Recombinant human IL-1α or IL-1β (R&D Systems) proteins were added in 10µl medium to a final concentration of 0,1 ng/ml and plates were incubated for 5 hours at 37°C/5% CO_2. 20µl Steady-Glo™ (Promega) solution were added to each well, mixed thoroughly and plates were incubated for 10 minutes at room temperature before luminescence was measured using a Tecan M1000 plate reader. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 7: IL-1α and IL-1β functional neutralization assay – A-549 IL6-release assay

A549 cells were seeded out at a density of 6,000 cells/well in 25µl medium in 384-well clear cell culture treated plates (Corning) in DMEM, 10 % FCS, 1 % Pen/Strep. Cells were incubated over night at 37 °C/5% CO_2. Medium was removed by aspiration and monoclonal or polyclonal (goat-anti-human-IL-1R3, AF676, R&D Systems) antibodies were added at various concentrations in a volume of 12.5µl medium and incubated for three hours at 37°C/5% CO_2. Recombinant human IL-1α or IL-1β (R&D Systems) proteins were added in 12,5µl medium to a final concentration of 0,1 ng/ml and plates were incubated for 48 hours at 37°C/5% CO_2. Secreted human-IL-6 levels in the cell supernatant were measured using the DuoSet human IL-6 ELISA kit (R&D Systems, Cat.No. DY206-05) according to the manufacturer's instructions. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 8: IL-33 functional neutralization assay

HEK-Blue™ IL-33 cells (InvivoGen) were cultivated in DMEM, 10 % FCS for 5 days before they were seeded out in 384-well clear, flat bottom, cell culture treated microplates (Corning) at a cell density of 25,000 cells/well in 15µl medium. Various concentrations of monoclonal or polyclonal

(goat-anti-human-IL-1R3, AF676, R&D Systems) antibodies were added in a volume of 5µl medium and plates were incubated for 60 minutes at 37°C/5% CO_2. Recombinant human IL-33 (R&D Systems) protein was added in 5µl medium to a final concentration of 5 ng/ml and plates were incubated over night at 37°C/5% CO_2. 5µl cell supernatants were transferred to clear, flat bottom polystyrene NBS™ microplates (Corning) containing 20µl 2xQUANTI-Blue reagent (InvivoGen). Plates were incubated at 37°C for 45 minutes and optical density measured at 655 nm using a Tecan M1000 plate reader. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 9: IL-36 functional neutralization assay

HEK293/17-IF Cells (MAB Discovery GmbH) were cultivated in DMEM, 10 % FCS, 20µg/ml hygromycin for 5 days before they were seeded out in 384-well white, flat bottom, cell culture treated plates (Corning) at a cell density of 30,000 cells/well in 20µl medium. Cells were incubated over night at 37°C/5% CO_2. Medium was removed by aspiration and various concentrations of monoclonal or polyclonal (goat-anti-human-IL-1R3, AF676, R&D Systems) antibodies were added in a volume of 10µl medium. Plates were incubated for 60 minutes at 37°C/5% CO_2. Recombinant human IL-36g (R&D Systems) protein was added in 10µl medium to a final concentration of 15 ng/ml and plates were incubated for 5 hours at 37°C/5% CO_2. 20µl Steady-Glo™ (Promega) solution was added to each well, mixed thoroughly and plates were incubated for 10 minutes at room temperature before luminescence was read using a Tecan M1000 plate reader. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 10: Neutralization of IL-1α, IL-33 and IL-36α

The functions of anti-IL-1R3 antibodies were tested on three different cell lines with either IL-1α, IL-33 or IL-36α to determine the impact on the signaling pathways involving the three IL-1 receptors (IL-1R1, -R4 or –R6) dependent upon IL-1R3 for signaling.

The human epithelial lung cell line A549 was stimulated with IL-1α as a model of IL-1 dependent diseases such as auto-inflammatory diseases. The cell line was cultured in T75 flasks (37°C, 5% CO_2) in complete F-12K media (10%FCS, 1% Pen/Strep) and split on average 2 times /week, not exceeding 15 passages before assaying. A549 cells were seeded out (50.000/well) in a 96 flat-bottom plate, rested for 3hrs before pre-incubating 1hr with MAB-16-0030 (20µg/mL – 1µg/mL) or IL-1Ra (10µg/mL). Cells were then stimulated with recombinant human IL-1α (50pg/mL, Peprotech) for 24hrs before harvesting supernatants and assaying for IL-6 production (Duoset ELISA, RnD Systems).

A human mast cell line (HMC-1) was investigated for IL-33-dependent induction of IL-8 production. The cell line was cultured in T75 flasks (37°C, 5% CO_2) in complete Iscove´s modified Dulbeccos´s medium (IMDM, 10%FCS, 1% Pen/Strep) and split on average 3 times/week, not having a cell density above $2*10^6$/mL nor exceeding 15 passages before assaying. HMC-1 cells were seeded out (30.000/well) in a 96 flat-bottom plate, rested for 3hrs before pre-incubating 1hr with MAB-16-0030 (20µg/mL – 1µg/mL) or IL-1Ra (10µg/mL). Cells were then stimulated with recombinant human IL-33 (20ng/mL, RnD systems) for 24hrs before harvesting supernatants and assaying for IL-8 production (Duoset ELISA, RnD Systems).

The impact on IL-36 signaling was investigated using a human keratinocytic cell line (HaCaT). The cell line was cultured in T75 flasks (37°C, 5% CO_2) in complete DMEM (10%FCS, 1% Pen/Strep) and split on average 3 times/week not exceeding 15 passages before assaying. HaCaT cells were seeded out (50.000/well) in a 96 flat-bottom plate, rested for 3hrs before pre-incubating 1hr with MAB-16-0030 (20µg/mL – 1µg/mL) or IL-1Ra (10µg/mL). Cells were then stimulated with recombinant human IL-36α (50ng/mL, RnD systems) for 24hrs before harvesting supernatants and assaying for IL-8 production (Duoset ELISA, RnD Systems).

Example 11: Viability and IL-6 release of PBMC

The impact of anti-hIL-1R3 antibody MAB-16-0030 on the viability of unstimulated PBMCs (500.000/well) from three healthy donors was tested using a conventional MTT reduction assay. Briefly, PBMCs (200µL) were incubated with either media alone or MAB-16-0030 (20µg/mL). After 24hrs, 3 and 5days, PBMCs were incubated for 2hrs with MTT (20µL), before measuring

absorbance at 570nM on an ELISA reader. Using the known linearity between absorbance and viable cells converting MTT, the number of viable cells was calculated using media alone as the control set to 100%. At the same day of MTT analysis, supernatants from PBMCs incubated under same conditions and from same donors, were harvested and subsequently assayed for IL-6 production (Duoset ELISA, RnD systems) to evaluate any possible stimulatory effect of MAB-16-0030 alone.

Example 12: Functional blockage of PBMCs

Freshly isolated PBMCs from healthy donors were used to evaluate the impact of MAB-16-0030 on human cells stimulated with diverse antigens. For all stimuli, the experiments were carried out using 500.000 PBMCs/well, stimulating in a total volume of 200µL. Cells were seeded out and incubated with either media alone, MAB-16-0030 (20 – 0.1µg/mL) or IL-1Ra (10µg/mL) for 1hr before stimulation. The following stimuli were used; LPS (10ng/mL, 24hrs, RPMI no FCS), anti-human CD3/CD28 (1.25µg/mL;0.5µg/mL (eBioscience) 3days, RPMI 10%FCS), IL-12 /-33 (2ng/mL;20ng/mL (Peprotech;RnD Systems)), 3days, RPMI 10%FCS) or heat-inactivated *Candida albicans* ($0.5*10^6$/mL, 5days, RPMI 10%FCS). After stimulation, supernatants were harvested and assayed for cytokine production using Duoset ELISAs (RnD Systems) according to manufactures protocol.

Example 13: Functional blockage of immune cells in whole blood

Heat-inactivated *Candida albicans* were used to stimulate whole blood. Freshly harvested blood from healthy donors (EDTA tubes) were distributed in micro-centrifuge tubes (250µL/ tube) and pre-incubated with either media alone (RPMI, no FCS), MAB-16-0030 (20 – 0.1µg/mL) or IL-1Ra (10µg/mL) for 1hr before stimulation with *Candida albicans* ($0.5*10^6$/mL) to a final volume of 1mL. After 24hrs incubation (37°C, 5% CO_2), supernatants were harvested and assayed for cytokine production by ELISA (Duoset, RnD Systems).

Example 14: Mixed Lymphocyte Reactions (MLR)

PBMCs from healthy, non-matching donors were mixed in a 1:1 ratio (250.000 /donor) and incubated for 5 days (RPMI, 10%FCS) with either media alone, MAB-16-0030 (20 – 1µg/mL) or IL-1Ra (10µg/mL). Cytokine production were assayed using a Quansys multiplex platform according to manufacturer's protocol.

Example 15: NFkB Luciferase Gene Reporter assay

NFkB Luciferase Reporter NIH 3T3 cell (Signosis) were seeded out at 20,000 cells in 25 µL DMEM, 10 % FCS, 1 % Pen/Strep medium per well (conc. = 0.8 x10^6 cells/mL) in white cell-culture treated, flat bottom 384 well plate. Cells were incubated over night at 37°C/5% CO_2. Medium was aspirated and 12.5 µL of the antibody solution with MAB-16-0531 was added to the cells at diverse concentrations. After incubation for 1 h at 37°C/5% CO_2, 12.5 µL mouse-IL-1β was added in medium to a final concentration of 50 pg/ml. Cells were incubated for 5 h at 37°C/5% CO_2. 25µl Steady-Glo™ (Promega) solution was added to each well, mixed thoroughly and plates were incubated for 10 minutes at room temperature before luminescence was measured using a Tecan M1000 plate reader. Fitting curves and EC50 calculation were obtained by using Excel (Microsoft) and XLfit (IDBS).

Example 16: NIH-3T3 IL6-release assay

NIH 3T3 cell were seeded out at 12,500 cells in 15 µL DMEM + 1 % FCS medium per well (conc. = 0.83 x10^6 cells/mL) in a cell-culture treated, flat bottom 384 well plate. Cells were incubated for 2 hours at 37°C/5% CO_2. 10µL antibody MAB-16-0531 was added in medium to the cells at diverse concentrations. After incubation for 1,5 h at 37°C/5% CO_2, 25 µL human-IL-1β was added in medium to a final concentration of 50 pg/ml. Cells were incubated over night at 37°C/5% CO_2. Secreted mouse-IL6 in culture supernatants was quantified by ELISA (DuoSet ELISA; R&D Systems; Cat. No. 840171) according to manufacturer's instructions. Fitting curves and EC50 calculation were done using Excel (Microsoft) and XLfit (IDBS).

Example 17: Monosodium urate crystal (MSU)-induced mouse peritonitis model

3mg of MSU (Invitrogen) per mouse was used for intraperitoneal injection (I.P) as a stimulant, and anti-IL-1R3 (MAB-16-0531, 500µg/mouse) or IL-1Ra (10mg/kg) for inhibition. Saline was used both as control for stimulation and inhibition. The four groups were comprised of 4 mice as control of stimuli (Saline (inhib.) + Saline(stimuli)), 8 mice with MSU alone (Saline+MSU), 8 mice with MAB-16-0531 (500µg/mouse + MSU) and 8 mice with IL-1Ra (10mg/kg + MSU). MAB-16-0531 and IL-1Ra were injected I.P. 1hr before MSU stimulation. 6 hours after MSU or saline injection the mice were euthanized. Blood was collected in micro-centrifuge tubes containing EDTA and peritoneal fluid collected by lavage using 10mL of ice-cold PBS. Bone-marrow cells were isolated, and organs immediately frozen in liquid nitrogen. The number of cells in the peritoneal fluid was counted (HESKA HemaTrue).

Example 18: Neutrophil activation and cytokine production in MSU peritonitis

Neutrophils are the most abundant cell type in gout and activation correlates with elastase production. IP fluid and IP cell lysates from Example 17 were analyzed for levels of neutrophil elastase marker and MPO levels. IP lysates were prepared in TritonX 0.5%. Cytokines were measured in both IP fluid and IP cell lysates. For low abundance cytokines in the IP fluid, 8mL of fluid was concentrated (end range: 4.7- 10.9x concentrated) in pre-boiled (15min) dialysis membranes (MWCO 3.5kDa., Spectra/Por3 Dialysis membrane, Spectrumlabs) submerged in polyethylene glycol (MN 6-8000, Sigma Aldrich) as the hygroscopic solution at 4°C. Initial concentrations were calculated by dividing with the dialysis concentration factor. Spleen and whole blood lysates were assayed for cytokine levels and normalized to protein concentration of the lysates. Cytokine concentrations were measured according to protocol using Duoset ELISA (R&D Systems) or multiplex assays (Quansys Biosciences). Protein levels in spleen lysates and IP fluid were assayed with a standard Bradford assay, using protein assay dye reagent (BioRad) and BSA as standard. As shown in Figure 20 a-c, treatment with a-mIL1R3 antibody MAB-16-0531 significantly reduces MSU-induced intracellular Elastase and Elastase in the IP fluid. IL-6, G-CSF, KC and CCL-2 levels are strongly reduced in the IP fluid in MAB-16-0531 mice. Systemically, MPO and KC are also reduced in spleen lysates, IL-6 and G-CSF are reduced in plasma (Figure 20 d).

Example 19: OVA allergic asthma in vivo model

An OVA-induced allergic asthma model has been applied as an IL-33 dependent in vivo model. Wild-type 6 weeks old C57BL/6 male mice (Jackson Laboratories) were sensitized IP using OVA (15μg/ 100μL, Sigma-Aldrich) mixed 1:1 with Imject Alum Adjuvant (100μL, ThermoFischer). Mice were injected at day 1, 14 and 21. At day 25-28 mice were injected IP with MAB-16-0531 (500μg/mouse, MAB Discovery) or mouse IgG2a-LALA control (500μg/mouse, MAB Discovery, groups "Vehicle" and "OVA"). Intratracheal instillation of OVA (50μg/mouse in 50μL) was done 30min post-injection at day 26-28 in short-term carbon dioxide anesthesia. Bronchoalveolar lavage (BAL) was carried out by inserting a catheter into the trachea and washing the airways with 3 x 1ml washes. This was followed by cell phenotyping using flow cytometry. The following monoclonal antibodies (mAbs) against mouse targets were used for flow cytometry following mouse Fc Block (BD Biosciences): PE-Cy7 CD11c (N418), PerCP-Cy5.5 CD11b (M1/70), FITC-Ly6G (1A8-Ly6G) (all from eBioscience); PE-Siglec-F (E250-4440) (from BD Biosciences) (stained in DPBS containing 10mg/ml BSA, 0.1mg/ml NaN_3). Cells were analyzed on a Canto II flow cytometer using FlowJo software (Treestar). BAL cells were enumerated by trypan blue exclusion. Following BAL, lungs were inflated with pre-warmed 3% low melt agarose in DPBS and allowed to cool before removal into phosphate buffered formalin overnight. Lungs were embedded in paraffin, sectioned and stained with H&E and PAS. Histology was evaluated using a Leica DM2000 LED microscope and LAS V4.12 software. Figure 21 a-b shows that MAB-16-0531 treatment significantly reduced total BAL white blood cell count (WBC), eosinophils and neutrophils. In Figure 21 c, lung section HE staining confirm a reduced pathology by MAB-16-0531 treatment and PAS staining demonstrates a reduced amount of mucus producing goblet cells in the airways (PAS).

Example 20: Imiquimod induced psoriasis in vivo model

IL-36 has a prominent role in skin inflammation and mutations in the IL-36Ra are linked to human pustular psoriasis. Therefore, application of an anti-IL1R3 therapy to skin inflammatory diseases has been tested using an imiquimod induced psoriasis in vivo model. WT twelve weeks old C57BL/6 mice (Jackson Laboratories) were back-skin shaved and treated with hair removal cream (Nair). Application of 75mg IMQ (Aldara 5% IMQ) or control cream (Vaseline cream) was done

daily (day 1- 5) on back-skin (IMQ; IMQ (n=10) and a-mIL1R3 (n=9) group, control cream; vehicle group (n=3)) and IP injections every other day (day 1, 3 and 5). Vehicle and IMQ groups received mouse IgG control (20mg/kg, MAB Discovery), treatment group received MAB-16-0531 (20mg/kg, MAB Discovery). Ears were concurrently applied with control cream on left ear (all mice; 5mg Vaseline cream) and group appropriate stimuli cream on right ear (Vehicle; 5mg Vaseline cream, IMQ and a-mIL1R3; 5mg IMQ cream).

Body weight was monitored daily. Mice were euthanized day 6, left and right ear thickness was measured using a gauge. Whole blood cell counts were assessed using a HemaTrue analyzer (HESKA). Pictures of back-skin were visually scored (erythema and scaling, score 0 (no response) to 4 (maximum affected)) by 6 blinded people. RNA was isolated from skin puncture biopsies. RNA was extracted from lysates and cDNA was produced from 0.8 μg RNA (NanoDrop) (High Capacity cDNA Reverse Transcription Kit (Applied Biosystems)). 50ng cDNA was used in real time qPCR reaction using SYBR Green master mix (Applied Biosystems) and 0.1 μM of cytokine specific primer. GAPDH was used as reference gene, and ratios calculated using the Pfaffl method including analyzed primer efficiencies.

Myeloperoxidase (MPO) levels were measured in a freshly obtained skin biopsy by ELISA. MPO levels were normalized to total protein measurements (determined by the Bradford method).
Figures 22 and 23 demonstrate that treatment with MAB-16-0531 significantly reduces imiquimod-induced skin inflammation which is also associated with a reduction in skin granulocyte infiltration, MPO levels and IL17F mRNA expression.

Example 21: Activation of Fc-receptor mediated effector function by IgG1 and IgG1-LALA anti-IL1R3 antibodies

To test the activity of IgG-1 and IgG1-LALA versions of a humanized anti-IL1R3 antibody in eliciting Fc-mediated effector cell functions such as ADCC, MAB-16-0030 was produced as an IgG1 or IgG1-LALA antibody. hIL1R3 expressing target cells SK-MEL-30 cells were seeded in a 384-well tissue-culture treated plate at a density of 2500 cells/well in 25μl RPMI medium containing 10% FCS. 24h after seeding, 4000 effector cells/well (ADCC Bioassay Effector cells, Jurkat, Promega Cat.#G701A) were added in RPMI medium containing 4% low-IgG-FCS. Antibodies were then added to final

concentrations ranging from 10000 to 0.002 ng/ml and the plate was incubated for 6 hours at 37°C and 5 % CO_2. Activation of NF-kB signaling in luciferase gene reporter Jurkat cells was measured according to manufacturer's instructions (Bio-Glo Luciferase Assay) and using a Tecan M1000 microplate reader. "Fold of induction" values represent RLU (antibody treated – background) / RLU (no antibody control – background). Fitting curves and EC50 calculation were obtained by using Excel (Microsoft) and XLfit (IDBS). As shown in Figure 24, only the IgG1-version of MAB-16-0030 induces NF-kB signaling in effector Jurkat reporter cells, while effector cell activation with the IgG1-LALA version is abolished.

Figure legend

Fig. 1: Sequences (amino acids in one letter code)

Complete sequences of Variable Regions (VR):

Heavy chain:	VH complete:	SEQ ID NO: 1-34 and SEQ ID NO: 173 and 176
Light chain:	VL complete:	SEQ ID NO: 35-68 and SEQ ID NO: 174 and 177

Complementary Determining Regions (CDR):

Heavy Chain:	CDRH1:	SEQ ID NO: 69-85 and 178
	CDRH2:	SEQ ID NO: 86-102 and 179
	CDRH3:	SEQ ID NO: 103-119 and 180
Light Chain:	CDRL1:	SEQ ID NO: 120-136 and 181
	CDRL2:	SEQ ID NO: 137-153 and 182
	CDRL3:	SEQ ID NO: 154-170 and 175 and 183

Constant Regions (CR):

Light Chain:	CR-L:	SEQ ID NO: 171
Heavy Chain:	CR-H:	SEQ ID NO: 172

In the following Figures, AF676 is a commercial polyclonal antibody preparation purchased from the following link: https://www.rndsystems.com/products/human-il-1-racp-il-1-r3-antibody_af676

Fig.2: Human IL-1R3 ELISA

A 384-microtiter plate was coated with human Il-1R3 protein representing the human extracellular domain of IL-1R3 (0.5 mg/ml, at least 1h). After an intensive washing step followed by a blocking step, antibodies were added (12,5µl per well) and incubated for 1h at RT. Unbound antibody was washed out intensively. The amount of bound antibody was identified by incubating the microtiter plate with a Peroxidase labelled anti-human detection antibody (1h at RT). The Peroxidase reaction was initiated by adding TMB and measuring the absorbance at 450nm/620 nm.

Fig. 3: HEK293 reporter assay

HEK293T/17-FR cells were stable transfected with the pGL4.32[*luc2P*/NF-κB-RE/Hygro] vector (Promega) and seeded in 384well PDL Costar Cell Culture plates followed by 30 min incubation with the antibodies. The cells were then stimulated with IL-1ß for 5 hours before

the NF-kB activity was determined using the Steady-Glo Luciferase Assay Kit (Promega) according to manufacturer's protocol.

Fig. 4: NFκB luciferase reporter assay using an A549 stable cell line

A549-NFkB-RE-Luc stable transfected cells (purchased from Signosis) have been cultivated for 3 days (1,7E+04 cells/cm^3). 384-well low flange white flat bottom polystyrene TC-treated microtiter plates (Corning) were filled with $4x10^4$ cells per well. After a cultivation period of 10h the cells were incubated with the antibodies for 1 h before the cells were stimulated with 10µl IL-1β for another 5 h. NFkB modulation has been measured by Steady-Glo™ Luciferase Assay System (Promega) determining relative luminescence units of each well in relation to non-stimulated cells.

Fig. 5: Cell binding analysis: Binding to IL-1R3 expressing cells

Humanized anti-IL-1R3 IgG1-LALA antibodies were tested for binding to cell lines with different IL-1R3 receptor densities using flow cytometry. Humanized anti-IL-1R3 IgG1-LALA antibodies bind to low- and high-IL-1R3-expressing cell lines. Antibodies do not bind to mouse NIH-3T3 cells. Experiments were carried out according to the method described in Example 4.

Fig. 6: Cell binding analysis: Cell binding on human-IL-1R3 high expressing cell line SK-MEL-30

EC50 cell binding values of humanized anti-IL-1R3 IgG1-LALA antibodies were determined by binding to high-IL-1R3-expressing cell line SK-MEL-30 using flow cytometry. Humanized anti-IL-1R3 IgG1-LALA antibodies MAB-16-0030 and MAB-16-0149 show cell binding of 307 and 306 ng/ml, respectively. Experiments were carried out according to the method described in Example 4.

Fig. 7: Human-IL-1R3 biochemical ELISA

Binding of humanized anti-IL-1R3 IgG1-LALA antibodies to recombinant human IL-1R3 protein was tested in biochemical ELISA. Exemplified antibodies show EC50 binding values of 16,3ng/ml and 29,1ng/ml, respectively. Experiments were carried out according to the method described in Example 5.

Fig. 8: Inhibition of human IL-1a and IL-1b mediated NfKB signaling in A549-NFkB-RE-Luc cells

Functional neutralization of IL-1a and IL-1b was tested in a cell based gene reporter assay using A549-NFkB-RE-Luc cells stimulated with 0,1 ng/ml IL-1a and IL-1b, respectively.

Humanized anti-IL-1R3 IgG1-LALA antibodies show EC50 values superior to that of goat-anti-human-IL1-R3 polyclonal antibody AF676 (R&D Systems). Experiments were carried out according to the method described in Example 6.

Fig. 9: IL-1α and IL-1β functional neutralization assay - Inhibition of human IL-1a and IL-1b mediated IL-6 release by A-549 cells

Neutralization of IL-1a and IL-1b mediated cellular release of IL-6 by humanized anti-IL-1R3 IgG1-LALA antibodies was tested using A-549 cells. EC50 values demonstrate that humanized anti-IL-1R3 IgG1-LALA antibodies are superior to that of goat-anti-human-IL1-R3 polyclonal antibody AF676 (R&D Systems). Experiments were carried out according to the method described in Example 7.

Fig. 10: IL-33 functional neutralization assay - Inhibition of human IL-33 mediated NfkB-signaling in HEK-Blue-IL33™ cells

Neutralization of IL-33 mediated cell signaling by humanized anti-IL-1R3 IgG1-LALA antibodies was tested using IL-33 stimulated gene reporter HEK-Blue-IL33™ cells (InvivoGen). EC50 values demonstrate that humanized anti-IL-1R3 IgG1-LALA antibodies are superior to that of goat-anti-human-IL1-R3 polyclonal antibody AF676 (R&D Systems). Experiments were carried out according to the method described in Example 8.

Fig. 11: IL-36 functional neutralization assay - Inhibition of human IL-36 mediated NfkB-signaling in HEK-293/17-IF cells

Neutralization of IL-36 mediated cell signaling by humanized anti-IL-1R3 IgG1-LALA antibodies was tested using IL-36g stimulated gene reporter HEK-293/17-IF cells. Typical humanized anti-IL-1R3 IgG1-LALA antibodies show EC50 values superior to that of goat-anti-human-IL1-R3 polyclonal antibody AF676 (R&D Systems). Experiments were carried out according to the method described in Example 9.

Fig. 12: Neutralization of IL-1a, IL-33 and IL-36a mediated cellular cytokine release

Neutralization of IL-1a, IL-33 and IL-36a mediated cellular cytokine release was tested using specific IL-1a, IL-33 and IL-36a dependent cell systems. The Inhibition of cytokine release by A representative humanized anti-IL-1R3 IgG1-LALA antibody according to the invention (MAB-16-0030) was tested and compared to IL-1Ra. While the antibody according to the invention was able to inhibit cytokine release mediated by all three stimuli, IL-1Ra affected only IL-1a mediated cytokine release. Experiments were carried out according to the method described in Example 10.

Fig. 13: Viability and IL-6 release of unstimulated PBMC treated with a humanized anti-IL-1R3 IgG1-LALA antibody

Binding of antibodies to immune cells may result in cell depleting and deleterious effects, e.g. by direct induction of apoptotic signaling pathways, stimulation of excessive cytokine release or antibody-dependent cellular cytotoxicity (ADCC). To exclude that humanized anti-IL-1R3 IgG1-LALA antibodies directly affect the viability of PBMCs, the viability of PBMCs of three donors and IL-6 release was investigated after incubation with different concentrations of a representative humanized anti-IL-1R3 IgG1-LALA antibody according to the invention (MAB-16-0030) for 1,3 and 5 days. Neither viability nor IL-6 release was affected. These results support that the humanized anti-IL-1R3 IgG1-LALA antibodies block IL-1R3 function on immune cells without circumstantial cell-depletion and induction of cell-deleterious effects. Experiments were carried out according to the method described in Example 11.

Fig. 14: Functional blockage of PBMCs activated with different stimuli

To test whether humanized anti-IL-1R3 IgG1-LALA antibodies inhibit activation of PBMCs stimulated with specific or complex stimuli, PBMCs of 10 donors were stimulated with LPS, heat-inactivated Candida albicans, IL-12/IL-33 or anti-CD3/CD28 antibodies. A representative humanized anti-IL-1R3 IgG1-LALA antibody according to the invention (MAB-16-0030) was able to inhibit cytokine release mediated by all tested stimuli. Experiments were carried out according to the method described in Example 12.

Fig. 15: Functional blockage of immune cells in whole blood activated with *Candida albicans*

To test whether humanized anti-IL-1R3 IgG1-LALA antibodies inhibit activation of immune cells in whole blood, whole blood of 8 donors was stimulated with heat-inactivated Candida albicans. A representative humanized anti-IL-1R3 IgG1-LALA antibody according to the invention (MAB-16-0030) was able to inhibit Candida induced IL-6 cytokine release. Experiments were carried out according to the method described in Example 13.

Fig. 16: Blockage of cytokine release in Mixed Lymphocyte Reactions (MLR)

The ability of humanized anti-IL-1R3 IgG1-LALA antibodies to block release of diverse cytokines was tested in mixed lymphocyte reactions (MLR) using PBMCs of healthy, unmatched donors. A representative humanized anti-IL-1R3 IgG1-LALA antibody according to the invention (MAB-16-0030) was able to inhibit release of IFNg, IL-6, TNF-a, IL-13, IL-17 and IL-10. Experiments were carried out according to the method described in Example 14.

Fig. 17: Neutralization of IL-1b mediated signaling in murine cells

Functional neutralization of IL-1b by an anti-mouse-IL-1R3 antibody according to the invention was tested using a mouse NIH-3T3 cell based NFkB luciferase gene reporter assay. A representative antibody according to the invention (MAB-16-0531) showed dose-dependent inhibition of IL-1b mediated NFkB signaling with an EC50 of 805 ng/ml. Experiments were carried out according to the method described in Example 15.

Fig. 18: Neutralization of IL-1b mediated IL-6 release from murine cells

Inhibition of IL-6 release from mouse cells by an anti-mouse-IL-1R3 antibody according to the invention was tested in IL-1b stimulated NIH-3T3 cells. A representative antibody according to the invention (MAB-16-0531) showed dose-dependent inhibition of IL-6 release with an EC50 of 1560 ng/ml. Experiments were carried out according to the method described in Example 16.

Fig. 19: Monosodium urate crystal (MSU)-induced mouse peritonitis model

To test the rationale of applying an anti-IL-R3 therapy to gout patients, a monosodium urate crystal (MSU)-induced mouse peritonitis model was used. The administration of MSU produces a strong inflammatory response in the peritoneal cavity, inducing the influx of several inflammatory cells (such as monocytes and neutrophils), mimicking a classic inflammatory profile of an acute gout response. A representative anti-IL1R3 antibody according to the invention (MAB-16-0531) or IL-1Ra were administered I.P. one hour before injection of 3 mg MSU in the peritoneum. Measurements of cells in the peritoneal cavity show that anti-IL-1R3 antibody treatment significantly inhibits MSU induced infiltration of lymphocytes, monocytes and granulocytes. Experiments were carried out according to the method described in Example 17.

Fig. 20: Neutrophil activation and cytokine production in MSU peritonitis

Attenuation of neutrophil activation including local and systemic markers of inflammation in MSU peritonitis. (a) Levels of the neutrophil protease Elastase in IP fluid. (b) Total levels of intracellular Elastase in cells from IP fluid. (c) Total levels of intracellular MPO in cells from IP fluid. (d) Cyto- and chemokine concentrations locally (IP fluid) and systemically. WB; lysed whole blood, norm.; normalized per mg of protein in spleen. MSU; vehicle+MSU. a-mIL1R3; a-mIL1R3 +MSU. IL 1Ra; IL 1Ra+MSU. Inhibitor treated groups compared to MSU stimulated group. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$ (Student's t-test, mean +SEM, except: (b), G CSF, KC (WB) and KC (spleen); Mann-Whitney U-test, median with IQR).

Fig. 21: OVA allergic asthma in vivo model

a-mIL1R3 antibody decreases OVA induced cell influx in vivo. (a) Total WBC from BAL fluid. (b) Flow defined cell differentials from (a). (c) Histology from group average (WBC) thick dot marked mice using H&E and PAS stained lung tissue. Comparisons between OVA stimulated + a-mIL1R3 (MAB-16-0531) treated mice and OVA alone. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ (Student's t-test). Mean +SEM.

Fig. 22: Imiquimod psoriasis in vivo model

(a) IL 36α mRNA induction in skin. (b) Fold change in ear thickness between IMQ and control cream applied ears. (c) Visual scoring by n=6 blinded people at end of study (0; unaffected – 4; maximum affected (erythema and scaling)). (d) MPO concentration in skin, normalized per mg of protein. (e) Spearman correlation between data from (c) and (d). (e) Granulocyte concentrations in whole blood. Comparisons between inhibitor treated and IMQ stimulated groups. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$, ((b,f) Mann-Whitney U-test (d,e) Student's t-test, mean ± SEM except (d) median with IQR).

Fig. 23: Imiquimod psoriasis in vivo model

IL36α/β/γ, IL17F and TNFa mRNA levels in skin biopsies of imiquimod-treated mice

Fig. 24: Effector cell mediated function of anti-IL1R3 IgG1 and IgG1-LALA antibodies

Anti-IL1R3 antibody MAB-16-0030, either containing an IgG1-LALA or an IgG1 Fc-part was tested for activation of Fc-receptor mediated NF-kB signaling in effector cells. Binding of increasing concentrations of the IgG1 antibody to hIL1R3 expressing SK-MEL-30 cells elicit Fc-receptor mediated signaling in Jurkat gene reporter effector cells in contrast to the IgG1-LALA antibody

Claims

1. Use of antibody or antigen binding fragment thereof that specifically binds IL-1R3 in the manufacture of a medicament for treating an IL1R3-mediated inflammatory condition and/or disorder in a subject

wherein the antibody or antigen binding fragment thereof comprises:

a) a heavy chain variable region (VH) comprising the complementarity determining regions comprising CDR-H1, CDR-H2, and CDR-H3,

wherein the CDR-H1 region comprises an amino acid sequence set forth in SEQ ID NO: 79,

wherein the CDR-H2 region comprises an amino acid sequence set forth in SEQ ID NO: 96,

and wherein the CDR-H3 region comprises an amino acid sequence set forth in SEQ ID NO: 113; and

b) a light chain variable region (VL) comprising the complementarity determining regions comprising CDR-L1, CDR-L2, and CDR-L3,

wherein the CDR-L1 region comprises an amino acid sequence set forth in SEQ ID NO: 130,

wherein the CDR-L2 region comprises an amino acid sequence set forth in SEQ ID NO: 147, and

wherein the CDR-L3 region comprises an amino acid sequence set forth in SEQ ID NO: 175.

2. A method for treating an IL1R3-mediated inflammatory condition and/or disorder in a subject, comprising administering to the subject an antibody or antigen binding fragment thereof that specifically binds IL-1R3,

wherein the antibody or antigen binding fragment thereof comprises:

a) a heavy chain variable region (VH) comprising the complementarity determining regions comprising CDR-H1, CDR-H2, and CDR-H3,

wherein the CDR-H1 region comprises an amino acid sequence set forth in SEQ ID NO: 79,

wherein the CDR-H2 region comprises an amino acid sequence set forth in SEQ ID NO: 96,

and wherein the CDR-H3 region comprises an amino acid sequence set forth in SEQ ID NO: 113; and

b) a light chain variable region (VL) comprising the complementarity determining regions comprising CDR-L1, CDR-L2, and CDR-L3,
wherein the CDR-L1 region comprises an amino acid sequence set forth in SEQ ID NO: 130,
wherein the CDR-L2 region comprises an amino acid sequence set forth in SEQ ID NO: 147, and
wherein the CDR-L3 region comprises an amino acid sequence set forth in SEQ ID NO: 175.

3. The use according to claim 1 or the method according to claim 2, wherein the inflammatory condition and/or disorder is selected from the group consisting of an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, an ophthalmologic disorder, Hereditary Systemic Inflammatory Diseases, and Systemic and Local Inflammatory Diseases.

4. The use or method according to claim 3, wherein the inflammatory condition is a metabolic rheumatic disorder associated with hyperuricemia.

5. The use or method according to claim 4, wherein the metabolic rheumatic disorder is selected from the group of gout, pseudogout, drug-induced gout and chronic active (refractory) gout.

6. The use or method according to claim 5, wherein an IL1R3 antagonistic antibody is to be administered in combination with a therapeutic agent for the treatment of gout.

7. The use or method according to claim 3, wherein the inflammatory condition is a cancer associated chronic inflammation.

8. The use or method according to claim 7, wherein an IL1R3 antagonistic antibody is to be administered or is administered in combination with one or more cytotoxic, cytostatic and/or targeted anti-cancer agents.

9. The use or method according to claims 7 or 8, wherein the subject is characterized in being resistant to treatment with one or more cytotoxic, cytostatic and/or targeted anti-cancer agents.

10. The use or method according to any of claims 1 to 9, wherein the antibody or antigen binding fragment thereof has reduced or is lacking its effector functions.

11. The use or method according to any of claims 1 to 10, wherein the antibody or antigen binding fragment thereof does not induce immune cell depletion.

12. The use or method according to claims 10 or 11, wherein the antibody or antigen binding fragment thereof does not induce ADCC.

13. The use or method according to any one of claims 10 to 12, wherein said antibody or antigen binding fragment thereof comprises at least amino acid substitutions L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region or a corresponding functional mutation, wherein the numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system.

14. The use or method according to any one of claims 1 to 13, wherein the subject is a human subject, and the antibody or antigen binding fragment thereof comprises a heavy chain variable (VH) region that is at least 90 % identical to a VH region as set forth in SEQ ID NO: 28, and a light chain variable (VL) region that is at least 90% identical to a VL region as set forth in SEQ ID NO: 174.

15. The use or method according to any one of claims 1 to 14, wherein the subject is a human subject, and the antibody or antigen binding fragment thereof comprises a VH region as set forth in SEQ ID NO: 28, and a VL region as set forth in SEQ ID NO: 174.

16. The use or method according to any one of claims 1 to 15, wherein the IL1R3-mediated inflammatory condition and/or disorder is Hidradenitis Suppurativa.

Figures

Fig. 1: Sequences (amino acids in one letter code)

VH complete: SEQ ID NO: 1-34 and SEQ ID NO: 173 and 176
VL complete: SEQ ID NO: 35-68 and SEQ ID NO: 174 and 177

CDR-H1: SEQ ID NO: 69-85 and 178
CDR-H2: SEQ ID NO: 86-102 and 179
CDR-H3: SEQ ID NO: 103-119 and 180

CDR-L1: SEQ ID NO: 120-136 and 181
CDR-L2: SEQ ID NO: 137-153 and 182
CDR-L3: SEQ ID NO: 154-170 and 175 and 183

CR-L: SEQ ID NO: 171
CR-H: SEQ ID NO: 172

mAB name	SEQ ID NO.	Complete Heavy-chain VR sequence
MAB-15-0139	1	EVQLEESGGGLVQPGGSLRLSCAASGFSFSSSYWICWVRQAPGKGLEWVSCIYTGSGGTY YASWEKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDPGYSSWLWGQGTLVTVSS
MAB-15-0106	2	EVQLEESGGDLVQPGGSLRLSCAASGFSFSSSHYMCWVRQAPGKGLEWVSCIYAGSSGN TYYANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARVDASSSGSWDLWGQGTL VTVSS
MAB-15-0108	3	EVQLEESGGRLVQPGGSLRLSCAVSGIDLSSYAMGWVRQAPGKGLEYVSVITSSATTYYAS WAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARGGPGYSTNTHYAFDPWGQGTLV TVSS
MAB-15-0110	4	EVQLEESGGRVVQPGRSLRLSCAVSGIDLDNYAMGWVRQAPGKGLEYVAVISSDGFFYD ASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDRGTSTGSLDLWGQGTLVTVS S
MAB-15-0117	5	EVQLEESGGRLVQPGGSLRLSCAASGFSLSSYYMSWVRQAPGKGLEWVSIISGSASTYYAT WAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARTHYAAVAGYGYASRLDLWGQGTL VTVSS
MAB-15-0121	6	EVQLEESGGDLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLELVSCIYTSTGNTW YASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDLLVVTSFNLWGQGTLVTVSS
MAB-15-0140	7	EVQLEESGGDLVQPGGSLRLSCAASGFSFSSSYYMCWVRQAPGKGLEWVSCIYAGSSGV TYYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCASETDGNYFNLWGQGTLVTV SS
MAB-15-0115	8	EVQLEQSGGGLVQPGGSLRLSCAASGFSLSTSYWRCWVRQAPGKGLEWVSCIYAGSGDV TYYANWVNGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASGVGFGYFNLWGQGTLVT VSS
MAB-15-0125	9	EVQLEESGGGLVQPGGSLRLSCAASGIDFSSYYYMCWVRQAPGKGLEWVSCIFIGYGDVT WYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARALGSSGYRVNLWGQGTLV TVSS
MAB-15-0119	10	EVQLEESGGRLVQPGGSLRLSCAASGFSLSSYWMSWVRQAPGKGLEWVSMIYGSGYTYY ASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDPQYFILWGQGTLVTVSS
MAB-15-0109	11	EVQLEESGGRLVQPGGSLRLSCAVSGFSLSSYDMSWVRQAPGKGLEWVSTIYIGGTTAYA SWPKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARLQGANYYNSLALWGQGTLVTVS S
MAB-15-	12	EVQLVESGGGLVQPGGSLRLSCAASGFDFSSNYYMCWVRQAPGKGLELVSCIYTNSGNT

0097		WSASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDLNYPDTSNLWGQGTLVT VSS
MAB-15-0135	13	EVQLEESGGDLVQPGGSLRLSCAASGFSFSFGYYMCWVRQAPGKGLEWVSCIYGDSSDT LYANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARYPGGSYYNLWGQGTLVTVS S
MAB-15-0133	14	EVQLEESGGDLVQPGGSLRLSCAASGFSFSSTYYMCWVRQAPGKGLEWVSCIYAGSSGST YYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARVDGSSSGSWDLWGQGTLV TVSS
MAB-15-0107	15	EVQLEESGGDLVQPGGSLRLSCAASGISFSSSDFMCWVRQAPGKGLEWVSCIYAGSSVSI YYATWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARSTGSVGRGFNLWGQGTLVT VSS
MAB-15-0128	16	EVQLVESGGGLVQPGGSLRLSCAASGFSFSSIYYMCWVRQAPGKGLEWVSCIYTGNSDFT YYANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARFRDDYASLKLWGQGTLVTV SS
MAB-15-0116	17	EVQLEESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWVSCIYTGSGST YYANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARNSNDWMYFNLWGQGTLV TVSS
MAB-16-0004	18	EVQLEQSGGGLVQPGGSLRLSCAASGFSFSSSYWICWVRQAPGKGLEWVACIYTGSGGT YYASWEKGRFTISKTSSTTLYLQMNSLRAEDTAVYFCARDPGYSSWLWGQGTLVTVSS
MAB-16-0009	19	EVQLEESGGDLVQPGASLRLSCAASGFSFSSSHYMCWVRQAPGKGLEWVACIYAGSSGN TYYANWAKGRFTISKTNSKNTLYLQMNSLRAEDTAVYFCARVDASSSGSWDLWGQGTL VTVSS
MAB-16-0028	20	EVQLLESGGRLVQPGTSLRLSCAVSGIDLSSYAMGWVRQAPGKGLEYVGVITSSATTYYAS WAKGRFTISKTSSTTLYLQMNSLRAEDTAVYFCARGGPGYSTNTHYAFDPWGQGTLVTV SS
MAB-16-0031	21	EVQLEESGGRVVQPGTSLRLSCAVSGIDLDNYAMGWVRQAPGKGLEYVAVISSDGFFYD ASWAKGRFTISKANSKNTLYLQMNSLRAEDTAVYFCARDRGTSTGSLDLWGQGTLVTVS S
MAB-16-0043	22	QVQLEESGGRLVQPGTSLRLSCAASGFSLSSYYMSWVRQAPGKGLEWVAIISGSASTYYA TWAKGRFTISKTSTTLYLQMNSLRAEDTAVYFCARTHYAAVAGYGYASRLDLWGQGTLV TVSS
MAB-16-0049	23	QVQLQESGGDLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLELVACIYTSTGNT WYASWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCARDLLVVTSFNLWGQGTLVTV SS
MAB-16-0045	24	EVQLVESGGDLVQPGASLRLSCAASGFSFSSSYYMCWVRQAPGKGLEWVACIYAGSSGV TYYASWAKGRFTISDTSSTTLYLQMNSLRAEDTAVYFCASETDGNYFNLWGQGTLVTVSS
MAB-16-0040	25	EVQLEQSGGGLVQPGGSLRLSCAASGFSLSTSYWRCWVRQAPGKGLEWVACIYAGSGD VTYYANWVNGRFTISRDNSKSTLYLQMNSLRAEDTAVYYCASGVGFGYFNLWGQGTLVT VSS
MAB-16-0036	26	EVQLEESGGGLVQPGGSLRLSCAASGIDFSSYYYMCWVRQAPGKGLEWVACIFIGYGDVT WYASWAKGRFTISKANSKNTLYLQMNSLRAEDTAVYFCARALGSSGYRVNLWGQGTLV TVSS
MAB-16-0046	27	QVQLEESGGRLVQPGASLRLSCAASGFSLSSYWMSWVRQAPGKGLEWVAMIYGSGYTY YASWAKGRFTISTTSTTLYLQMNSLRAEDTAVYFCARDPQYFILWGQGTLVTVSS
MAB-16-0030	28	EVQLEESGGRLVQPGTSLRLSCAVSGFSLSSYDMSWVRQAPGKGLEWVSTIYIGGTTAYA SWPKGRFTISKTNSKNTLYLQMNSLRAEDTAVYFCARLQGANYYNSLALWGQGTLVTVS S
MAB-16-0021	29	QVQLVESGGGLVQPGGSLRLSCAASGFDFSSNYYMCWVRQAPGKGLELVACIYTNSGNT WSASWAKGRFTISKTNSTTLYLQMNSLRAEDTAVYFCARDLNYPDTSNLWGQGTLVTVS S
MAB-16-	30	EVQLEESGGDLVQPGGSLRLSCAASGFSFSFGYYMCWVRQAPGKGLEWVACIYGDSSDT

0019		LYANWAKGRFTISKTNSKNTLYLQMNSLRAEDTAVYFCARYPGGSYYNLWGQGTLVTVS S
MAB-16-0015	31	QVQLQESGGDLVQPGASLRLSCAASGFSFSSTYYMCWVRQAPGKGLEWVACIYAGSSGS TYYASWAKGRFTISKNSSTLYLQMNSLRAEDTAVYFCARVDGSSSGSWDLWGQGTLVTV SS
MAB-16-0027	32	EVQLEESGGDLVQPGASLRLSCAASGISFSSSDFMCWVRQAPGKGLEWVACIYAGSSVSI YYATWAKGRFTISKASSTTLYLQMNSLRAEDTAVYFCARSTGSVGRGFNLWGQGTLVTVS S
MAB-16-0048	33	EVQLVESGGGLVQPGGSLRLSCAASGFSFSSIYYMCWVRQAPGKGLEWVGCIYTGNSDF TYYANWAKGRFTISRDNSKSTLYLQMNSLRAEDTAVYFCARFRDDYASLKLWGQGTLVT VSS
MAB-16-0041	34	QVQLQESGGGLVQPGGSLRLSCTASGFSFSSGYDMCWVRQAPGKGLEWVGCIYTGSGS TYYANWAKGRFTISKDNSKTTLYLQMNSLRAEDTAVYFCARNSNDWMYFNLWGQGTLV TVSS

mAb Name	SEQ ID NO.	Complete k-Light chain VR sequence
MAB-15-0139	35	DIVMTQSPSSLSASVGDRVTITCQASESISNYLSWYQQKPGQAPKLLIYLASTLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQNWWVIEHNGAAFGGGTKVVIK
MAB-15-0106	36	DIQMTQSPSSLSASVGDRVTITCQASESIYSNLAWYQQKPGQAPKLLIYAASLLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQSASYSTGPDWTFGQGTKVVIK
MAB-15-0108	37	DIQMTQSPSSLSASVGDRVTITCQASQSIYIYLSWYQQKPGQAPKLLIYDASKLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQGATTYNVDNVFGQGTKVVIK
MAB-15-0110	38	DIVMTQSPSSLSASVGDRVTITCQASENIGNGLAWYQQKPGQAPKLLIYGASTLASGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQCTYWNPDYIGGAFGGGTKVVIK
MAB-15-0117	39	DIQMTQSPSSLSASVGDRVTITCLASEDIYSGISWYQQKPGKAPKLLIYAASNLESGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCLGGYSYSNTGPTFGQGTKVEIK
MAB-15-0121	40	DIVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYGASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVCTDISTDDLYNAFGQGTKVVIK
MAB-15-0140	41	DIVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYRASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVYTYSTDIHAFGGGTKVVIK
MAB-15-0115	42	DIVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYDASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVYTHISADNAFGGGTKVVIK
MAB-15-0125	43	DIQMTQSPSSLSASVGDRVTITCQASENIYSSLAWYQQKPGQAPKLLIYDASDLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGYYSGGTDNDVFGGGTKVVIK
MAB-15-0119	44	DIVMTQSPSSLSASVGDRVTITCQSSQSVDGNNLLSWYQQKPGQAPKLLIYDASNLASGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQGSYYSSSWYNVFGQGTKVVIK
MAB-15-0109	45	DIQMTQSPSSLSASVGDRVTITCQASQSIYSFLSWYQQKPGQAPKLLIYAASDLESGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQCNYIIDYGAFGQGTKVVIK
MAB-15-0097	46	DIQMTQSPSSLSASVGDRVTITCQASQSIGYYLAWYQQKPGQAPKLLIYRASTLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQSYYNSDSDAFGQGTKVVIK
MAB-15-0135	47	DIVMTQSPSSLSASVGDRVTITCQASQTISINLAWYQQKPGQAPKLLIYYASTLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQGYTEDNIDNTFGQGTKVVIK
MAB-15-0133	48	DIQMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPGQAPKLLIYAASLLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQGAVYSGNTEWAFGQGTKVVIK
MAB-15-0107	49	DIVMTQSPSSLSASVGDRVTITCQASQSVYNSNHLSWYQQKPGQAPKLLIYSASTLASGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQGEFSCVSADCIAFGGGTKVVIK
MAB-15-0128	50	DIQMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQQKPGQAPKLLIYGASNLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQCTYYDNNYGGAFGGGTKVVIK

MAB-15-0116	51	DIVMTQSPSSLSASVGDRVTITCQASESISANYWSWYQQKPGQAPKLLIYGASTLASGVPS RFSGSGSGTDFTLTISSLQPEDFATYFCQSWYYSGSGSYHSWAFGQGTKVVIK
MAB-16-0004	52	DIVMTQSPSSLSASVGDRVTITCQASESISNYLSWYQQKPGQAPKLLIYLASTLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQNWWVIEHNGAAFGGGTKVVIK
MAB-16-0009	53	AIQMTQSPSSLSASVGDRVTITCQASESIYSNLAWYQQKPGQAPKLLIYAASLLASGVPSRF SGSGSGTDYTLTISSLQPEDFATYYCQSASYSTGPDWTFGQGTKVVIK
MAB-16-0028	54	AIRMTQSPSSLSASVGDRVTITCQASQSIYIYLSWYQQKPGQAPKLLIYDASKLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQGATTYNVDNVFGQGTKVVIK
MAB-16-0031	55	ELVMTQSPSSLSASVGDRVTITCQASENIGNGLAWYQQKPGQAPKLLIYGASTLASGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQCTYWNPDYIGGAFGGGTKVVIK
MAB-16-0043	56	AIQMTQSPSSLSASVGDRVTITCLASEDIYSGISWYQQKPGKAPKLLIYAASNLESGVPSRFS GSGSGTDYTLTISSLQPEDFATYYCLGGYSYSNTGPTFGQGTKVEIK
MAB-16-0049	57	DIVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYGASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVCTDISTDDLYNAFGQGTKVVIK
MAB-16-0045	58	DIVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYRASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVYTYSTDIHAFGGGTKVVIK
MAB-16-0040	59	ELVMTQSPSSLSASVGDRVTITCQASEDIYSNLAWFQQKPGQAPKLLIYDASTLASGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCLGVYTHISADNAFGGGTKVEIK
MAB-16-0036	60	ALQMTQSPSSLSASVGDRVTITCQASENIYSSLAWYQQKPGQAPKLLIYDASDLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGYYSGGTDNDVFGGGTKVVIK
MAB-16-0046	61	NIVMTQSPSSLSASVGDRVTITCQSSQSVDGNNLLSWYQQKPGQAPKLLIYDASNLASGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQGSYYSSSWYNVFGQGTKVVIK
MAB-16-0030	62	DVQMTQSPSSLSASVGDRVTITCQASQSIYSFLSWYQQKPGQAPKLLIYAASDLESGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQCNYIIDYGAFGQGTKVVIK
MAB-16-0021	63	DIQMTQSPSSLSASVGDRVTITCQASQSIGYYLAWYQQKPGQAPKLLIYRASTLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQSYYNSDSDAFGQGTKVVIK
MAB-16-0019	64	AIVMTQSPSSLSASVGDRVTITCQASQTISINLAWYQQKPGQAPKLLIYYASTLASGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQGYTEDNIDNTFGQGTKVVIK
MAB-16-0015	65	AIQMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPGQAPKLLIYAASLLASGVPSR FSGSGSGTDYTLTISSLQPEDFATYYCQGAVYSGNTEWAFGQGTKVVIK
MAB-16-0027	66	DIVMTQSPSSLSASVGDRVTITCQASQSVYNSNHLSWYQQKPGQAPKLLIYSASTLASGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQGEFSCVSADCIAFGGGTKVVIK
MAB-16-0048	67	DVVMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQQKPGQAPKLLIYGASNLASGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQCTYYDNNYGGAFGGGTKVEIK
MAB-16-0041	68	DIVMTQSPSSLSASVGDRVTITCQASESISANYWSWYQQKPGQAPKLLIYGASTLASGVPS RFSGSGSGTDFTLTISSLQPEDFATYFCQSWYYSGSGSYHSWAFGQGTKVVIK

mAB name		SEQ ID NO.	CDR-H1	SEQ ID NO.	CDR-H2	SEQ ID NO.	CDR-H3
MAB-15-0139	**MAB-16-0004**	69	SSYWIC	86	CIYTGSGGTYYASWEKG	103	DPGYSSWL
MAB-15-0106	**MAB-16-0009**	70	SSHYMC	87	CIYAGSSGNTYYANWAKG	104	VDASSSGSWDL
MAB-15-0108	**MAB-16-0028**	71	SYAMG	88	VITSSATTYYASWAKG	105	GGPGYSTNTHYAFDP
MAB-	**MAB-**	72	NYAMG	89	VISSDGFFYDASWAKG	106	DRGTSTGSLDL

15-0110	16-0031						
MAB-15-0117	MAB-16-0043	73	SYYMS	90	IISGSASTYYATWAKG	107	THYAAVAGYGYASRLDL
MAB-15-0121	MAB-16-0049	74	SNYWIC	91	CIYTSTGNTWYASWAKG	108	DLLVVTSFNL
MAB-15-0140	MAB-16-0045	75	SSYYMC	92	CIYAGSSGVTYYASWAKG	109	ETDGNYFNL
MAB-15-0115	MAB-16-0040	76	TSYWRC	93	CIYAGSGDVTYYANWVNG	110	GVGFGYFNL
MAB-15-0125	MAB-16-0036	77	SYYYMC	94	CIFIGYGDVTWYASWAKG	111	ALGSSGYRVNL
MAB-15-0119	MAB-16-0046	78	SYWMS	95	MIYGSGYTYYASWAKG	112	DPQYFIL
MAB-15-0109	MAB-16-0030	79	SYDMS	96	TIYIGGTTAYASWPKG	113	LQGANYYNSLAL
MAB-15-0097	MAB-16-0021	80	SNYYMC	97	CIYTNSGNTWSASWAKG	114	DLNYPDTSNL
MAB-15-0135	MAB-16-0019	81	FGYYMC	98	CIYGDSSDTLYANWAKG	115	YPGGSYYNL
MAB-15-0133	MAB-16-0015	82	STYYMC	99	CIYAGSSGSTYYASWAKG	116	VDGSSSGSWDL
MAB-15-0107	MAB-16-0027	83	SSDFMC	100	CIYAGSSVSIYYATWAKG	117	STGSVGRGFNL
MAB-15-0128	MAB-16-0048	84	SIYYMC	101	CIYTGNSDFTYYANWAKG	118	FRDDYASLKL
MAB-15-0116	MAB-16-0041	85	SGYDMC	102	CIYTGSGSTYYANWAKG	119	NSNDWMYFNL

mAB name		SEQ ID NO.	CDR-L1	SEQ ID NO.	CDR-L2	SEQ ID NO.	CDR-L3
MAB-15-0139	MAB-16-0004	120	QASESISNYLS	137	LASTLAS	154	QNWWVIEHNGAA
MAB-	MAB-	121	QASESIYSNLA	138	AASLLAS	155	QSASYSTGPDWT

15-0106	**16-0009**						
MAB-15-0108	**MAB-16-0028**	122	QASQSIYIYLS	139	DASKLAS	156	QQGATTYNVDNV
MAB-15-0110	**MAB-16-0031**	123	QASENIGNGLA	140	GASTLAS	157	QCTYWNPDYIGGA
MAB-15-0117	**MAB-16-0043**	124	LASEDIYSGIS	141	AASNLES	158	LGGYSYSNTGPT
MAB-15-0121	**MAB-16-0049**	125	QASEDIYSNLA	142	GASTLAS	159	LGVCTDISTDDLYNA
MAB-15-0140	**MAB-16-0045**	126	QASEDIYSNLA	143	RASTLAS	160	LGVYTYSTDIHA
MAB-15-0115	**MAB-16-0040**	127	QASEDIYSNLA	144	DASTLAS	161	LGVYTHISADNA
MAB-15-0125	**MAB-16-0036**	128	QASENIYSSLA	145	DASDLAS	162	QQGYYSGGTDNDV
MAB-15-0119	**MAB-16-0046**	129	QSSQSVDGNNLLS	146	DASNLAS	163	QGSYYSSSWYNV
MAB-15-0109	**MAB-16-0030**	130	QASQSIYSFLS	147	AASDLES	164	QCNYIIDYGA
MAB-15-0097	**MAB-16-0021**	131	QASQSIGYYLA	148	RASTLAS	165	QSYYNSDSDA
MAB-15-0135	**MAB-16-0019**	132	QASQTISINLA	149	YASTLAS	166	QQGYTEDNIDNT
MAB-15-0133	**MAB-16-0015**	133	QASQNIYSNLA	150	AASLLAS	167	QGAVYSGNTEWA
MAB-15-0107	**MAB-16-0027**	134	QASQSVYNSNHLS	151	SASTLAS	168	QGEFSCVSADCIA
MAB-15-0128	**MAB-16-0048**	135	QASQSISSYLS	152	GASNLAS	169	QCTYYDNNYGGA
MAB-15-0116	**MAB-16-0041**	136	QASESISANYWS	153	GASTLAS	170	QSWYYSGSGSYHSWA

SEQ ID NO.	Constant region sequences (CR)
171	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
172	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

mAB name	SEQ ID NO.	Complete Heavy-chain VR seq
MAB-16-0150	173	EVQLLESGGRLVQPGTSLRLSCAVSGIDLSSYAMGWVRQAPGKGLEYVGVITSSATTYYAS WAKGRFTISKTSSKNTLYLQMNSLRAEDTAVYFCARGGPGYSTNTHYAFDPWGQGTLVT VSS

mAB name	SEQ ID NO.	Complete light-chain VR seq
MAB-16-0149	174	DVQMTQSPSSLSASVGDRVTITCQASQSIYSFLSWYQQKPGQAPKLLIYAASDLESGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQSNYIIDYGAFGQGTKVVIK
		CDR-L3
MAB-16-0149	175	QSNYIIDYGA

mAB name	CDR-H1 SEQ ID NO.	CDR-H2 SEQ ID NO.	CDR-H3 SEQ ID NO.	CDR-L1 SEQ ID NO.	CDR-L2 SEQ ID NO.	CDR-L3 SEQ ID NO.	VH SEQ ID NO.	VL SEQ ID NO.
MAB-16-0150	71	88	105	122	139	156	173	54
MAB-16-0149	79	96	113	130	147	175	28	174

mAB name	SEQ ID NO.	Complete heavy-chain VR seq
MAB-16-0531	176	QSLEESGGGLVKPEGSLTLTCKASGIDFSQDYYMCWVRQAPGKGLEWIACIYTGNDITYY ASWAKGRFTVSKTSSTTVTLQMTSLTAADTATYFCARDGGANYYFKFWGQGTLVTVSS
		Complete light-chain VR seq
MAB-16-0531	177	DIVMTQTPASVEAAVGGTVTIKCQASQSISNLLAWYQQKPGQPPKLLIYGASTLESGVPSR FKGSGSGTEFTLTISDLGSADAATYYCQNYAYSSGSWYSFGGGTEVVVK

MAB-16-0531	CDR-H1	CDR-H2	CDR-H3	CDR-L1	CDR-L2	CDR-L3
SEQ ID NO.	178	179	180	181	182	183
	QDYYMC	CIYTGNDITYY ASWAKG	DGGANYYFKF	QASQSISNLLA	GASTLES	QNYAYSSG SWYS

Fig.2: Human IL-1R3 ELISA

Antibody ID	huIL1RaP ELISA EC50 [ng/ml]
MAB-16-0015	1,6
MAB-16-0019	28,1
MAB-16-0021	20,8
MAB-16-0004	8,0
MAB-16-0009	4,9
MAB-16-0027	5,3
MAB-16-0030	4,5
MAB-16-0040	6,6
MAB-16-0043	13,2
MAB-16-0046	7,4
MAB-16-0049	20,6
MAB-16-0028	6,0
MAB-16-0031	8,2
MAB-16-0041	15,2
MAB-16-0036	5,9
MAB-16-0045	28,4
MAB-16-0048	7,4
Reference AF676	79,6

Fig.3: HEK293 reporter assay

Antibody ID	HEK reporter assay (IL1b) EC50 [ng/ml]
MAB-16-0015	27,3
MAB-16-0019	2,5
MAB-16-0021	33,0
MAB-16-0004	67,1
MAB-16-0009	18,2
MAB-16-0027	37,3
MAB-16-0030	8,7
MAB-16-0040	9,4
MAB-16-0043	27,0
MAB-16-0046	6,1
MAB-16-0049	42,6
MAB-16-0028	5,1
MAB-16-0031	23,3
MAB-16-0041	0,1
MAB-16-0036	9,5
MAB-16-0045	90,2
MAB-16-0048	16,3
Reference AF676	234

Fig. 4: NFkB luciferase reporter assay using an A549 stable cell line

Antibody ID	Signosis NFkB A549 (IL-1b) EC50 [ng/ml]
MAB-16-0015	+
MAB-16-0019	++
MAB-16-0021	+
MAB-16-0004	++
MAB-16-0009	+++
MAB-16-0027	++
MAB-16-0030	+++
MAB-16-0040	+
MAB-16-0043	+
MAB-16-0046	+++
MAB-16-0049	+
MAB-16-0028	+++
MAB-16-0031	+
MAB-16-0041	+
MAB-16-0036	+++
MAB-16-0045	+
MAB-16-0048	+
Reference AF676	+

Fig. 5: Cell binding analysis: Binding to IL-1R3 expressing cells

	NIH-3T3	A549	HEK-293	SK-MEL-30
Antibody	**MFI – fold over isotype control**			
MAB-16-0019	1,2	2,7	3,6	79,0
MAB-16-0030	0,9	2,4	2,8	69,7
MAB-16-0040	1,0	2,6	3,0	73,7
MAB-16-0036	1,1	2,0	3,0	70,6
MAB-16-0149	1,1	2,4	3,4	77,7
MAB-16-0150	1,1	3,2	4,8	87,1

Fig. 6: Cell binding analysis: Cell binding on human-IL-1R3 high expressing cell line SK-MEL-30

Antibody	EC50 (ng/mL)
MAB-16-0030	307
MAB-16-0149	306

Fig. 7: Human-IL-1R3 biochemical ELISA

Antibody	EC50 (ng/mL)
MAB-16-0149	16,3
MAB-16-0150	29,1

Fig. 8: Inhibition of human IL-1a and IL-1b mediated NfKB signaling in A549-NFkB-RE-Luc cells

	Stimulated with hIL-1a	Stimulated with hIL-1b
Antibody	**EC50 (ng/mL)**	**EC50 (ng/mL)**
MAB-16-0019	56	140
MAB-16-0030	156	149
MAB-16-0040	969	636
MAB-16-0036	199	25
MAB-16-0149	167	109
MAB-16-0150	211	11
AF676	3134	919

Fig. 9: IL-1α and IL-1β functional neutralization assay - Inhibition of human IL-1a and IL-1b mediated IL-6 release by A-549 cells

	Stimulated with hIL-1a	Stimulated with hIL-1b
Antibody	**EC50 (ng/mL)**	**EC50 (ng/mL)**
MAB-16-0019	546	180
MAB-16-0030	361	346
MAB-16-0040	2246	234
MAB-16-0036	378	253
MAB-16-0149	266	108
MAB-16-0150	1464	313
AF676	>10000	>10000

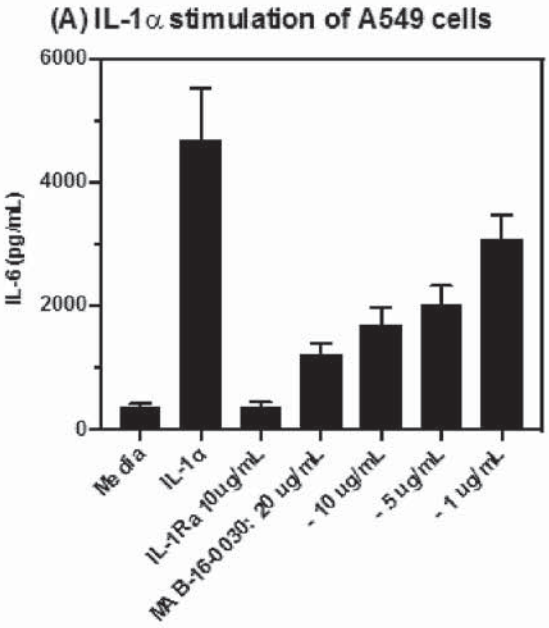
Fig. 10: IL-33 functional neutralization assay - Inhibition of human IL-33 mediated NfkB-signaling in HEK-Blue-IL33™ cells

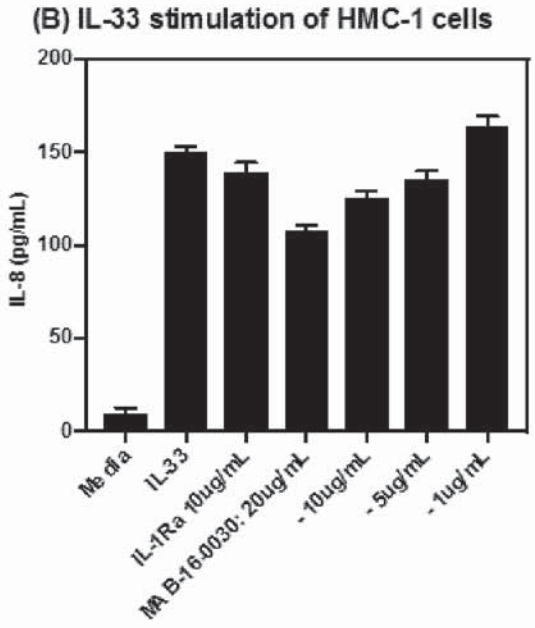
	Stimulated with hIL33
Antibody	**EC50 (ng/mL)**
MAB-16-0019	376
MAB-16-0030	909
MAB-16-0040	17195
MAB-16-0036	426
MAB-16-0149	432
MAB-16-0150	2115
AF676	26114

Fig. 11: IL-36 functional neutralization assay - Inhibition of human IL-36 mediated NfkB-signaling in HEK-293/17-IF cells

	Stimulated with hIL36
Antibody	**EC50 (ng/mL)**
MAB-16-0019	11
MAB-16-0030	13
MAB-16-0040	42
MAB-16-0036	14
MAB-16-0149	18
MAB-16-0150	13
AF676	502

Fig. 12: Neutralization of IL-1a, IL-33 and IL-36a - Neutralization of IL-1a, IL-33 and IL-36a mediated cellular cytokine release by IL-1Ra and MAB-16-0030





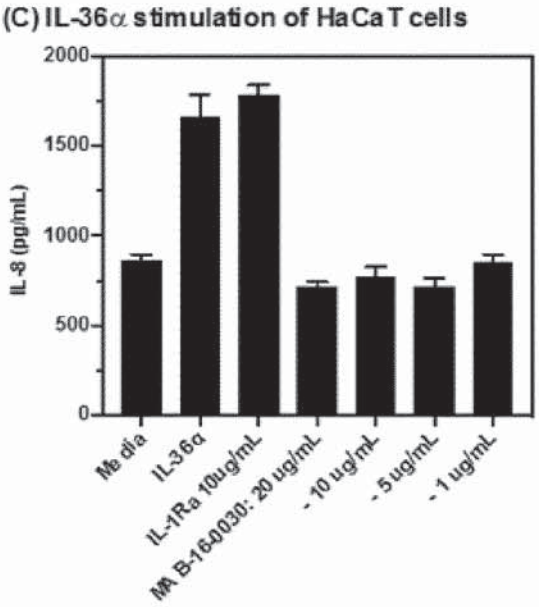


Fig. 13: Viability and IL-6 release of unstimulated PBMC treated with humanized anti-IL-1R3 IgG1-LALA antibody MAB-16-0030

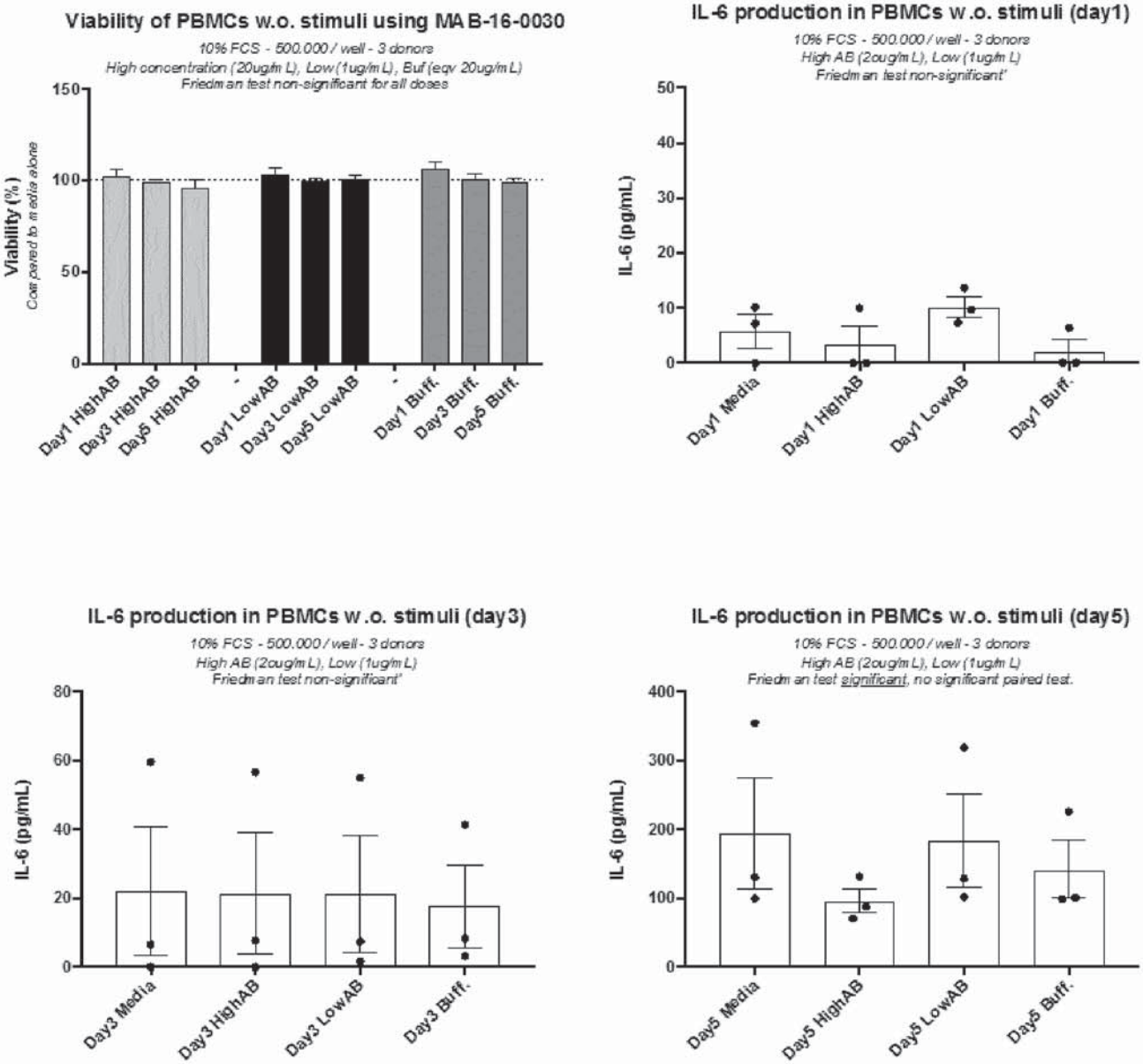
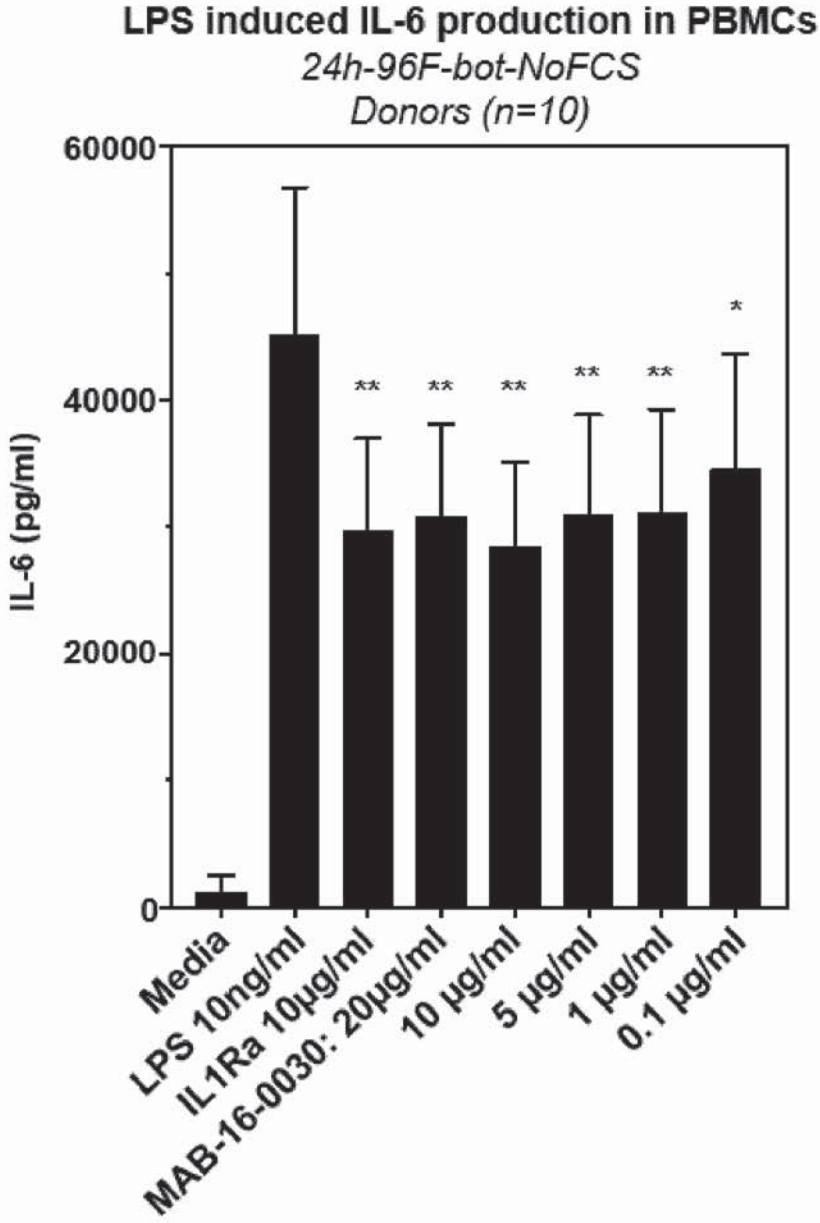


Figure 14: Functional blockage of PBMCs with different stimuli



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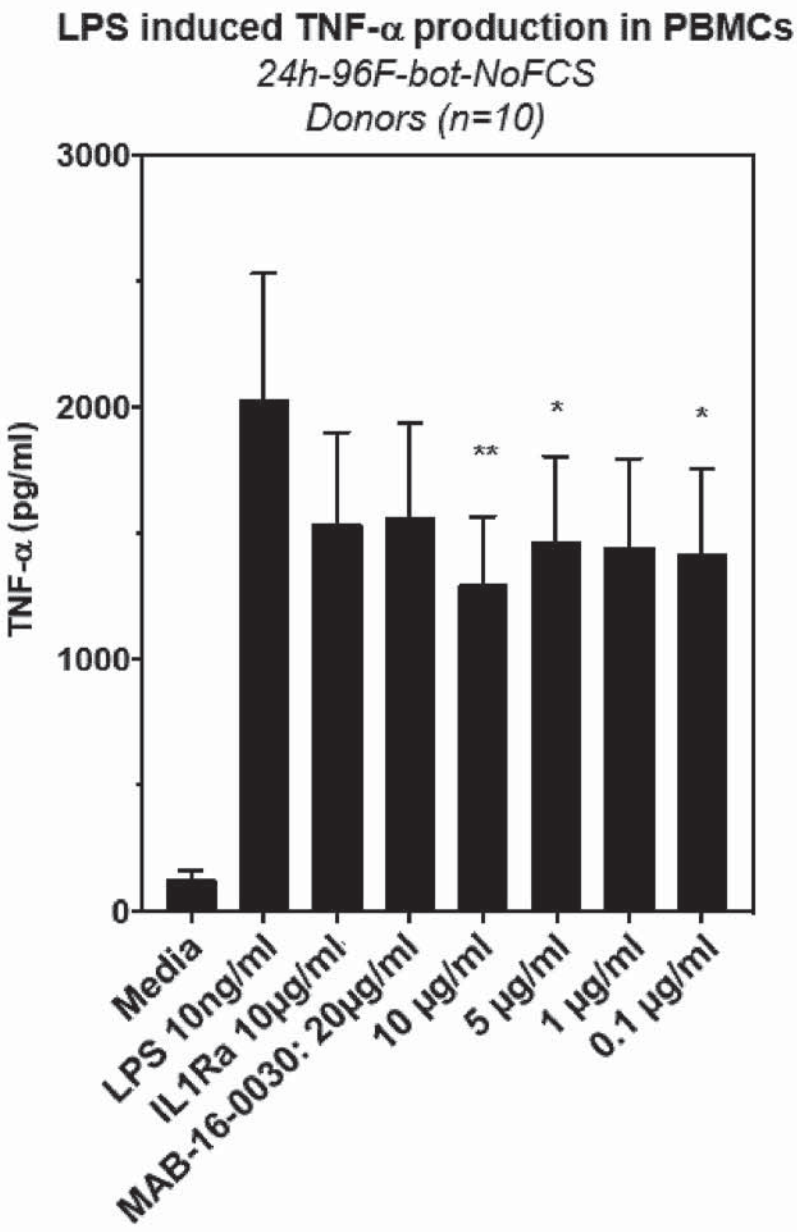

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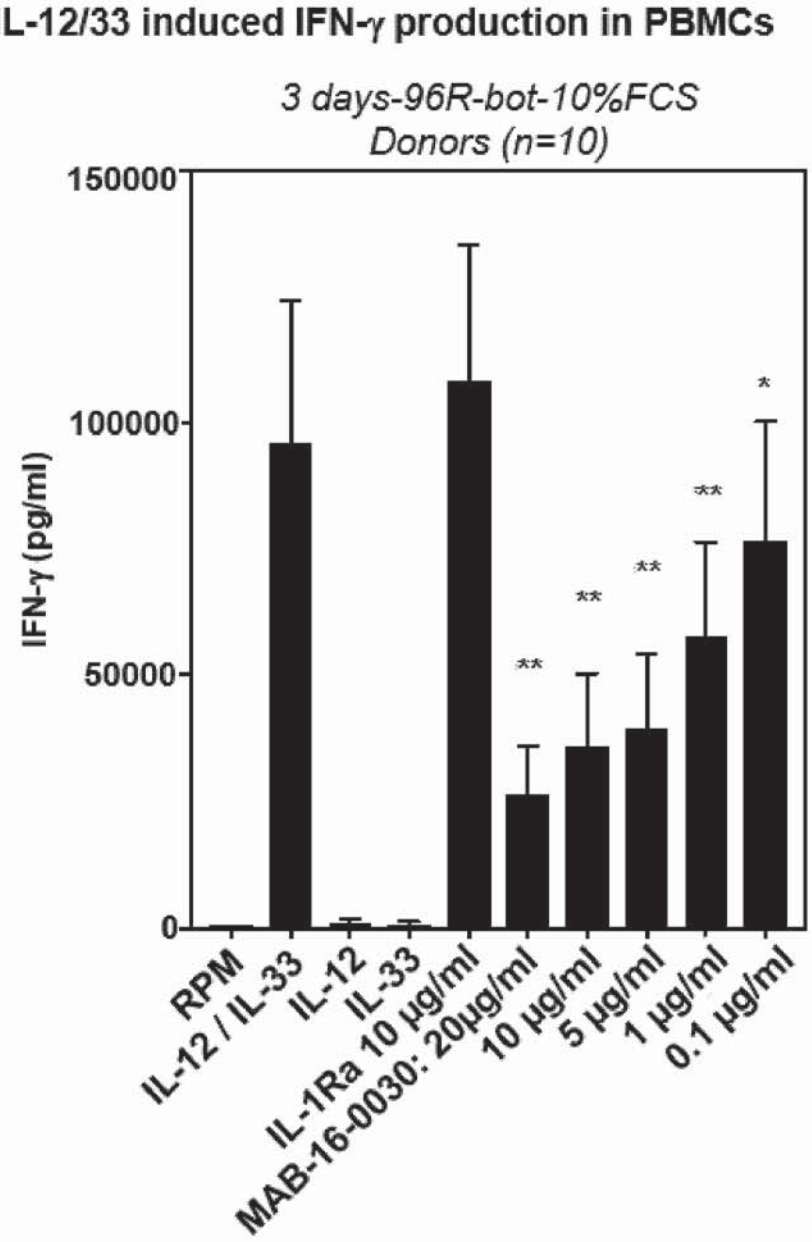

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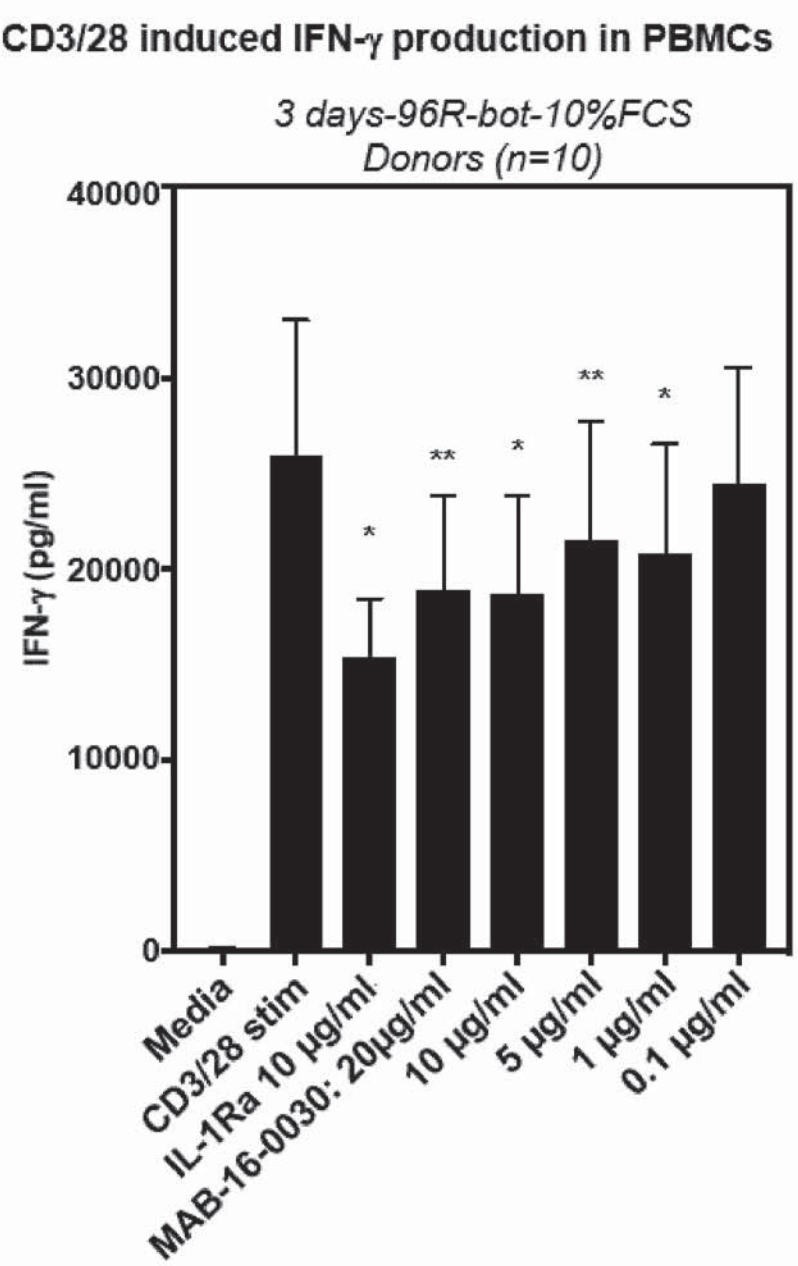

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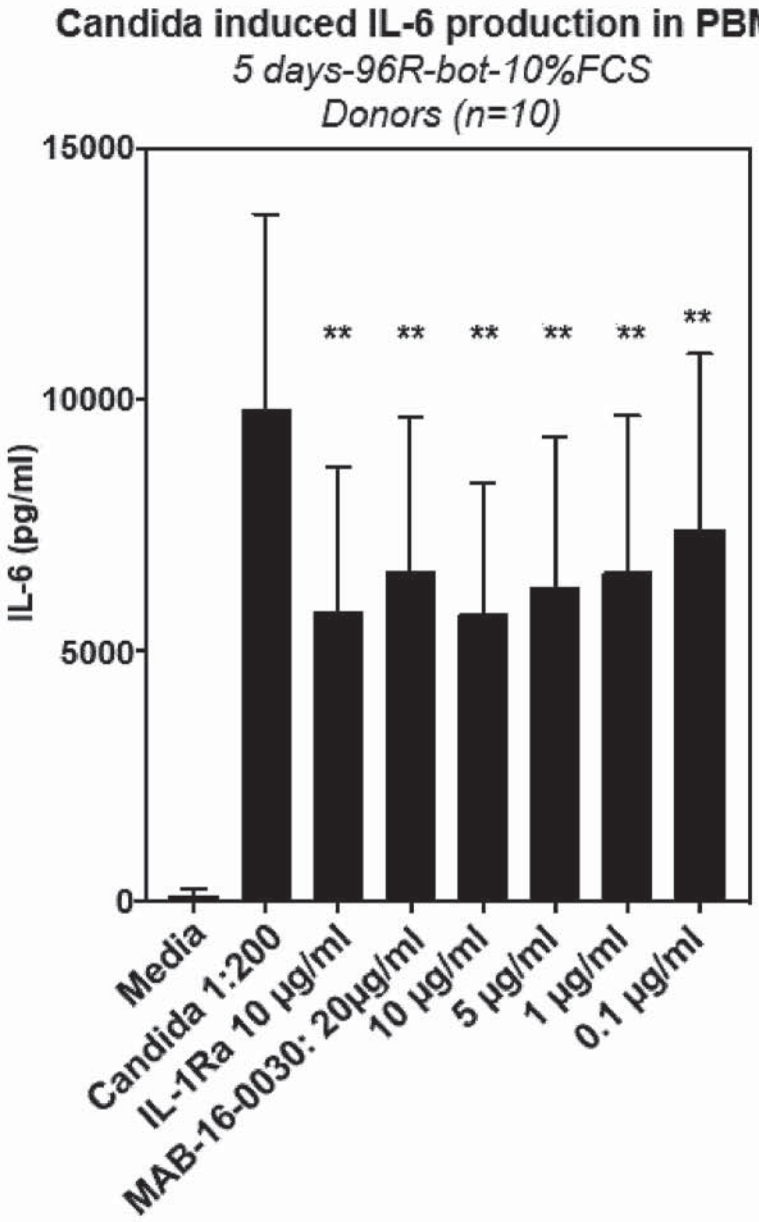

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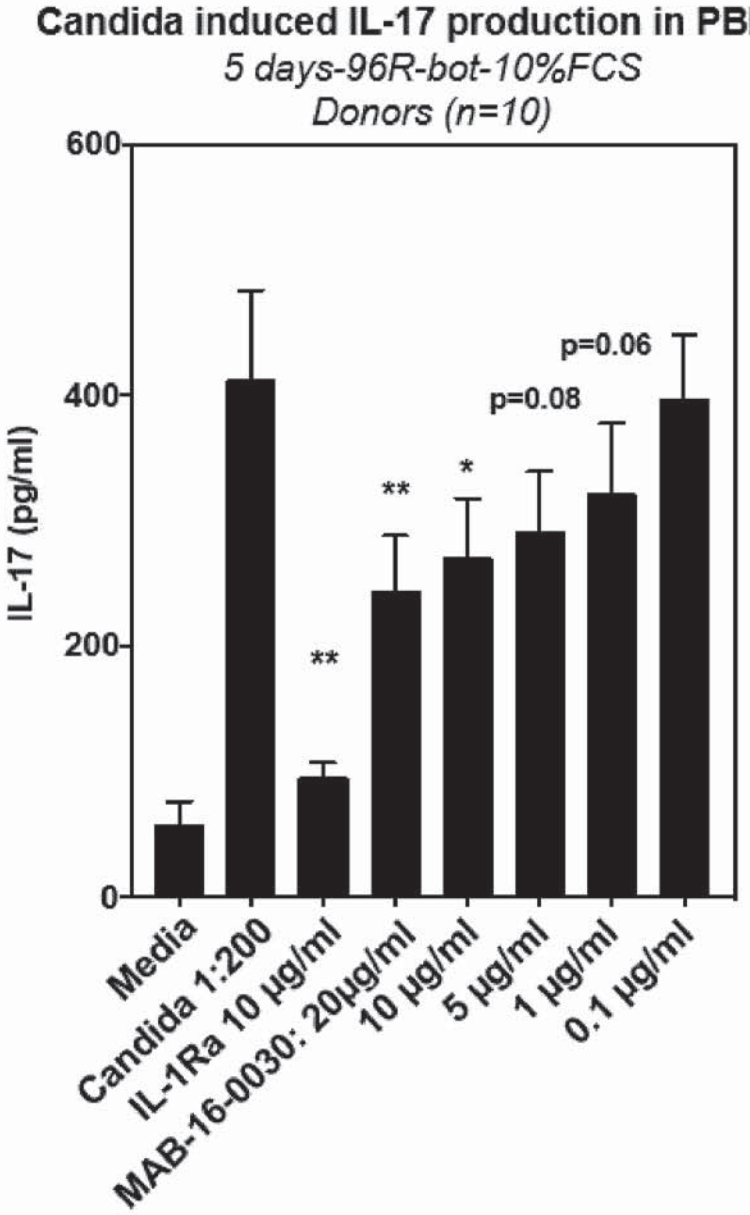


Figure 15: Functional blockage of immune cells in whole blood activated with *Candida albicans*

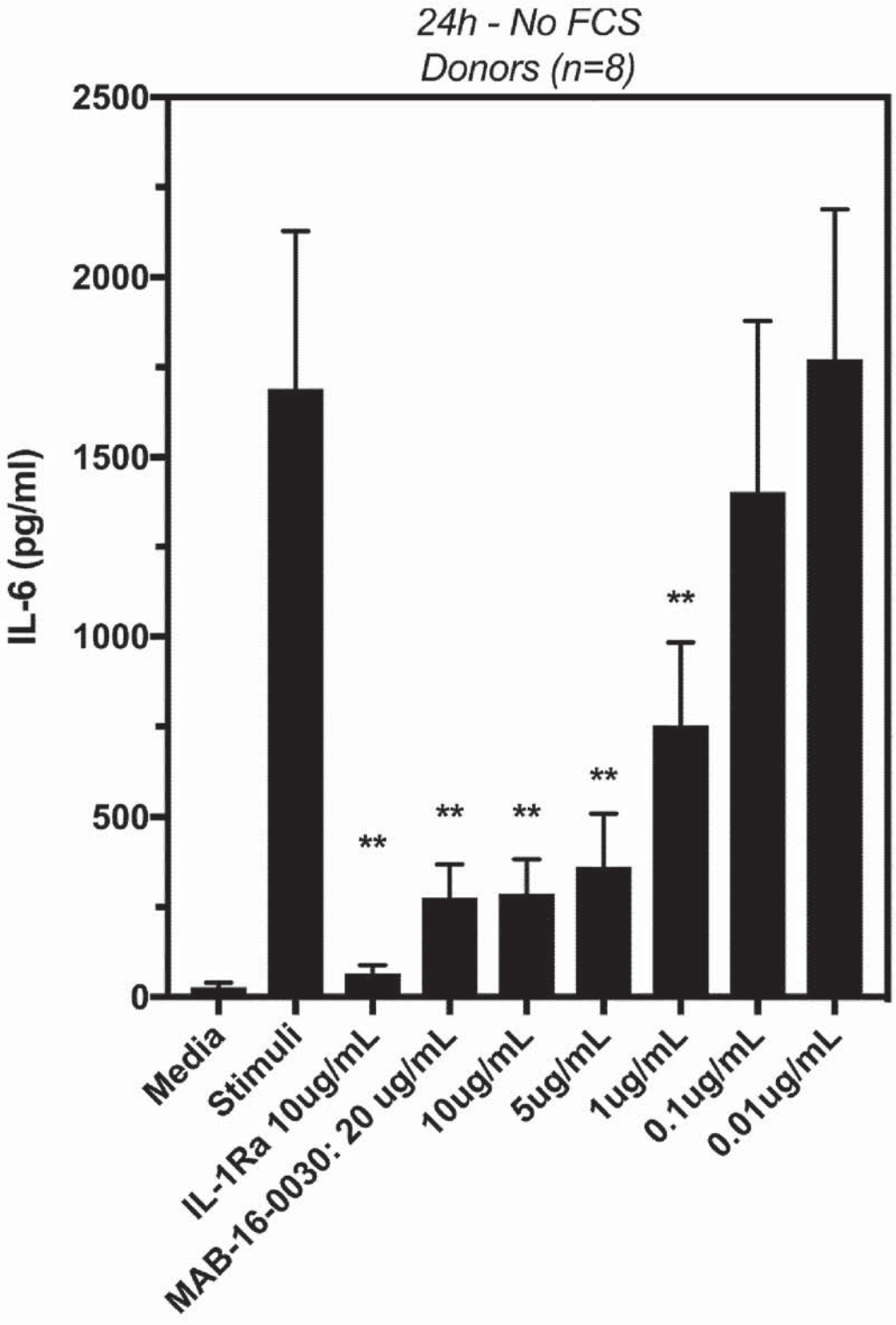
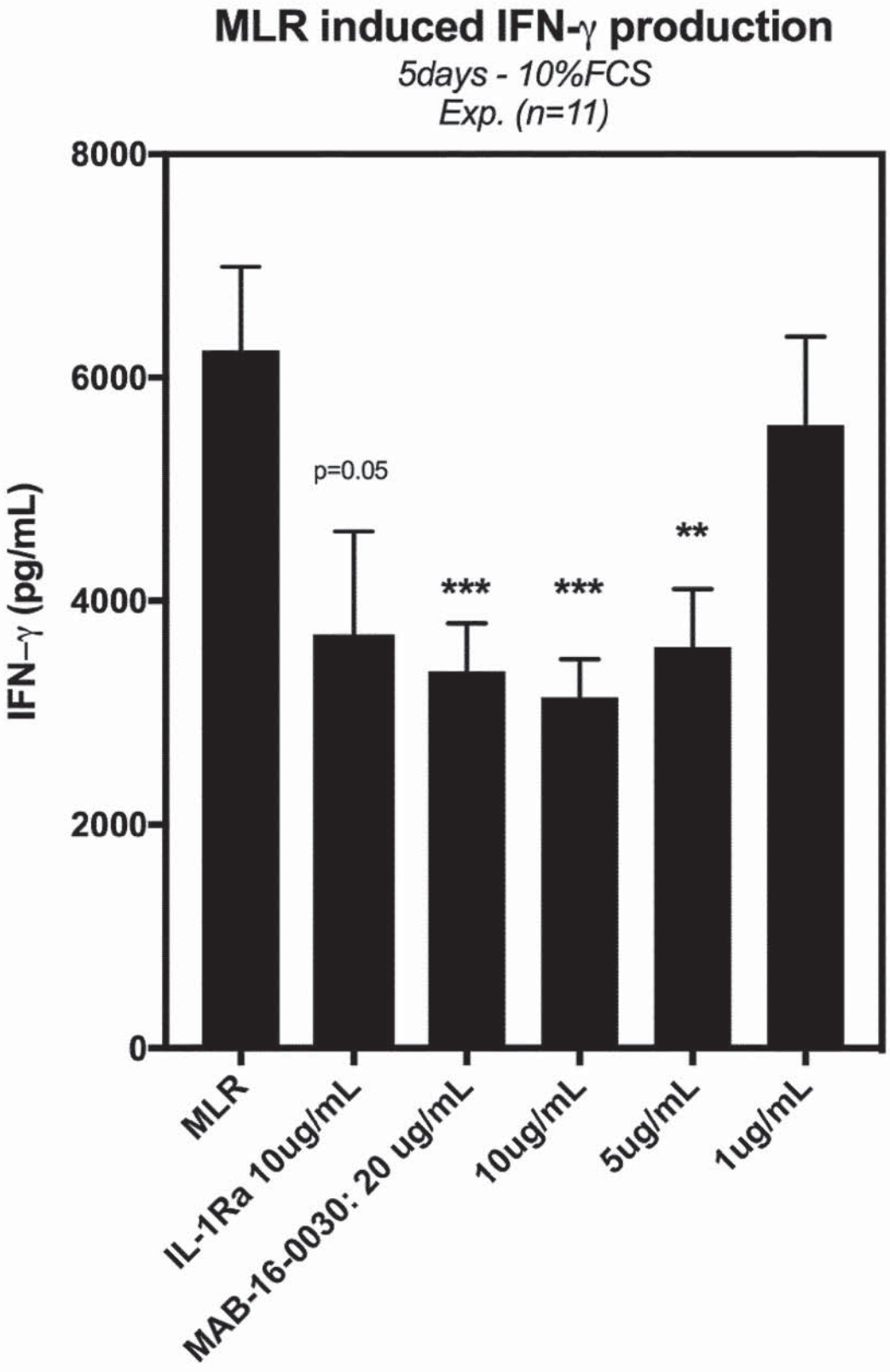


Figure 16: Blockage of cytokine release in Mixed Lymphocyte Reactions (MLR)



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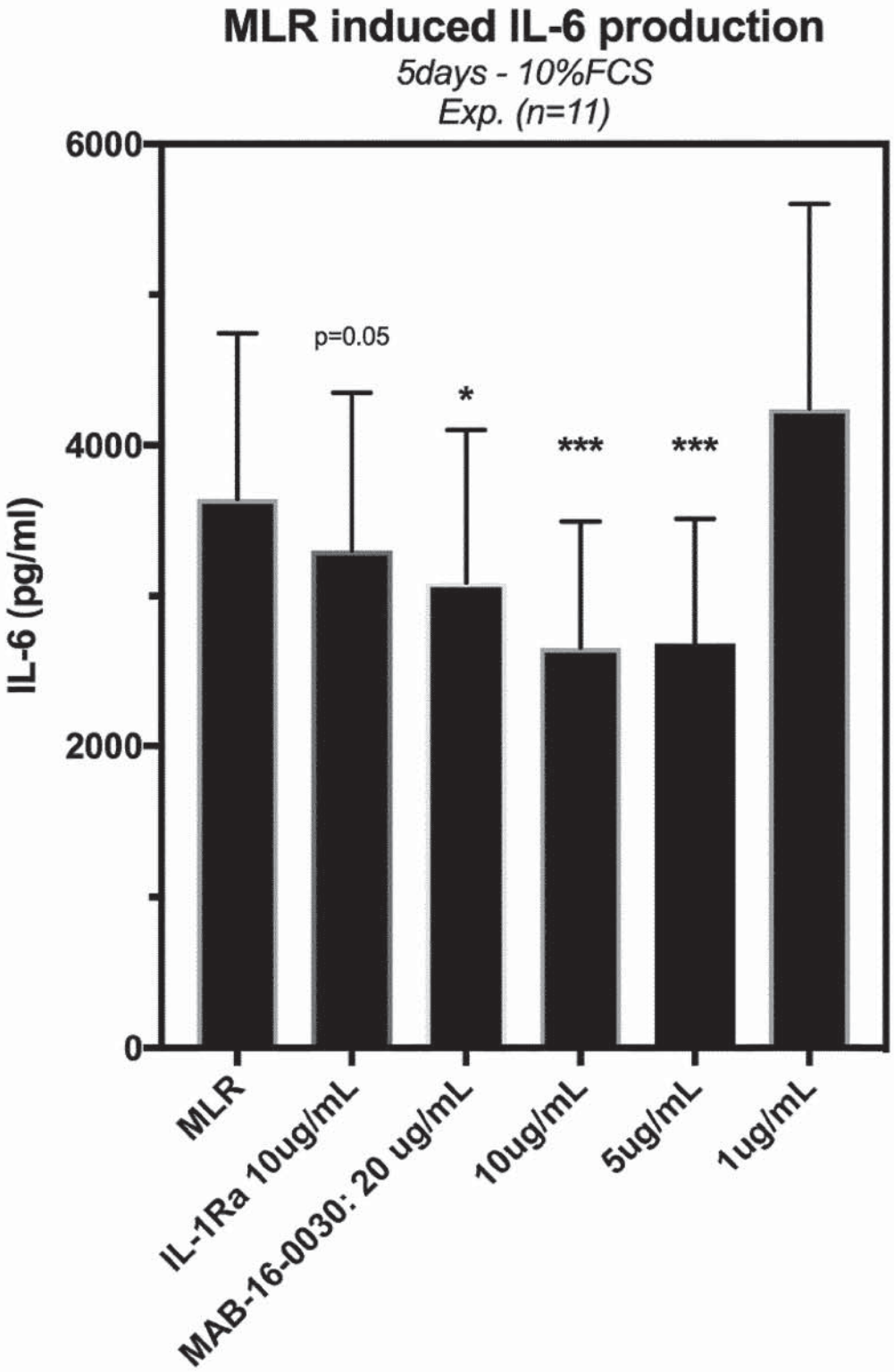

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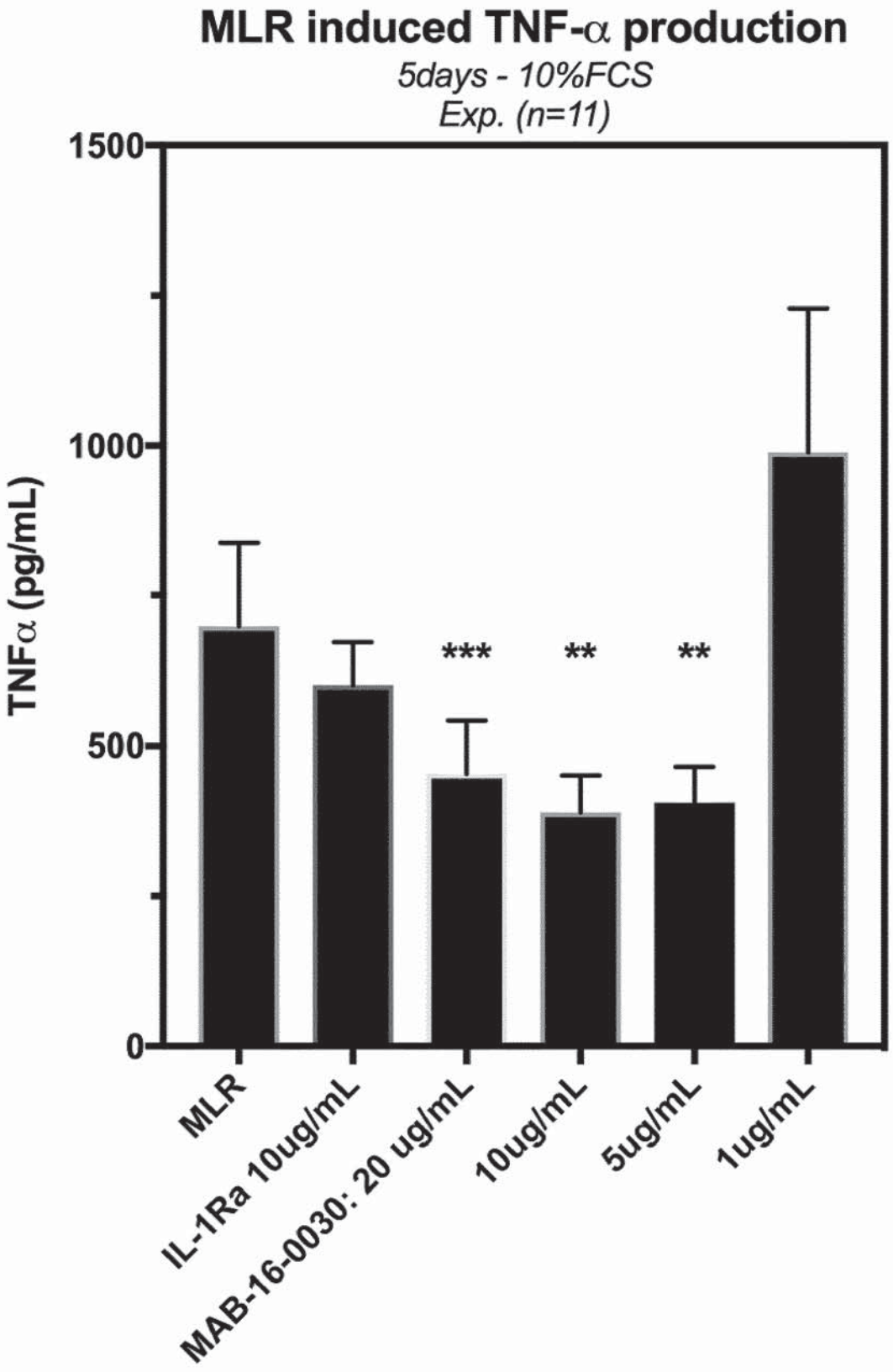

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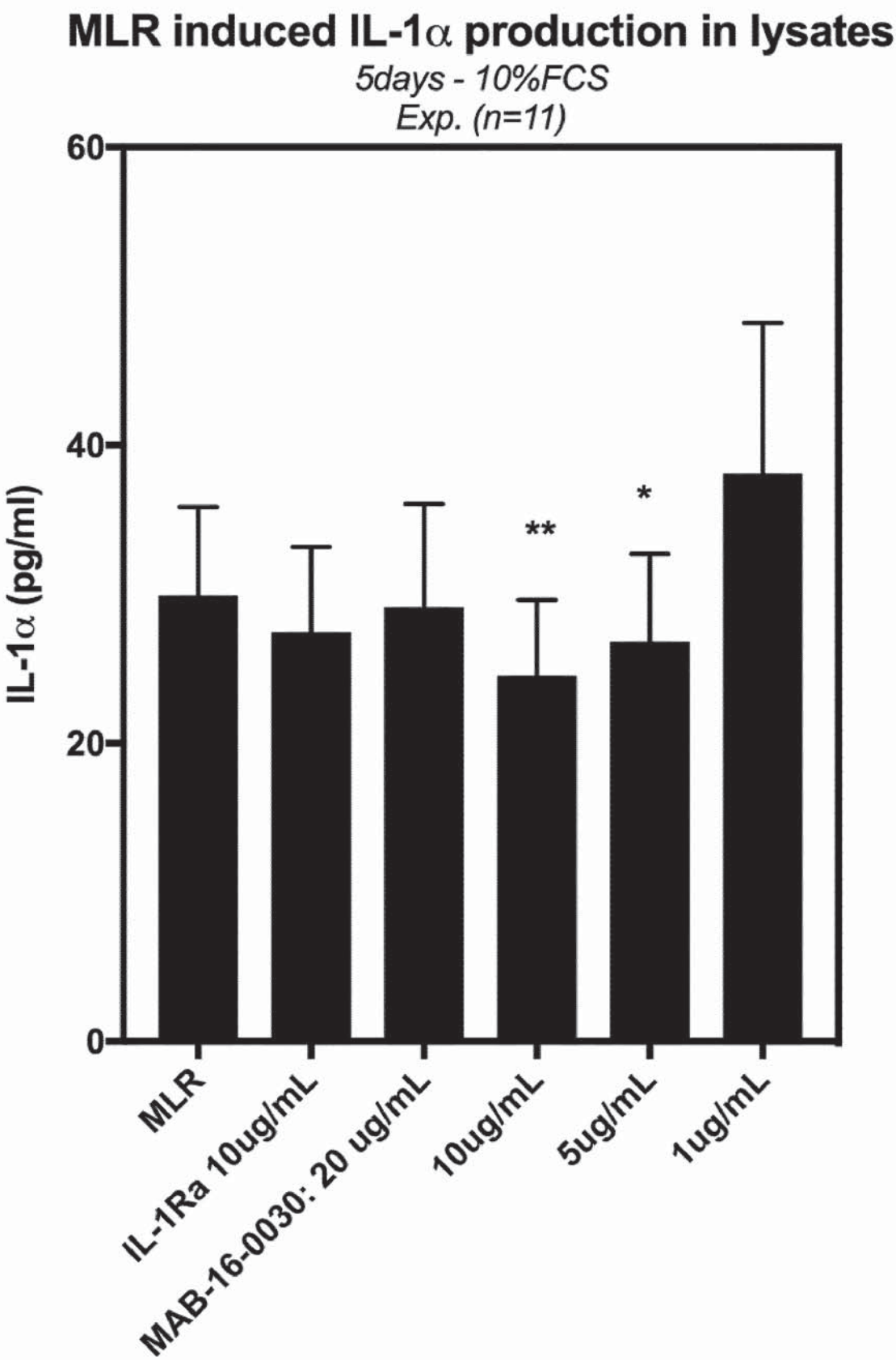

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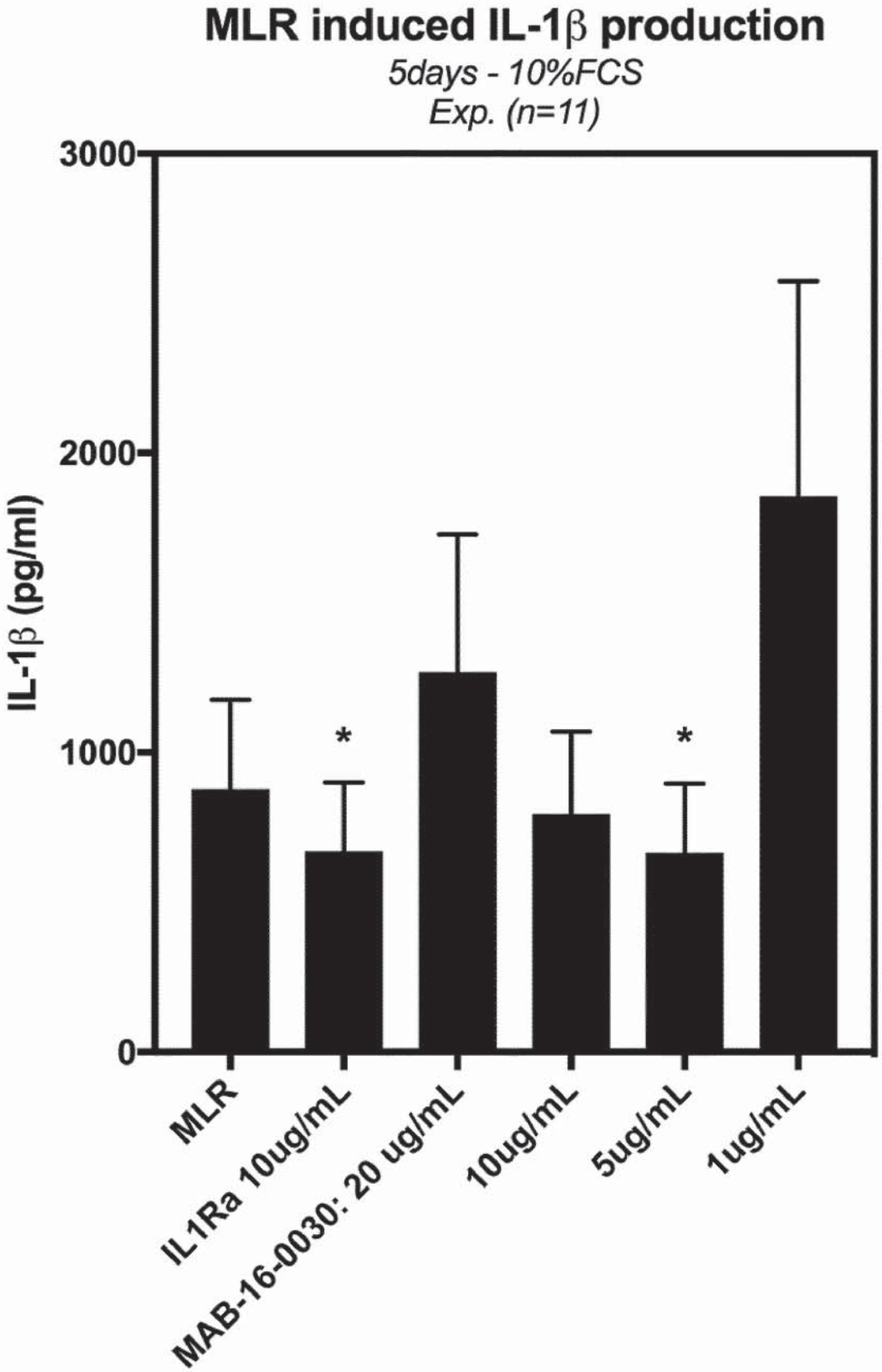

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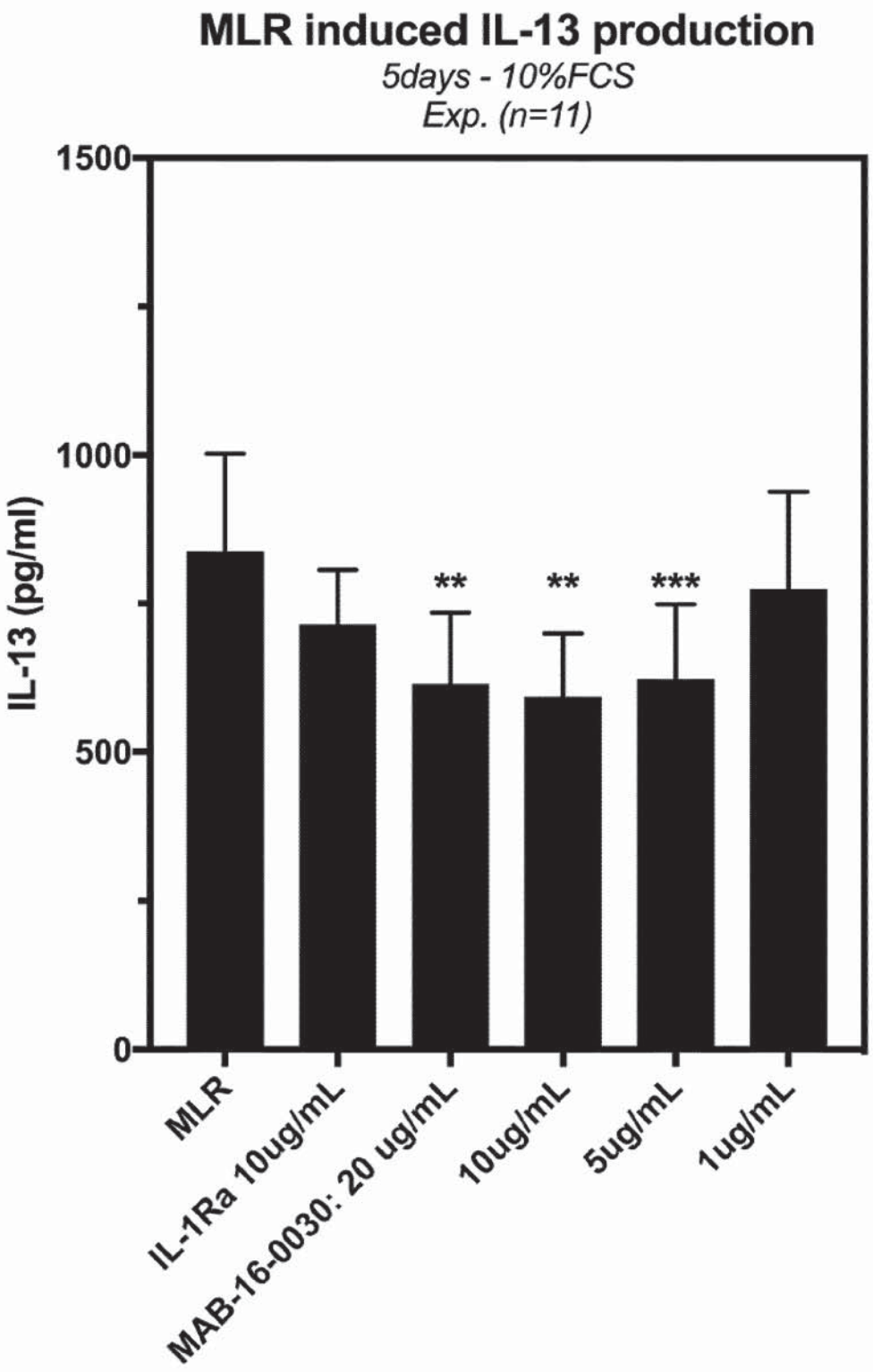

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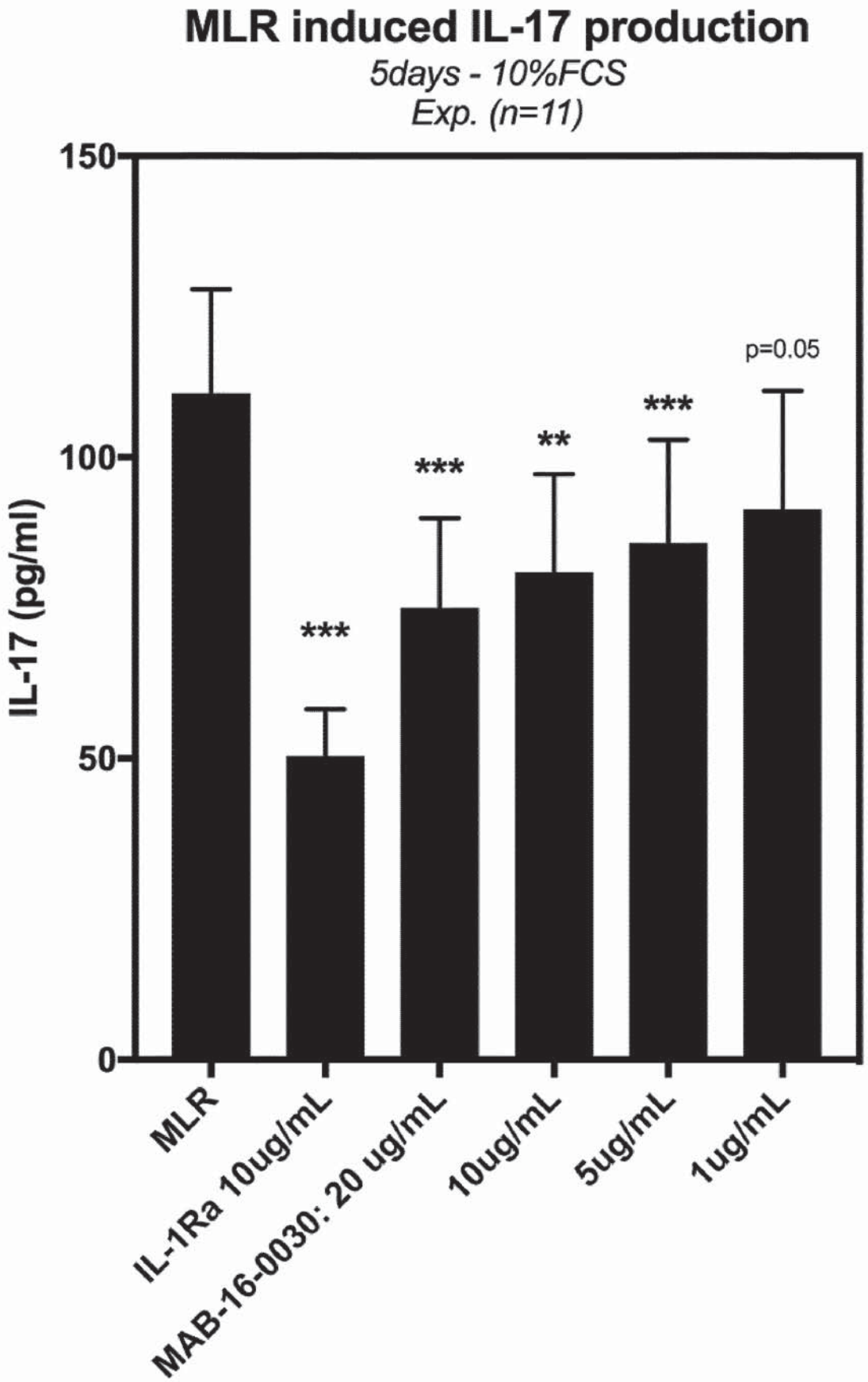

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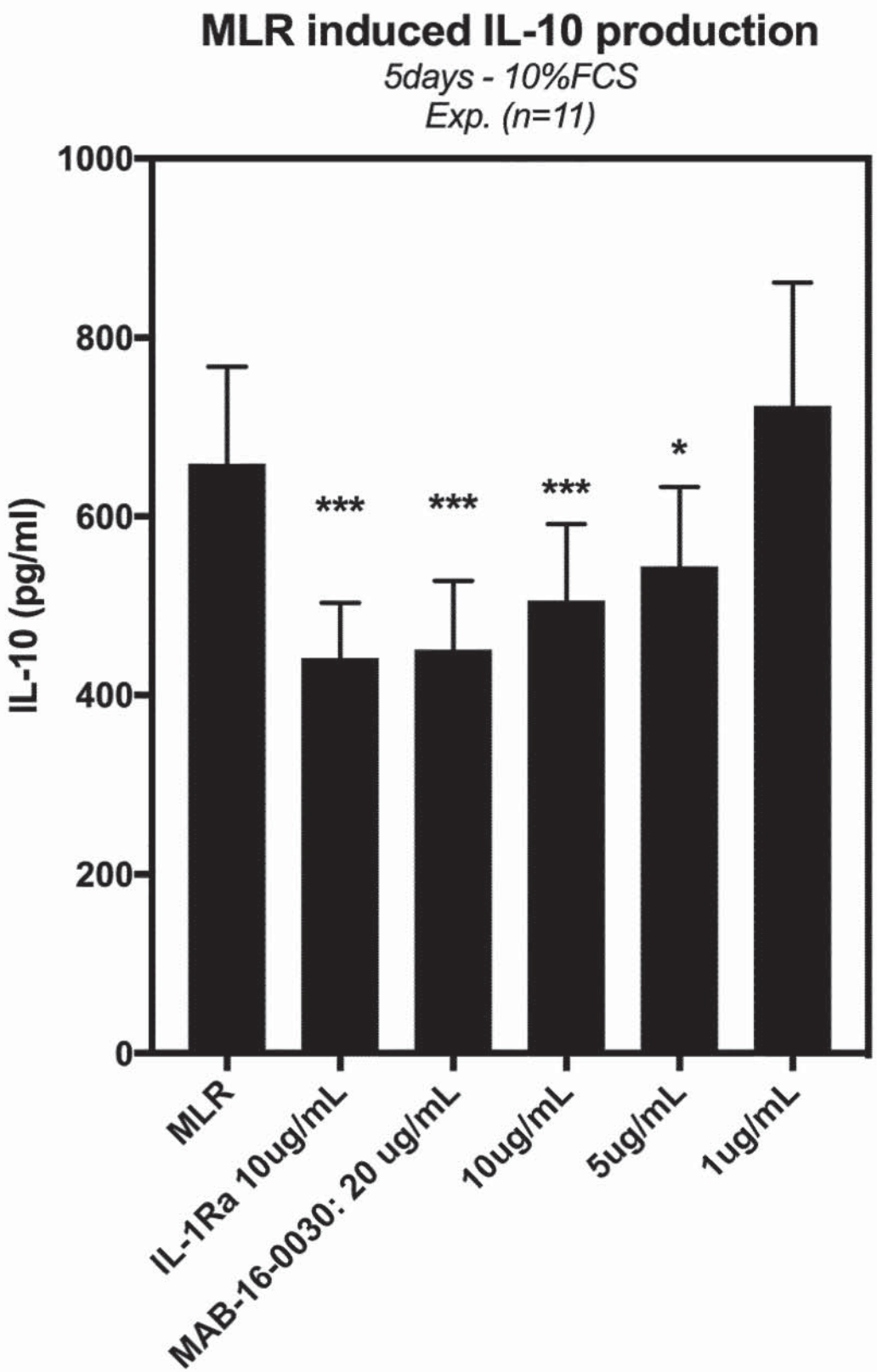


Figure 17: Neutralization of IL-1b mediated signaling in murine cells

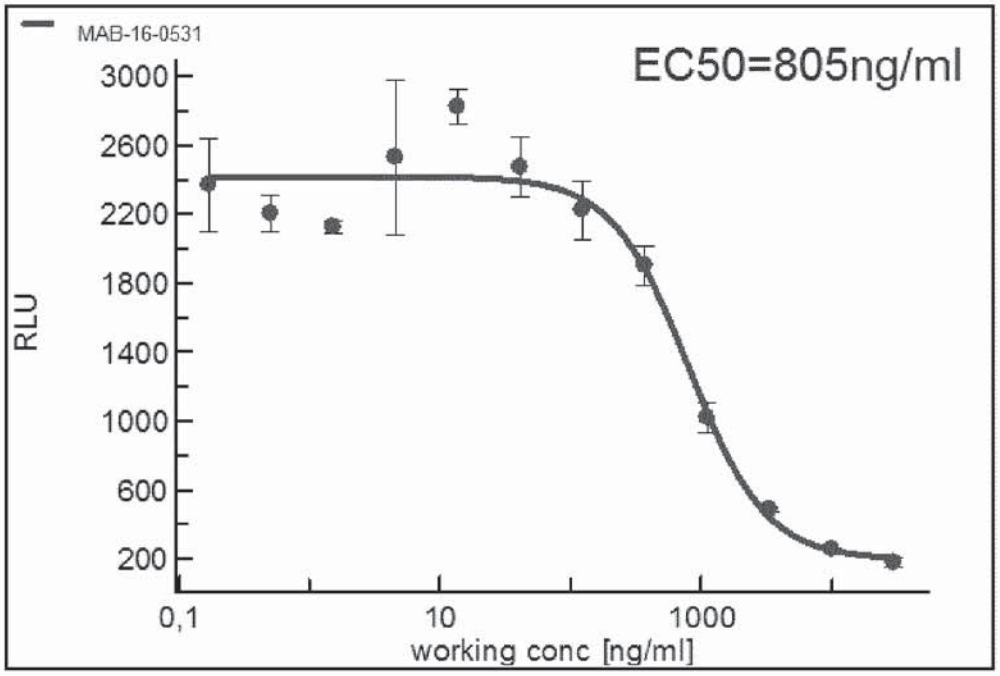


Figure 18: Neutralization of IL-1b mediated IL-6 release from murine cells

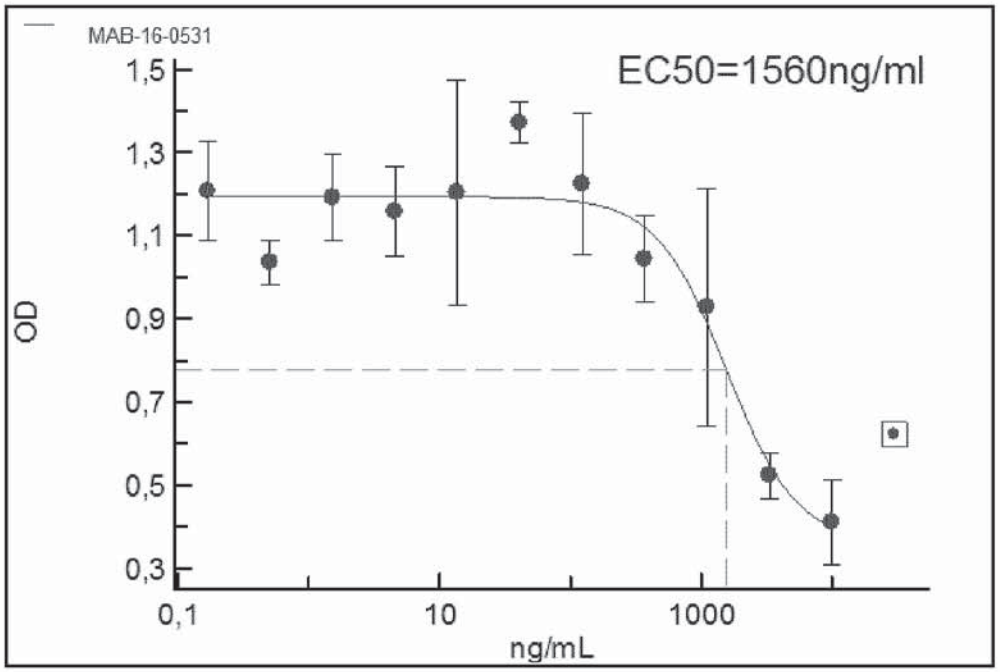
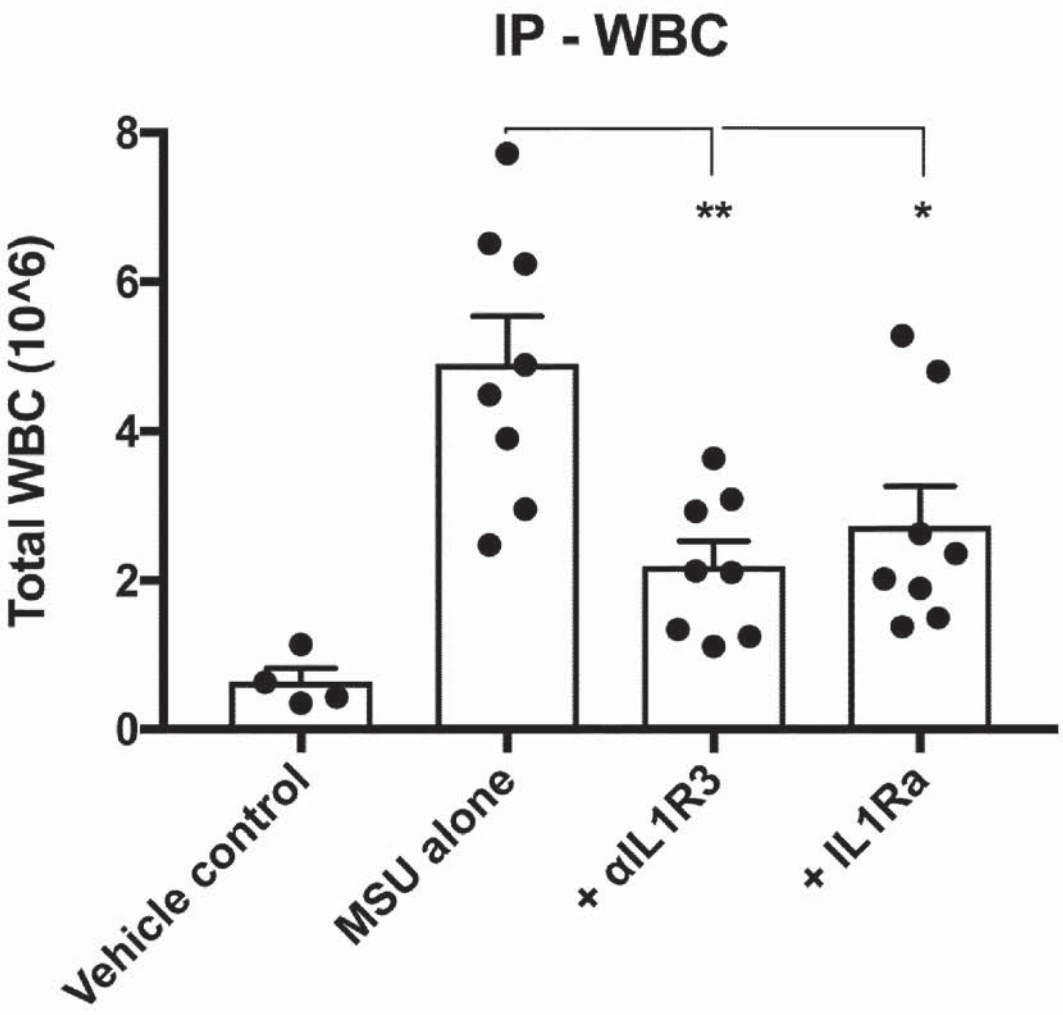


Fig. 19: Monosodium urate crystal (MSU)-induced mouse peritonitis model



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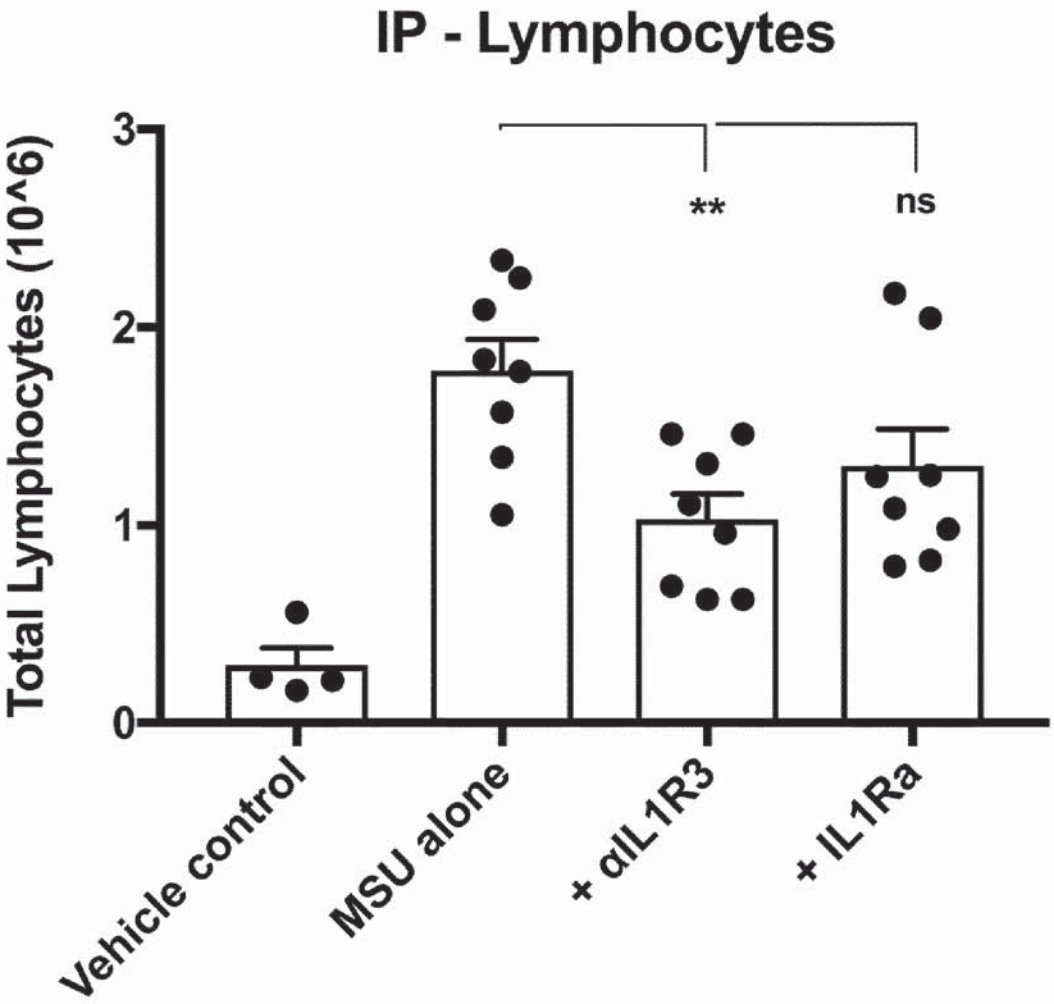

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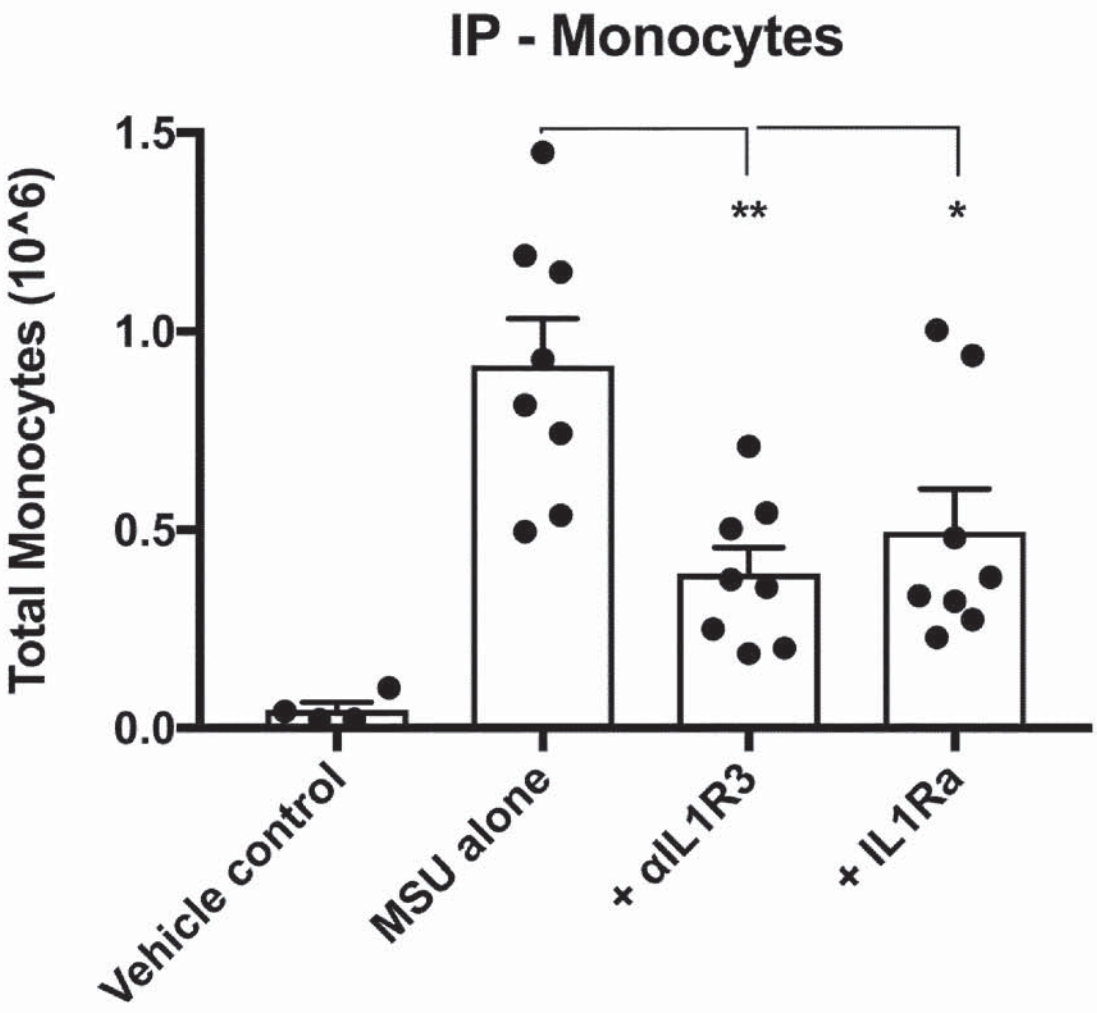

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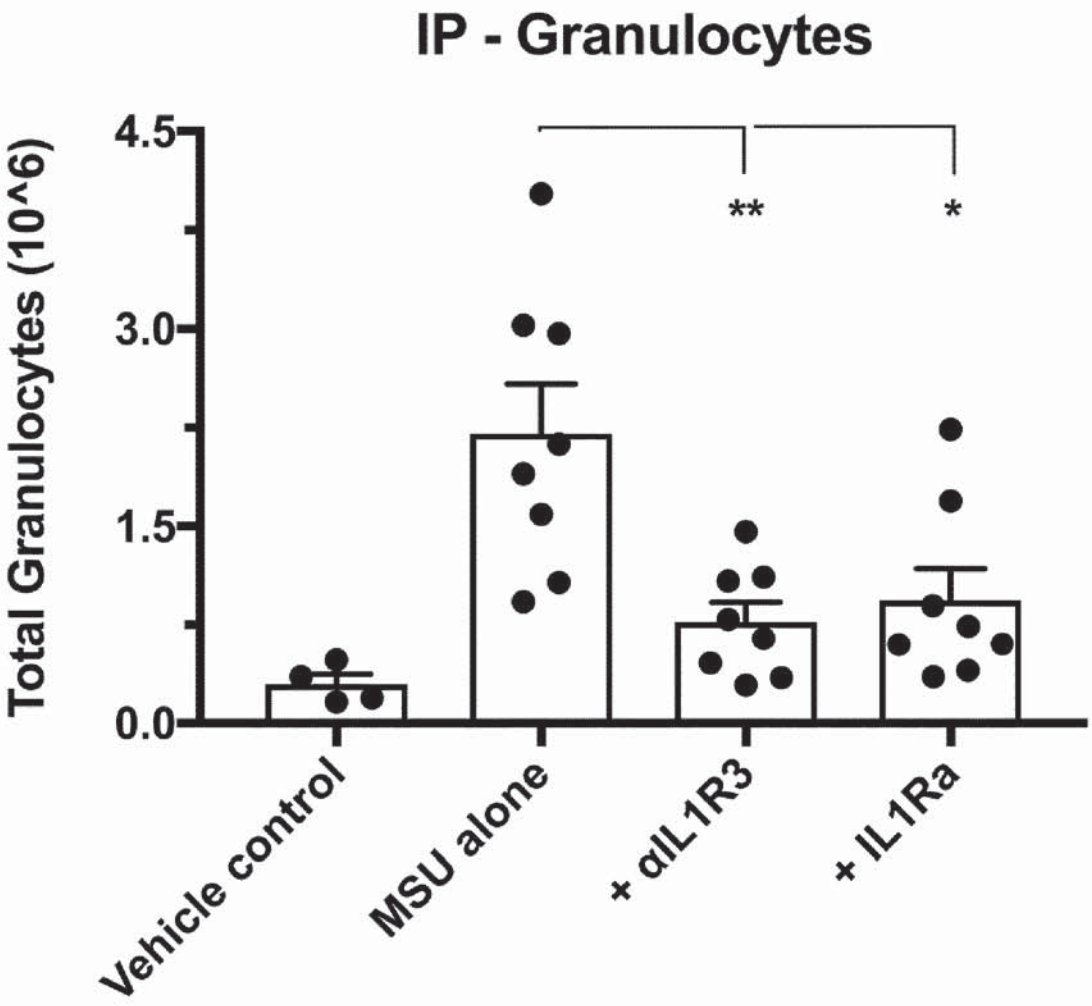

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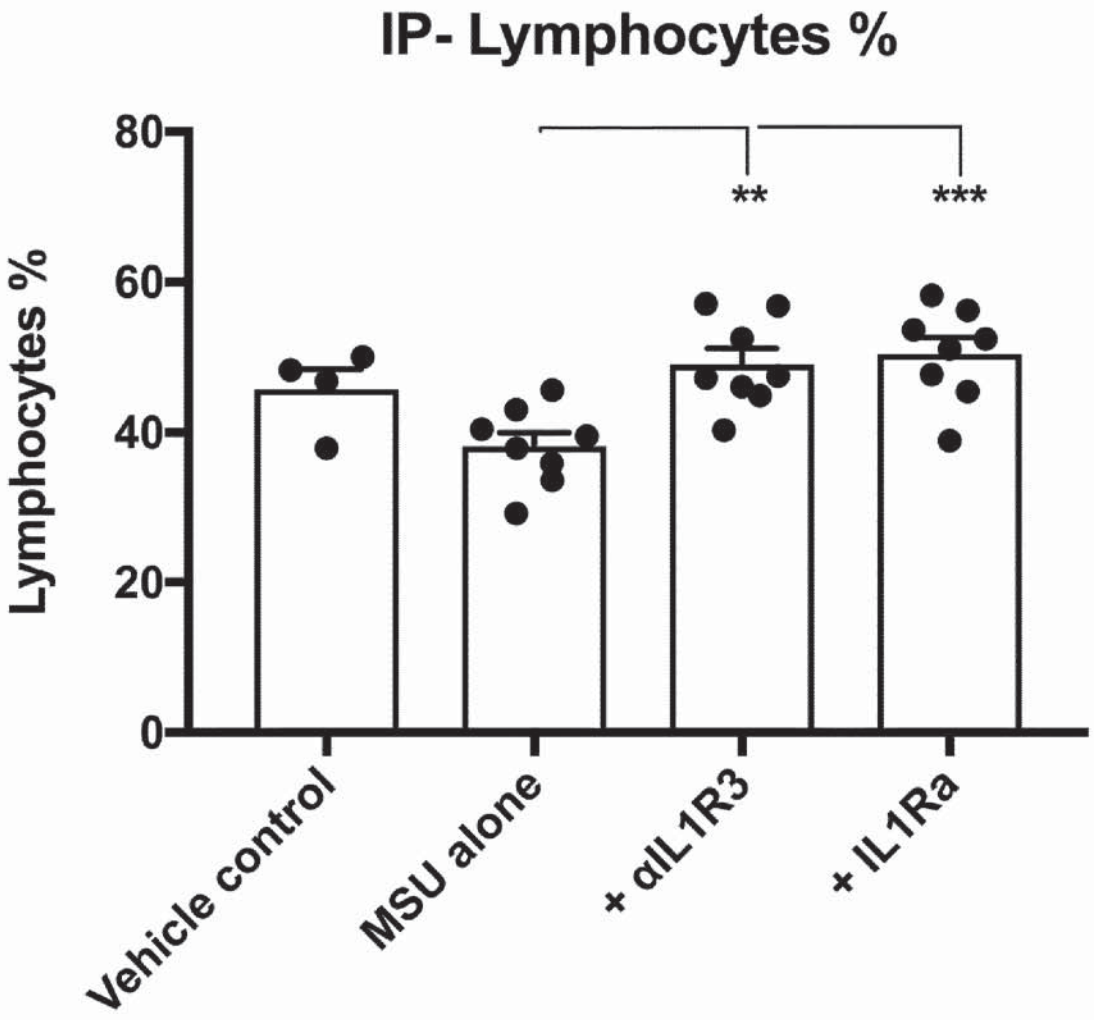

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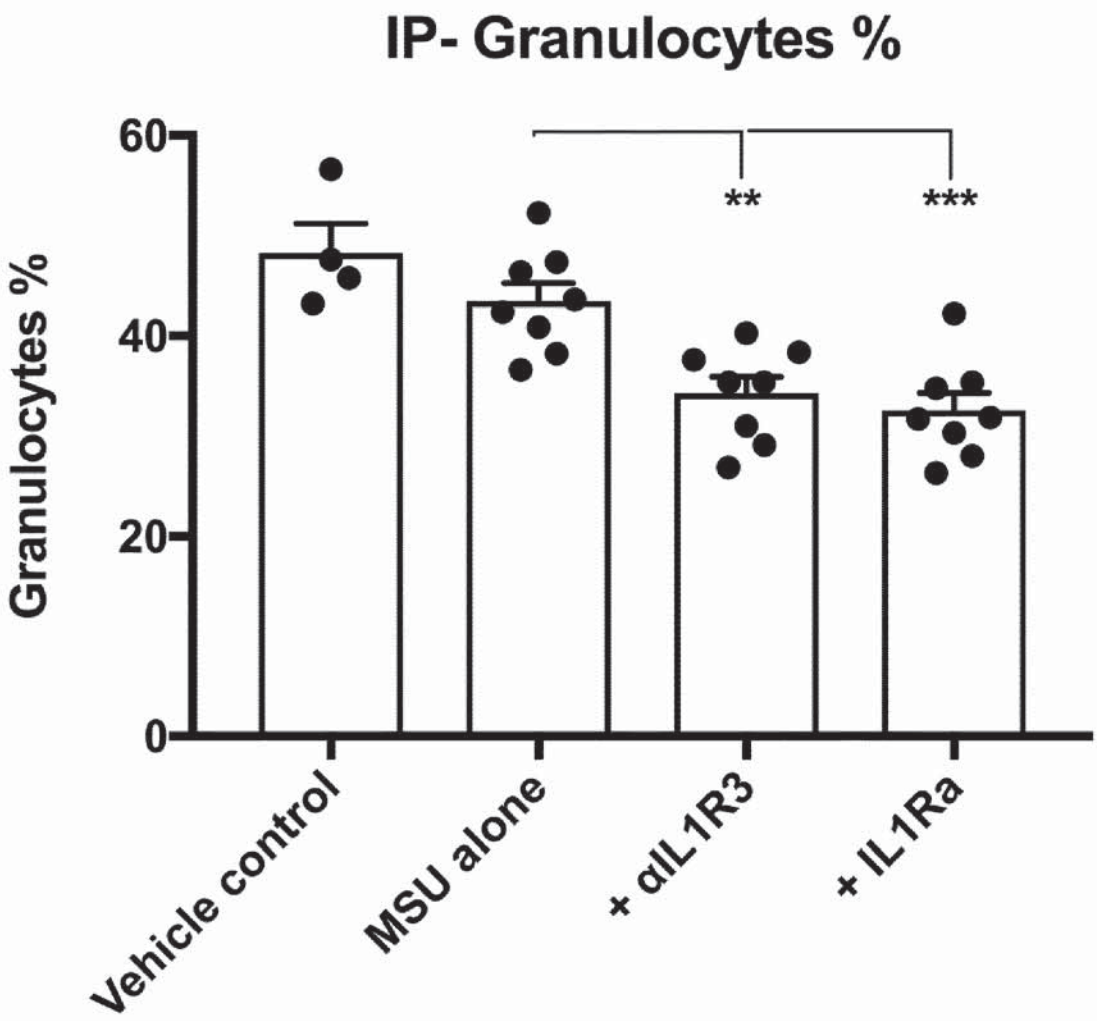

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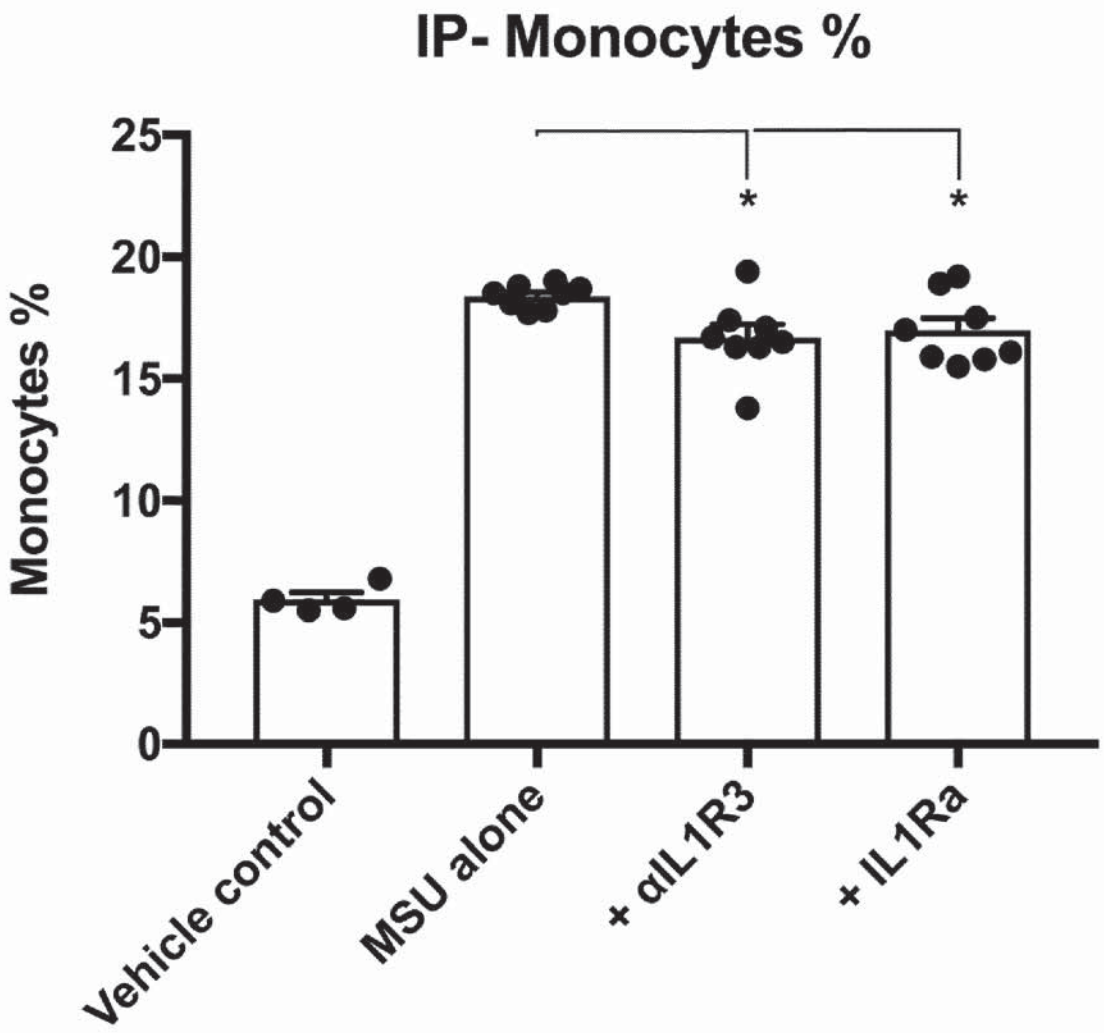
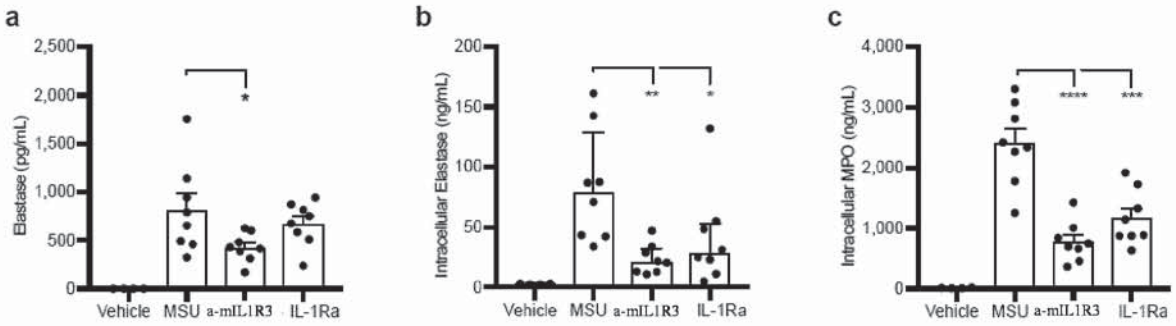


Fig. 20: Neutrophil activation and cytokine production in MSU peritonitis



d

IP fluid	Vehicle (n=4)	MSU stimulated (n=8)	a-mIL1R3 (n=8)	IL-1Ra (n=8)
IL-6 (pg/mL)	Below detection	65.0 ±14.9	19.8 ±5.8 **(p=0.014)**	36.9 ±14.4 (p=0.164)
G-CSF (pg/mL)	5.0 (2.8-5.5)	77.7 (53.6-97.3)	6.6 (4.9-33.0) **(p=0.015)**	8.6 (7.5-17.8) **(p=0.005)**
KC (pg/mL)	2.3 ±0.5	82.7 ±15.9	38.4 ±11.6 **(p=0.041)**	84.3. ±31.9 (p=0.965)
CCL-2 (pg/mL)	Below detection	62.5 ±11.9	26.2 ±3.6 **(p=0.011)**	74.2 ±14.5 (p=0.545)
CCL-3 (pg/mL)	1.2 ±0.1	4.9 ±0.8	3.6 ±0.5 (p=0.161)	5.7 ±0.9 (p=0.545)
Systemic				
IL-6 (pg/mL), plasma	5.0 ±3.4	69.8 ±19.4	22.7 ±5.7 **(p=0.011)**	29.5 ±8.5 **(p=0.078)**
G-CSF (pg/mL), plasma	294 ±28.4	6245 ±1055	3544 ±2743 **(p=0.010)**	1157 ±639 **(p=0.003)**
KC (pg/mL), WB	272 (243-719)	2525 (2178-2730)	1366 (811-1889) (p=0.065)	2269 (1511-3213) (p=0.959)
MPO (ng norm.), spleen	42.5 ±7.6	145 ±9.7	89.3 ±11.4 **(p=0.002)**	106 ±9.7 **(p=0.013)**
KC (pg norm.), spleen	16.2 (13.3-39.3)	189 (161-205)	72.5 (49.6-140) **(p=0.010)**	157 (95.3-238) (p=0.645)

Fig 21: OVA allergic asthma in vivo model

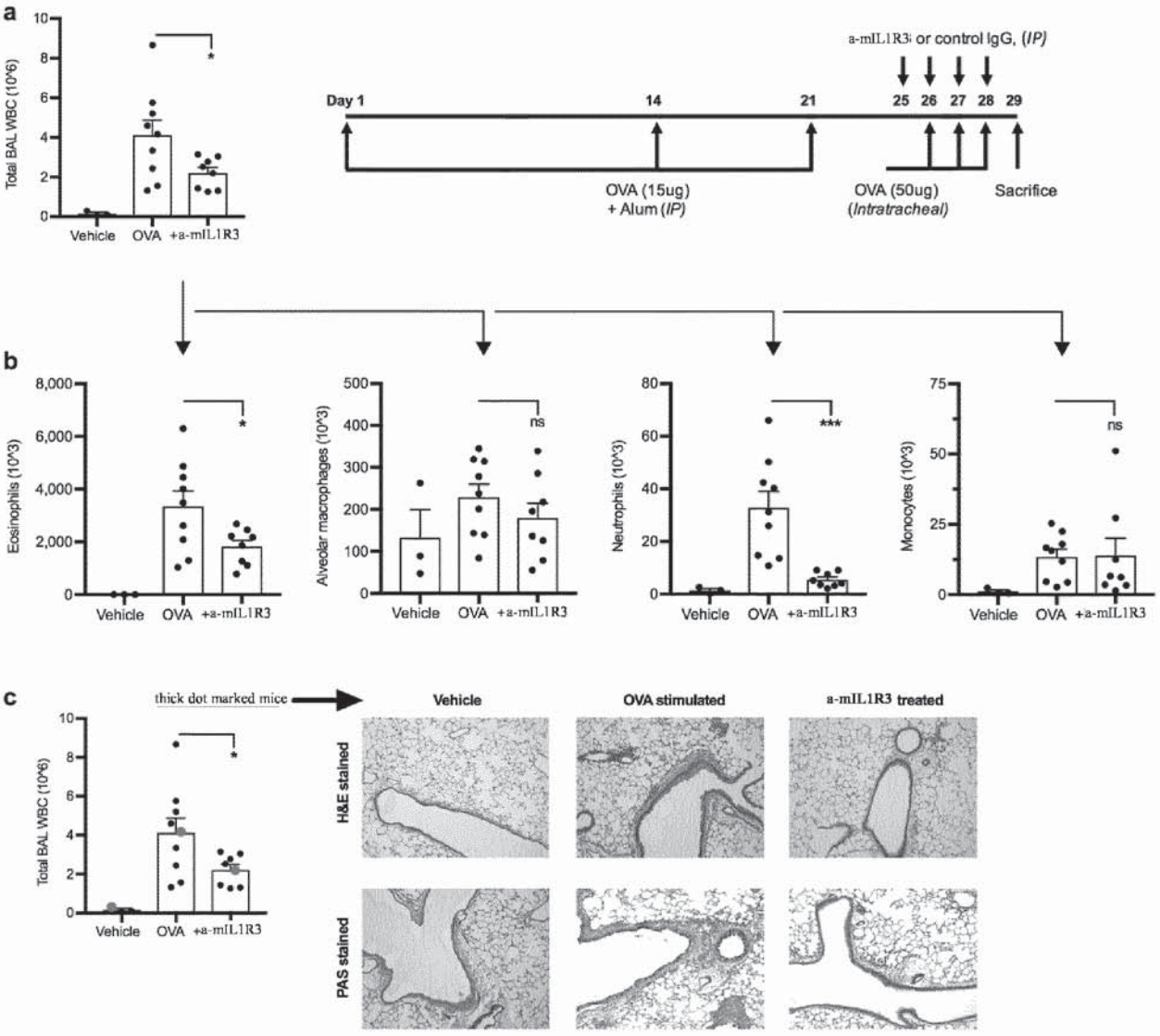


Fig. 22: Imiquimod psoriasis in vivo model

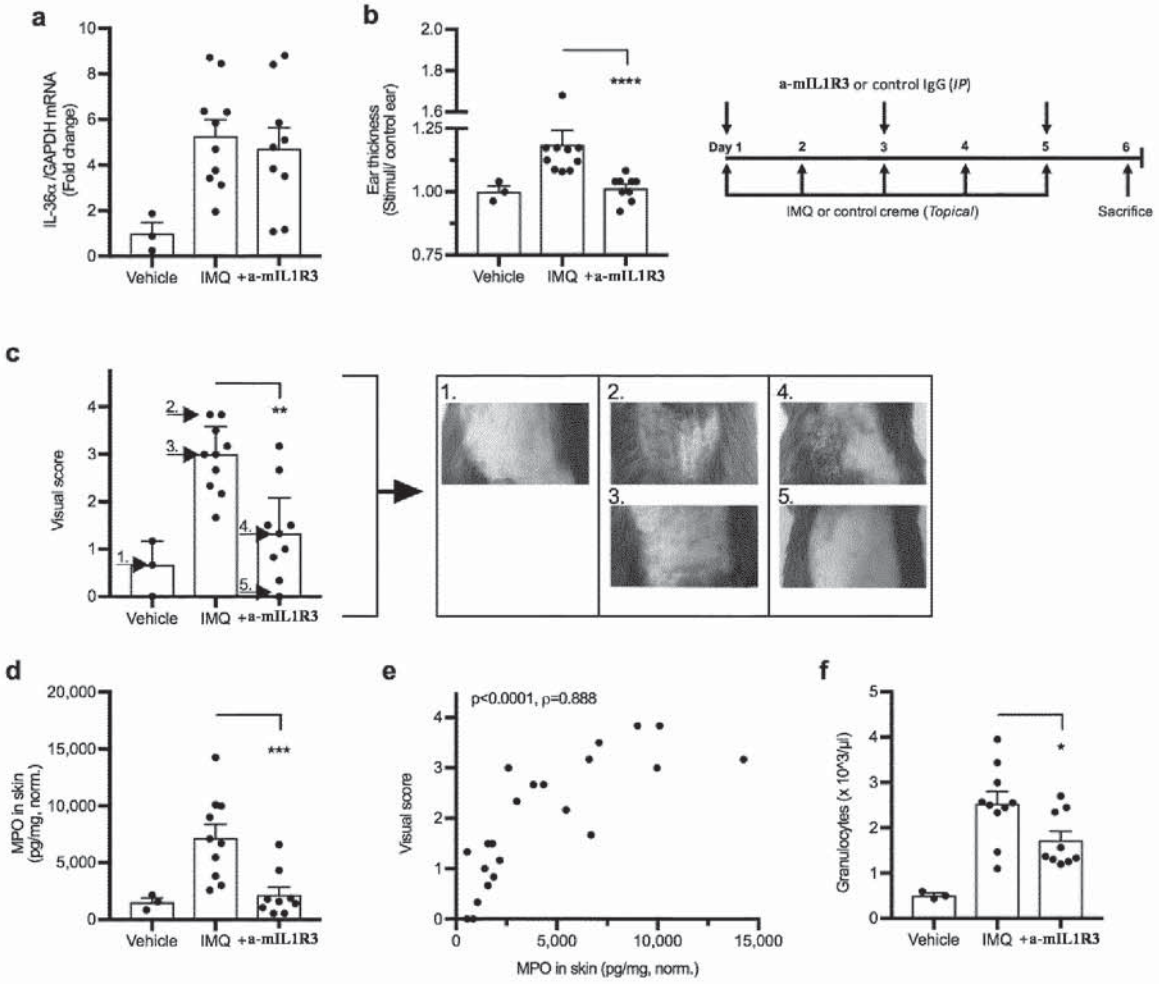


Fig. 23: Imiquimod psoriasis in vivo model

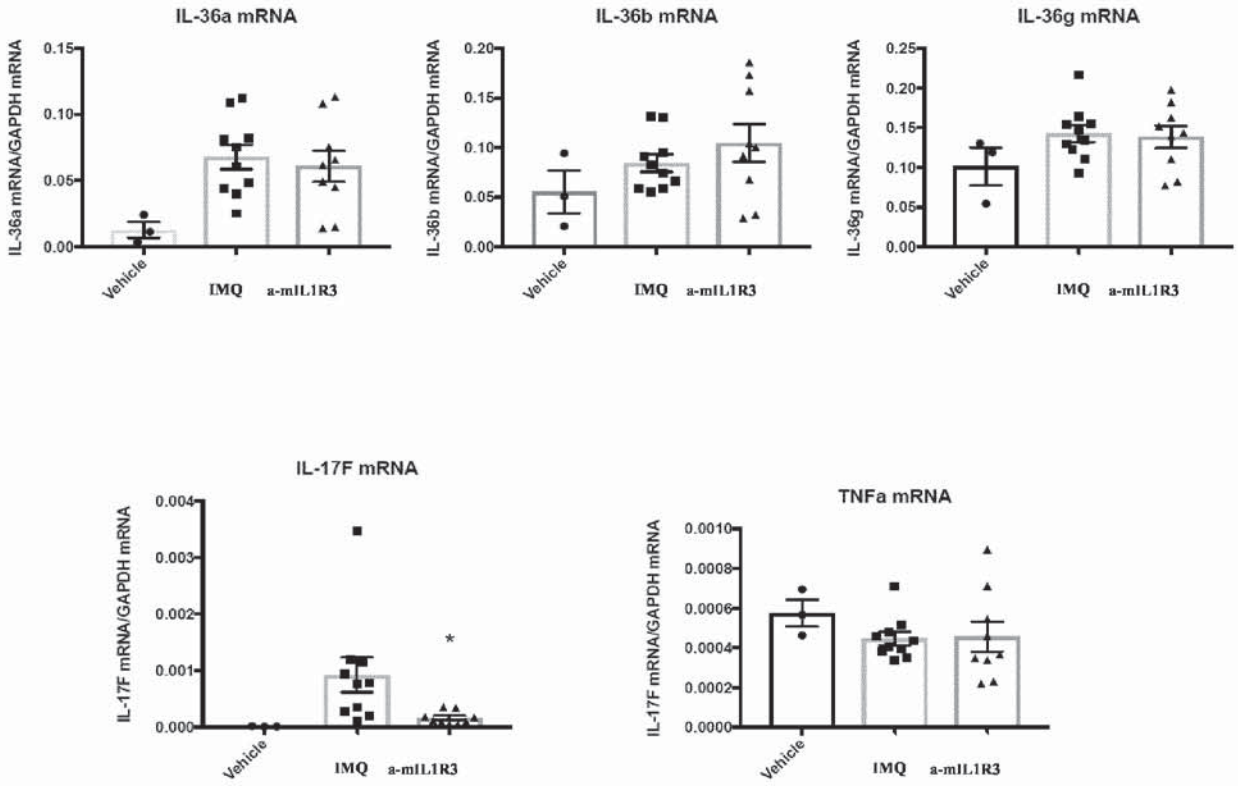
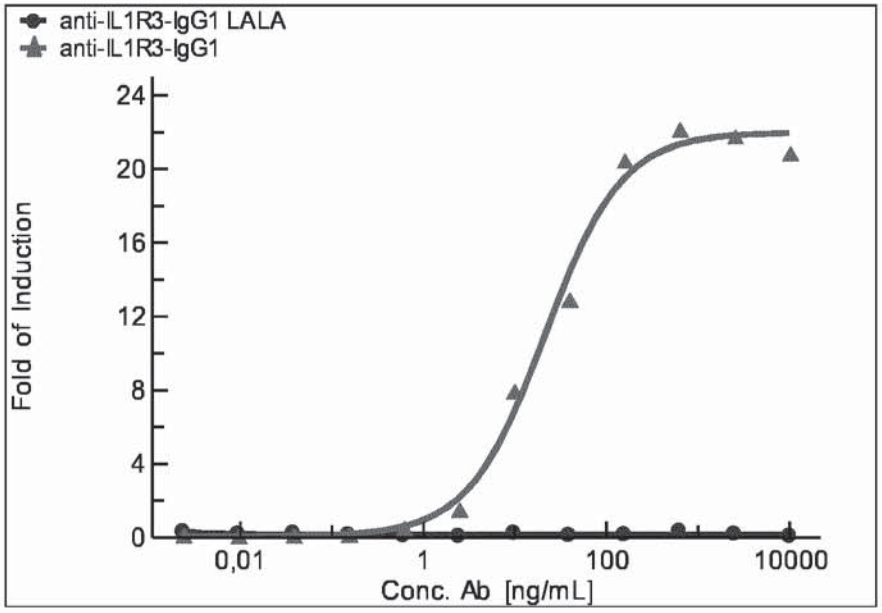


Fig. 24: Effector cell mediated function of anti-IL1R3 IgG1 and IgG1-LALA antibodies



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        35                  40                  45


Val Ser Cys Ile Tyr Thr Gly Ser Gly Gly Thr Tyr Tyr Ala Ser Trp
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Glu Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65                  70                  75                  80


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His Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
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Val Ser Cys Ile Tyr Ala Gly Ser Ser Gly Asn Thr Tyr Tyr Ala Asn
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Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
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        35                  40                  45


Ser Val Ile Thr Ser Ser Ala Thr Thr Tyr Tyr Ala Ser Trp Ala Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95


Arg Gly Gly Pro Gly Tyr Ser Thr Asn Thr His Tyr Ala Phe Asp Pro
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            20                  25                  30

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        35                  40                  45

Ala Val Ile Ser Ser Asp Gly Phe Phe Tyr Asp Ala Ser Trp Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95

Arg Asp Arg Gly Thr Ser Thr Gly Ser Leu Asp Leu Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


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<220>
<223>  humanized antibody

<400>  5

Glu Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Tyr
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ile Ile Ser Gly Ser Ala Ser Thr Tyr Tyr Ala Thr Trp Ala Lys
    50                  55                  60
```

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95


Arg Thr His Tyr Ala Ala Val Ala Gly Tyr Gly Tyr Ala Ser Arg Leu
            100                 105                 110


Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  6
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  6

Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Asn
            20                  25                  30


Tyr Trp Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu
        35                  40                  45


Val Ser Cys Ile Tyr Thr Ser Thr Gly Asn Thr Trp Tyr Ala Ser Trp
    50                  55                  60


Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
                85                  90                  95


Cys Ala Arg Asp Leu Leu Val Val Thr Ser Phe Asn Leu Trp Gly Gln
```

100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 7
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 7

Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ser
20 25 30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ser Cys Ile Tyr Ala Gly Ser Ser Gly Val Thr Tyr Tyr Ala Ser
50 55 60

Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Phe Cys Ala Ser Glu Thr Asp Gly Asn Tyr Phe Asn Leu Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 8
<211> 120
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 8

```
Glu Val Gln Leu Glu Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Tyr Trp Arg Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ser Cys Ile Tyr Ala Gly Ser Gly Asp Val Thr Tyr Tyr Ala Asn
    50                  55                  60


Trp Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Ser Gly Val Gly Phe Gly Tyr Phe Asn Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 9
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 9

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asp Phe Ser Ser Tyr
            20                  25                  30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Val Ser Cys Ile Phe Ile Gly Tyr Gly Asp Val Thr Trp Tyr Ala Ser
    50                  55                  60

Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Phe Cys Ala Arg Ala Leu Gly Ser Ser Gly Tyr Arg Val Asn Leu Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 10
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 10

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Met Ile Tyr Gly Ser Gly Tyr Thr Tyr Tyr Ala Ser Trp Ala Lys
```

50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Asp Pro Gln Tyr Phe Ile Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 11
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 11

Glu Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ser Leu Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Tyr Ile Gly Gly Thr Thr Ala Tyr Ala Ser Trp Pro Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

```
Arg Leu Gln Gly Ala Asn Tyr Tyr Asn Ser Leu Ala Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  12
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  12

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Ser Asn
            20                  25                  30


Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu
        35                  40                  45


Val Ser Cys Ile Tyr Thr Asn Ser Gly Asn Thr Trp Ser Ala Ser Trp
    50                  55                  60


Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
                85                  90                  95


Cys Ala Arg Asp Leu Asn Tyr Pro Asp Thr Ser Asn Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  13
```

<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 13

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Phe Gly
            20                  25                  30


Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ser Cys Ile Tyr Gly Asp Ser Ser Asp Thr Leu Tyr Ala Asn Trp
    50                  55                  60


Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
                85                  90                  95


Cys Ala Arg Tyr Pro Gly Gly Ser Tyr Tyr Asn Leu Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115
```

<210> 14
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 14

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
```

```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Thr
            20                  25                  30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Val Ser Cys Ile Tyr Ala Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Ser
    50                  55                  60

Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Phe Cys Ala Arg Val Asp Gly Ser Ser Ser Gly Ser Trp Asp Leu Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  15
<211>  122
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  15

Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Ser Phe Ser Ser Ser
            20                  25                  30

Asp Phe Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45
```

```
Val Ser Cys Ile Tyr Ala Gly Ser Ser Val Ser Ile Tyr Tyr Ala Thr
    50                  55                  60


Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Phe Cys Ala Arg Ser Thr Gly Ser Val Gly Arg Gly Phe Asn Leu Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  16
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  16

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ile
            20                  25                  30


Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ser Cys Ile Tyr Thr Gly Asn Ser Asp Phe Thr Tyr Tyr Ala Asn
    50                  55                  60


Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
```

85 90 95

Phe Cys Ala Arg Phe Arg Asp Asp Tyr Ala Ser Leu Lys Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 17
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 17

Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Gly
20 25 30

Tyr Asp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ser Cys Ile Tyr Thr Gly Ser Gly Ser Thr Tyr Tyr Ala Asn Trp
50 55 60

Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85 90 95

Cys Ala Arg Asn Ser Asn Asp Trp Met Tyr Phe Asn Leu Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 18
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 18

```
Glu Val Gln Leu Glu Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ser
            20                  25                  30


Tyr Trp Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ala Cys Ile Tyr Thr Gly Ser Gly Gly Thr Tyr Tyr Ala Ser Trp
    50                  55                  60


Glu Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Asp Pro Gly Tyr Ser Ser Trp Leu Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 19
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 19

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ala
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ser
            20                  25                  30


His Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ala Cys Ile Tyr Ala Gly Ser Ser Gly Asn Thr Tyr Tyr Ala Asn
    50                  55                  60


Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Asn Ser Lys Asn Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Phe Cys Ala Arg Val Asp Ala Ser Ser Ser Gly Ser Trp Asp Leu Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  20
<211>  122
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  20

Glu Val Gln Leu Leu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Thr
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Ser Tyr
            20                  25                  30


Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
```

```
        35                  40                  45

Gly Val Ile Thr Ser Ser Ala Thr Thr Tyr Tyr Ala Ser Trp Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Leu Tyr Leu Gln
65                  70                  75                  80

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
                85                  90                  95

Gly Gly Pro Gly Tyr Ser Thr Asn Thr His Tyr Ala Phe Asp Pro Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  21
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  21

Glu Val Gln Leu Glu Glu Ser Gly Gly Arg Val Val Gln Pro Gly Thr
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Asp Asn Tyr
            20                  25                  30

Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
        35                  40                  45

Ala Val Ile Ser Ser Asp Gly Phe Phe Tyr Asp Ala Ser Trp Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Lys Ala Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80
```

```
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95


Arg Asp Arg Gly Thr Ser Thr Gly Ser Leu Asp Leu Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115


<210>  22
<211>  123
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  22

Gln Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Thr
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Tyr
            20                  25                  30


Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ile Ile Ser Gly Ser Ala Ser Thr Tyr Tyr Ala Thr Trp Ala Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Leu Tyr Leu Gln Met
65                  70                  75                  80


Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Thr
                85                  90                  95


His Tyr Ala Ala Val Ala Gly Tyr Gly Tyr Ala Ser Arg Leu Asp Leu
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
```

115 120

<210> 23
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 23

Gln Val Gln Leu Gln Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Asn
20 25 30

Tyr Trp Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu
35 40 45

Val Ala Cys Ile Tyr Thr Ser Thr Gly Asn Thr Trp Tyr Ala Ser Trp
50 55 60

Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85 90 95

Cys Ala Arg Asp Leu Leu Val Val Thr Ser Phe Asn Leu Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 24
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 24

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ala
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ser
20 25 30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ala Cys Ile Tyr Ala Gly Ser Ser Gly Val Thr Tyr Tyr Ala Ser
50 55 60

Trp Ala Lys Gly Arg Phe Thr Ile Ser Asp Thr Ser Ser Thr Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85 90 95

Cys Ala Ser Glu Thr Asp Gly Asn Tyr Phe Asn Leu Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 25
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 25

Glu Val Gln Leu Glu Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

```
Tyr Trp Arg Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ala Cys Ile Tyr Ala Gly Ser Gly Asp Val Thr Tyr Tyr Ala Asn
    50                  55                  60


Trp Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Ser Gly Val Gly Phe Gly Tyr Phe Asn Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  26
<211>  122
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  26

Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Asp Phe Ser Ser Tyr
            20                  25                  30


Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ala Cys Ile Phe Ile Gly Tyr Gly Asp Val Thr Trp Tyr Ala Ser
    50                  55                  60


Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Ala Asn Ser Lys Asn Thr
```

65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Phe Cys Ala Arg Ala Leu Gly Ser Ser Gly Tyr Arg Val Asn Leu Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 27
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 27

Gln Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Ala
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Met Ile Tyr Gly Ser Gly Tyr Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Thr Thr Ser Thr Thr Leu Tyr Leu Gln Met
65 70 75 80

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Asp
85 90 95

Pro Gln Tyr Phe Ile Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 28
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 28

Glu Val Gln Leu Glu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Thr
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ser Leu Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Tyr Ile Gly Gly Thr Thr Ala Tyr Ala Ser Trp Pro Lys
50 55 60

Gly Arg Phe Thr Ile Ser Lys Thr Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Leu Gln Gly Ala Asn Tyr Tyr Asn Ser Leu Ala Leu Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 29
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 29

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Ser Asn
            20                  25                  30


Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Leu
        35                  40                  45


Val Ala Cys Ile Tyr Thr Asn Ser Gly Asn Thr Trp Ser Ala Ser Trp
    50                  55                  60


Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Asn Ser Thr Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Asp Leu Asn Tyr Pro Asp Thr Ser Asn Leu Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115
```

<210> 30
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 30

```
Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Phe Gly
```

20 25 30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ala Cys Ile Tyr Gly Asp Ser Ser Asp Thr Leu Tyr Ala Asn Trp
50 55 60

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Asn Ser Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85 90 95

Cys Ala Arg Tyr Pro Gly Gly Ser Tyr Tyr Asn Leu Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 31
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 31

Gln Val Gln Leu Gln Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ala
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Thr
20 25 30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ala Cys Ile Tyr Ala Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Ser
50 55 60

```
Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Asn Ser Ser Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Val Asp Gly Ser Ser Ser Gly Ser Trp Asp Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  32
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  32

Glu Val Gln Leu Glu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ala
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Ser Phe Ser Ser Ser
            20                  25                  30


Asp Phe Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Ala Cys Ile Tyr Ala Gly Ser Ser Val Ser Ile Tyr Tyr Ala Thr
    50                  55                  60


Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Ala Ser Ser Thr Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
                85                  90                  95


Cys Ala Arg Ser Thr Gly Ser Val Gly Arg Gly Phe Asn Leu Trp Gly
```

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 33
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 33

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Ile
20 25 30

Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Gly Cys Ile Tyr Thr Gly Asn Ser Asp Phe Thr Tyr Tyr Ala Asn
50 55 60

Trp Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Phe Cys Ala Arg Phe Arg Asp Asp Tyr Ala Ser Leu Lys Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 34
<211> 120
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 34

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Ser Phe Ser Ser Gly
            20                  25                  30


Tyr Asp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Val Gly Cys Ile Tyr Thr Gly Ser Gly Ser Thr Tyr Tyr Ala Asn Trp
    50                  55                  60


Ala Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Ser Lys Thr Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
                85                  90                  95


Cys Ala Arg Asn Ser Asn Asp Trp Met Tyr Phe Asn Leu Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 35
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 35

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
```

```
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Ser Asn Tyr
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Leu Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Trp Trp Val Ile Glu His
                85                  90                  95


Asn Gly Ala Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100                 105                 110


<210>  36
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Tyr Ser Asn
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Leu Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
```

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Ala Ser Tyr Ser Thr Gly
85 90 95

Pro Asp Trp Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 37
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 37

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Tyr Ile Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ala Thr Thr Tyr Asn
85 90 95

Val Asp Asn Val Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 38
<211> 111
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 38

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asn Ile Gly Asn Gly
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Thr Tyr Trp Asn Pro Asp
                85   90   95

Tyr Ile Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100   105   110

<210> 39
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 39

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Glu Asp Ile Tyr Ser Gly
            20   25   30

```
Ile Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Gly Tyr Ser Tyr Ser Asn
                85                  90                  95


Thr Gly Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  40
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  40

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
            20                  25                  30


Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Cys Thr Asp Ile Ser
```

85 90 95

Thr Asp Asp Leu Tyr Asn Ala Phe Gly Gln Gly Thr Lys Val Val Ile
100 105 110

Lys

<210> 41
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 41

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Tyr Thr Tyr Ser Thr
85 90 95

Asp Ile His Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 42
<211> 110
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 42

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
            20   25   30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Tyr Thr His Ile Ser
                85   90   95

Ala Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100   105   110

<210> 43
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 43

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asn Ile Tyr Ser Ser
            20   25   30

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Tyr Ser Gly Gly
                85                  90                  95


Thr Asp Asn Asp Val Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100                 105                 110


<210>  44
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  44

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Val Asp Gly Asn
            20                  25                  30


Asn Leu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu
        35                  40                  45


Leu Ile Tyr Asp Ala Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe
    50                  55                  60


Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80


Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Ser Tyr Tyr Ser
```

85 90 95

Ser Ser Trp Tyr Asn Val Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 45
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 45

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Tyr Ser Phe
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asp Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Asn Tyr Ile Ile Asp Tyr
85 90 95

Gly Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105

<210> 46
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 46

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Gly Tyr Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Tyr Tyr Asn Ser Asp Ser
                85                  90                  95


Asp Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105
```

<210> 47
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 47

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Thr Ile Ser Ile Asn
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Thr Glu Asp Asn
                85                  90                  95


Ile Asp Asn Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105                 110


<210>  48
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  48

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Tyr Ser Asn
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Leu Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Ala Val Tyr Ser Gly Asn
                85                  90                  95


Thr Glu Trp Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
```

100 105 110

<210> 49
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 49

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Val Tyr Asn Ser
20 25 30

Asn His Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Glu Phe Ser Cys
85 90 95

Val Ser Ala Asp Cys Ile Ala Phe Gly Gly Gly Thr Lys Val Val Ile
100 105 110

Lys

<210> 50
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 50

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Ala Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Thr Tyr Tyr Asp Asn Asn
                85                  90                  95


Tyr Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100                 105                 110
```

<210> 51
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 51

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Ser Ala Asn
            20                  25                  30


Tyr Trp Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu
        35                  40                  45
```

```
Ile Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80


Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Ser Trp Tyr Tyr Ser Gly
                85                  90                  95


Ser Gly Ser Tyr His Ser Trp Ala Phe Gly Gln Gly Thr Lys Val Val
            100                 105                 110


Ile Lys



<210>  52
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  52

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Ser Asn Tyr
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Leu Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Trp Trp Val Ile Glu His
```

85 90 95

Asn Gly Ala Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 53
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 53

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Leu Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Ala Ser Tyr Ser Thr Gly
85 90 95

Pro Asp Trp Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 54
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 54

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Tyr Ile Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Ala Thr Thr Tyr Asn
85 90 95

Val Asp Asn Val Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 55
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 55

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asn Ile Gly Asn Gly
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

```
Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Thr Tyr Trp Asn Pro Asp
                85                  90                  95

Tyr Ile Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100                 105                 110
```

<210> 56
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 56

```
Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Glu Asp Ile Tyr Ser Gly
            20                  25                  30

Ile Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Gly Tyr Ser Tyr Ser Asn
                85                  90                  95

Thr Gly Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
```

100 105 110

<210> 57
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 57

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Cys Thr Asp Ile Ser
85 90 95

Thr Asp Asp Leu Tyr Asn Ala Phe Gly Gln Gly Thr Lys Val Val Ile
100 105 110

Lys

<210> 58
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 58

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Tyr Thr Tyr Ser Thr
                85                  90                  95

Asp Ile His Ala Phe Gly Gly Gly Thr Lys Val Val Ile Lys
            100                 105                 110
```

<210> 59
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 59

```
Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Val Tyr Thr His Ile Ser
                85                  90                  95


Ala Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  60
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  60

Ala Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asn Ile Tyr Ser Ser
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Tyr Ser Gly Gly
                85                  90                  95


Thr Asp Asn Asp Val Phe Gly Gly Gly Thr Lys Val Val Ile Lys
```

100 105 110

<210> 61
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 61

Asn Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Val Asp Gly Asn
20 25 30

Asn Leu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Ala Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Ser Tyr Tyr Ser
85 90 95

Ser Ser Trp Tyr Asn Val Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 62
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 62

Asp Val Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

```
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Tyr Ser Phe
            20                  25                  30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Asp Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Asn Tyr Ile Ile Asp Tyr
                85                  90                  95

Gly Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105
```

<210> 63
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 63

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Gly Tyr Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

```
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Tyr Tyr Asn Ser Asp Ser
                85                  90                  95


Asp Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105


<210>  64
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  64

Ala Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Thr Ile Ser Ile Asn
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Thr Glu Asp Asn
                85                  90                  95


Ile Asp Asn Thr Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105                 110


<210>  65
```

<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 65

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Tyr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Leu Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Ala Val Tyr Ser Gly Asn
85 90 95

Thr Glu Trp Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
100 105 110

<210> 66
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 66

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Val Tyr Asn Ser

20 25 30

Asn His Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gly Glu Phe Ser Cys
85 90 95

Val Ser Ala Asp Cys Ile Ala Phe Gly Gly Gly Thr Lys Val Val Ile
100 105 110

Lys

<210> 67
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 67

Asp Val Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Thr Tyr Tyr Asp Asn Asn
                85                  90                  95


Tyr Gly Gly Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  68
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  humanized antibody

<400>  68

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Ser Ile Ser Ala Asn
            20                  25                  30


Tyr Trp Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80


Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Ser Trp Tyr Tyr Ser Gly
                85                  90                  95


Ser Gly Ser Tyr His Ser Trp Ala Phe Gly Gln Gly Thr Lys Val Val
            100                 105                 110


Ile Lys
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<210> 69
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 69

Ser Ser Tyr Trp Ile Cys
1   5

<210> 70
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 70

Ser Ser His Tyr Met Cys
1   5

<210> 71
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 71

Ser Tyr Ala Met Gly
1   5

<210> 72
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 72

Asn Tyr Ala Met Gly
1   5

<210> 73
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<400> 73

Ser Tyr Tyr Met Ser
1   5

<210> 74
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 74

Ser Asn Tyr Trp Ile Cys
1   5

<210> 75
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 75

Ser Ser Tyr Tyr Met Cys
1   5

<210> 76
<211> 6
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 76

Thr Ser Tyr Trp Arg Cys
1   5

<210> 77
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 77

Ser Tyr Tyr Tyr Met Cys
1   5

<210> 78
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<400> 78

Ser Tyr Trp Met Ser
1   5

<210> 79
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 79

Ser Tyr Asp Met Ser
1   5

<210> 80
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 80

Ser Asn Tyr Tyr Met Cys
1   5

<210> 81
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 81

Phe Gly Tyr Tyr Met Cys
1   5

<210> 82
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 82

Ser Thr Tyr Tyr Met Cys
1   5

<210> 83
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 83

Ser Ser Asp Phe Met Cys
1 5

<210> 84
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 84

Ser Ile Tyr Tyr Met Cys
1 5

<210> 85
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 85

Ser Gly Tyr Asp Met Cys
1 5

<210> 86
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 86

Cys Ile Tyr Thr Gly Ser Gly Gly Thr Tyr Tyr Ala Ser Trp Glu Lys
1 5 10 15

Gly

<210> 87

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 87

Cys Ile Tyr Ala Gly Ser Ser Gly Asn Thr Tyr Tyr Ala Asn Trp Ala
1 5 10 15

Lys Gly

<210> 88
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 88

Val Ile Thr Ser Ser Ala Thr Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 89
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 89

Val Ile Ser Ser Asp Gly Phe Phe Tyr Asp Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 90
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 90

Ile Ile Ser Gly Ser Ala Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 91
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 91

Cys Ile Tyr Thr Ser Thr Gly Asn Thr Trp Tyr Ala Ser Trp Ala Lys
1 5 10 15

Gly

<210> 92
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 92

Cys Ile Tyr Ala Gly Ser Ser Gly Val Thr Tyr Tyr Ala Ser Trp Ala
1 5 10 15

Lys Gly

<210> 93
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 93

Cys Ile Tyr Ala Gly Ser Gly Asp Val Thr Tyr Tyr Ala Asn Trp Val
1 5 10 15

Asn Gly

<210> 94
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 94

Cys Ile Phe Ile Gly Tyr Gly Asp Val Thr Trp Tyr Ala Ser Trp Ala
1 5 10 15

Lys Gly

<210> 95
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 95

Met Ile Tyr Gly Ser Gly Tyr Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 96
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 96

Thr Ile Tyr Ile Gly Gly Thr Thr Ala Tyr Ala Ser Trp Pro Lys Gly

1 5 10 15

<210> 97
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 97

Cys Ile Tyr Thr Asn Ser Gly Asn Thr Trp Ser Ala Ser Trp Ala Lys
1 5 10 15

Gly

<210> 98
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 98

Cys Ile Tyr Gly Asp Ser Ser Asp Thr Leu Tyr Ala Asn Trp Ala Lys
1 5 10 15

Gly

<210> 99
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 99

Cys Ile Tyr Ala Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Ser Trp Ala
1 5 10 15

Lys Gly

<210> 100
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 100

Cys Ile Tyr Ala Gly Ser Ser Val Ser Ile Tyr Tyr Ala Thr Trp Ala
1 5 10 15

Lys Gly

<210> 101
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 101

Cys Ile Tyr Thr Gly Asn Ser Asp Phe Thr Tyr Tyr Ala Asn Trp Ala
1 5 10 15

Lys Gly

<210> 102
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 102

Cys Ile Tyr Thr Gly Ser Gly Ser Thr Tyr Tyr Ala Asn Trp Ala Lys

1 5 10 15

Gly

<210> 103
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 103

Asp Pro Gly Tyr Ser Ser Trp Leu
1 5

<210> 104
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 104

Val Asp Ala Ser Ser Ser Gly Ser Trp Asp Leu
1 5 10

<210> 105
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 105

Gly Gly Pro Gly Tyr Ser Thr Asn Thr His Tyr Ala Phe Asp Pro
1 5 10 15

<210> 106
<211> 11
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 106

Asp Arg Gly Thr Ser Thr Gly Ser Leu Asp Leu
1   5   10

<210> 107
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 107

Thr His Tyr Ala Ala Val Ala Gly Tyr Gly Tyr Ala Ser Arg Leu Asp
1   5   10   15

Leu

<210> 108
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 108

Asp Leu Leu Val Val Thr Ser Phe Asn Leu
1   5   10

<210> 109
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 109

Glu Thr Asp Gly Asn Tyr Phe Asn Leu
1 5

<210> 110
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 110

Gly Val Gly Phe Gly Tyr Phe Asn Leu
1 5

<210> 111
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 111

Ala Leu Gly Ser Ser Gly Tyr Arg Val Asn Leu
1 5 10

<210> 112
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 112

Asp Pro Gln Tyr Phe Ile Leu
1 5

<210> 113
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 113

Leu Gln Gly Ala Asn Tyr Tyr Asn Ser Leu Ala Leu
1   5   10

<210> 114
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 114

Asp Leu Asn Tyr Pro Asp Thr Ser Asn Leu
1   5   10

<210> 115
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 115

Tyr Pro Gly Gly Ser Tyr Tyr Asn Leu
1   5

<210> 116
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 116

Val Asp Gly Ser Ser Ser Gly Ser Trp Asp Leu
1   5   10

<210> 117

<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 117

Ser Thr Gly Ser Val Gly Arg Gly Phe Asn Leu
1 5 10

<210> 118
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 118

Phe Arg Asp Asp Tyr Ala Ser Leu Lys Leu
1 5 10

<210> 119
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 119

Asn Ser Asn Asp Trp Met Tyr Phe Asn Leu
1 5 10

<210> 120
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 120

Gln Ala Ser Glu Ser Ile Ser Asn Tyr Leu Ser

1 5 10

<210> 121
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 121

Gln Ala Ser Glu Ser Ile Tyr Ser Asn Leu Ala
1 5 10

<210> 122
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 122

Gln Ala Ser Gln Ser Ile Tyr Ile Tyr Leu Ser
1 5 10

<210> 123
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 123

Gln Ala Ser Glu Asn Ile Gly Asn Gly Leu Ala
1 5 10

<210> 124
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 124

Leu Ala Ser Glu Asp Ile Tyr Ser Gly Ile Ser
1   5   10

<210> 125
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 125

Gln Ala Ser Glu Asp Ile Tyr Ser Asn Leu Ala
1   5   10

<210> 126
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 126

Gln Ala Ser Glu Asp Ile Tyr Ser Asn Leu Ala
1   5   10

<210> 127
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 127

Gln Ala Ser Glu Asp Ile Tyr Ser Asn Leu Ala
1   5   10

<210> 128
<211> 11
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 128

Gln Ala Ser Glu Asn Ile Tyr Ser Ser Leu Ala
1   5   10

<210> 129
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 129

Gln Ser Ser Gln Ser Val Asp Gly Asn Asn Leu Leu Ser
1   5   10

<210> 130
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 130

Gln Ala Ser Gln Ser Ile Tyr Ser Phe Leu Ser
1   5   10

<210> 131
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 131

Gln Ala Ser Gln Ser Ile Gly Tyr Tyr Leu Ala
1   5   10

<210> 132
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 132

Gln Ala Ser Gln Thr Ile Ser Ile Asn Leu Ala
1   5   10

<210> 133
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 133

Gln Ala Ser Gln Asn Ile Tyr Ser Asn Leu Ala
1   5   10

<210> 134
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 134

Gln Ala Ser Gln Ser Val Tyr Asn Ser Asn His Leu Ser
1   5   10

<210> 135
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 135

Gln Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ser
1 5 10

<210> 136
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 136

Gln Ala Ser Glu Ser Ile Ser Ala Asn Tyr Trp Ser
1 5 10

<210> 137
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 137

Leu Ala Ser Thr Leu Ala Ser
1 5

<210> 138
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 138

Ala Ala Ser Leu Leu Ala Ser
1 5

<210> 139
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 139

Asp Ala Ser Lys Leu Ala Ser
1   5

<210> 140
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 140

Gly Ala Ser Thr Leu Ala Ser
1   5

<210> 141
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 141

Ala Ala Ser Asn Leu Glu Ser
1   5

<210> 142
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 142

Gly Ala Ser Thr Leu Ala Ser
1   5

<210> 143

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 143

Arg Ala Ser Thr Leu Ala Ser
1 5

<210> 144
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 144

Asp Ala Ser Thr Leu Ala Ser
1 5

<210> 145
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 145

Asp Ala Ser Asp Leu Ala Ser
1 5

<210> 146
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 146

Asp Ala Ser Asn Leu Ala Ser

1 5

<210> 147
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 147

Ala Ala Ser Asp Leu Glu Ser
1 5

<210> 148
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 148

Arg Ala Ser Thr Leu Ala Ser
1 5

<210> 149
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 149

Tyr Ala Ser Thr Leu Ala Ser
1 5

<210> 150
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 150

Ala Ala Ser Leu Leu Ala Ser
1   5

<210> 151
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 151

Ser Ala Ser Thr Leu Ala Ser
1   5

<210> 152
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 152

Gly Ala Ser Asn Leu Ala Ser
1   5

<210> 153
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 153

Gly Ala Ser Thr Leu Ala Ser
1   5

<210> 154
<211> 12
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 154

Gln Asn Trp Trp Val Ile Glu His Asn Gly Ala Ala
1   5   10

<210> 155
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 155

Gln Ser Ala Ser Tyr Ser Thr Gly Pro Asp Trp Thr
1   5   10

<210> 156
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 156

Gln Gln Gly Ala Thr Thr Tyr Asn Val Asp Asn Val
1   5   10

<210> 157
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 157

Gln Cys Thr Tyr Trp Asn Pro Asp Tyr Ile Gly Gly Ala
1   5   10

<210> 158
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 158

Leu Gly Gly Tyr Ser Tyr Ser Asn Thr Gly Pro Thr
1   5   10

<210> 159
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 159

Leu Gly Val Cys Thr Asp Ile Ser Thr Asp Asp Leu Tyr Asn Ala
1   5   10   15

<210> 160
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 160

Leu Gly Val Tyr Thr Tyr Ser Thr Asp Ile His Ala
1   5   10

<210> 161
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 161

Leu Gly Val Tyr Thr His Ile Ser Ala Asp Asn Ala
1 5 10

<210> 162
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 162

Gln Gln Gly Tyr Tyr Ser Gly Gly Thr Asp Asn Asp Val
1 5 10

<210> 163
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 163

Gln Gly Ser Tyr Tyr Ser Ser Ser Trp Tyr Asn Val
1 5 10

<210> 164
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 164

Gln Cys Asn Tyr Ile Ile Asp Tyr Gly Ala
1 5 10

<210> 165
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 165

Gln Ser Tyr Tyr Asn Ser Asp Ser Asp Ala
1   5   10

<210> 166
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 166

Gln Gln Gly Tyr Thr Glu Asp Asn Ile Asp Asn Thr
1   5   10

<210> 167
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 167

Gln Gly Ala Val Tyr Ser Gly Asn Thr Glu Trp Ala
1   5   10

<210> 168
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 168

Gln Gly Glu Phe Ser Cys Val Ser Ala Asp Cys Ile Ala
1   5   10

<210> 169

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 169

Gln Cys Thr Tyr Tyr Asp Asn Asn Tyr Gly Gly Ala
1   5   10

<210> 170
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 170

Gln Ser Trp Tyr Tyr Ser Gly Ser Gly Ser Tyr His Ser Trp Ala
1   5   10   15

<210> 171
<211> 107
<212> PRT
<213> Homo sapiens

<400> 171

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1   5   10   15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20   25   30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35   40   45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50   55   60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65   70   75   80

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Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210>  172
<211>  329
<212>  PRT
<213>  Homo sapiens

<400>  172

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110


Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
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Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
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<210> 173
<211> 123
<212> PRT

<213> Artificial Sequence

<220>
<223> humanized antibody

<400> 173

Glu Val Gln Leu Leu Glu Ser Gly Gly Arg Leu Val Gln Pro Gly Thr
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Ser Tyr
            20   25   30

Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
        35   40   45

Gly Val Ile Thr Ser Ser Ala Thr Thr Tyr Tyr Ala Ser Trp Ala Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
                85   90   95

Arg Gly Gly Pro Gly Tyr Ser Thr Asn Thr His Tyr Ala Phe Asp Pro
            100   105   110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 174
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized antibody

<400> 174

Asp Val Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

```
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Tyr Ser Phe
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Asp Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Asn Tyr Ile Ile Asp Tyr
                85                  90                  95


Gly Ala Phe Gly Gln Gly Thr Lys Val Val Ile Lys
            100                 105


<210>  175
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Humanized antibody

<400>  175

Gln Ser Asn Tyr Ile Ile Asp Tyr Gly Ala
1               5                   10


<210>  176
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  VR

<400>  176

Gln Ser Leu Glu Glu Ser Gly Gly Gly Leu Val Lys Pro Glu Gly Ser
1               5                   10                  15
```

```
Leu Thr Leu Thr Cys Lys Ala Ser Gly Ile Asp Phe Ser Gln Asp Tyr
            20                  25                  30


Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Ala Cys Ile Tyr Thr Gly Asn Asp Ile Thr Tyr Tyr Ala Ser Trp Ala
    50                  55                  60


Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Ser Thr Thr Val Thr Leu
65                  70                  75                  80


Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala
                85                  90                  95


Arg Asp Gly Gly Ala Asn Tyr Tyr Phe Lys Phe Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  177
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  VR

<400>  177

Asp Ile Val Met Thr Gln Thr Pro Ala Ser Val Glu Ala Ala Val Gly
1               5                   10                  15


Gly Thr Val Thr Ile Lys Cys Gln Ala Ser Gln Ser Ile Ser Asn Leu
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Gly Ala Ser Thr Leu Glu Ser Gly Val Pro Ser Arg Phe Lys Gly
```

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Asp Leu Gly Ser
65 70 75 80

Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Asn Tyr Ala Tyr Ser Ser Gly
85 90 95

Ser Trp Tyr Ser Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

<210> 178
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 178

Gln Asp Tyr Tyr Met Cys
1 5

<210> 179
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 179

Cys Ile Tyr Thr Gly Asn Asp Ile Thr Tyr Tyr Ala Ser Trp Ala Lys
1 5 10 15

Gly

<210> 180
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 180

Asp Gly Gly Ala Asn Tyr Tyr Phe Lys Phe
1   5   10

<210> 181
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 181

Gln Ala Ser Gln Ser Ile Ser Asn Leu Leu Ala
1   5   10

<210> 182
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 182

Gly Ala Ser Thr Leu Glu Ser
1   5

<210> 183
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 183

Gln Asn Tyr Ala Tyr Ser Ser Gly Ser Trp Tyr Ser
1   5   10