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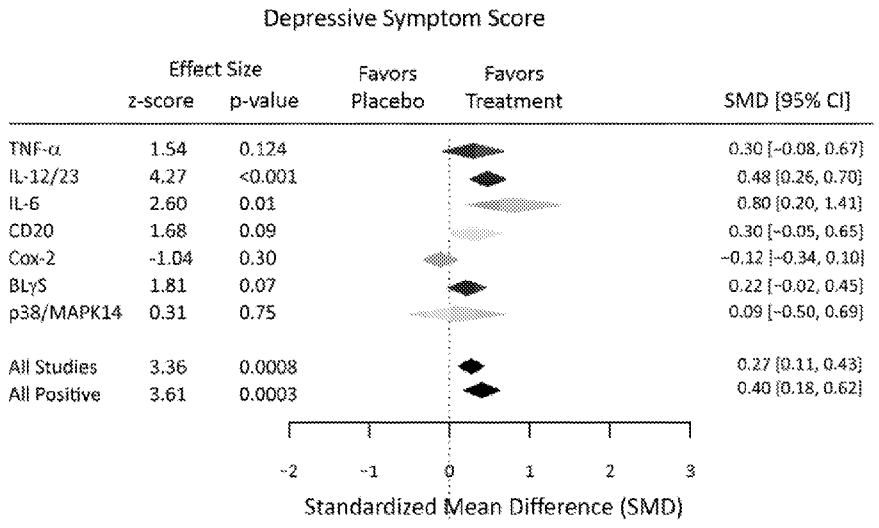
(54) Title: METHODS OF TREATING DEPRESSION USING IL-23 ANTIBODIES

Figure 1



(57) **Abstract:** A method for treating depression, anhedonia, or fatigue in a subject comprises administering an agent that blocks binding of IL-23 to IL-23 receptor, for example, an anti-IL-23 antibody or an antigen-binding fragment thereof that may comprise a heavy chain variable region and a light chain variable region of SEQ ID NO:106 and SEQ ID NO:116, respectively.

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METHODS OF TREATING DEPRESSION USING IL-23 ANTIBODIES

FIELD OF THE INVENTION

[0001] The invention relates to a method of treating depression, anhedonia, or fatigue. More particularly, the invention provides compositions and methods for treating depression using agents that block binding of IL-23 to IL-23 receptor, specifically using anti-IL-23 antibodies.

BACKGROUND OF THE INVENTION

[0002] Interleukin (IL)-12 is a secreted heterodimeric cytokine comprised of 2 disulfide-linked glycosylated protein subunits, designated p35 and p40 for their approximate molecular weights. IL-12 is produced primarily by antigen-presenting cells and drives cell-mediated immunity by binding to a two-chain receptor complex that is expressed on the surface of T cells or natural killer (NK) cells. The IL-12 receptor beta-1 (IL-12Rβ1) chain binds to the p40 subunit of IL-12, providing the primary interaction between IL-12 and its receptor. However, it is IL-12p35 ligation of the second receptor chain, IL-12Rβ2, that confers intracellular signaling (e.g. STAT4 phosphorylation) and activation of the receptor-bearing cell (Presky et al, 1996). IL-12 signaling concurrent with antigen presentation is thought to invoke T cell differentiation towards the T helper 1 (Th1) phenotype, characterized by interferon gamma (IFNγ) production (Trinchieri, 2003). Th1 cells are believed to promote immunity to some intracellular pathogens, generate complement-fixing antibody isotypes, and contribute to tumor immunosurveillance. Thus, IL-12 is thought to be a significant component to host defense immune mechanisms.

[0003] It was discovered that the p40 protein subunit of IL-12 can also associate with a separate protein subunit, designated p19, to form a novel cytokine, IL-23 (Oppman et al, 2000). IL-23 also signals through a two-chain receptor complex. Since the p40 subunit is shared between IL-12 and IL-23, it follows that the IL-12Rβ1 chain is also shared between IL-12 and IL-23. However, it is the IL-23p19 ligation of the second component of the IL-23 receptor complex, IL-23R, that confers IL-23 specific intracellular signaling (e.g., STAT3 phosphorylation) and subsequent IL-17 production by T cells (Parham et al, 2002; Aggarwal et al. 2003). Recent studies have demonstrated that the biological functions of IL-23 are distinct from those of IL-12, despite the structural similarity between the two cytokines (Langrish et al, 2005).

[0004] Abnormal regulation of IL-12 and Th1 cell populations has been associated with many immune-mediated diseases since neutralization of IL-12 by antibodies is effective in treating animal models of psoriasis, multiple sclerosis (MS), rheumatoid arthritis, inflammatory bowel disease, insulin-dependent

(type 1) diabetes mellitus, and uveitis (Leonard et al, 1995; Hong et al, 1999; Malfait et al, 1998; Davidson et al, 1998). However, since these studies targeted the shared p40 subunit, both IL-12 and IL-23 were neutralized *in vivo*. Therefore, it was unclear whether IL-12 or IL-23 was mediating disease, or if both cytokines needed to be inhibited to achieve disease suppression. Recent studies have confirmed through IL-23p19 deficient mice or specific antibody neutralization of IL-23 that IL-23 inhibition can provide equivalent benefit as anti-IL-12p40 strategies (Cua et al, 2003, Murphy et al, 2003, Benson et al 2004). Therefore, there is increasing evidence for the specific role of IL-23 in immune-mediated disease.

[0005] Accumulating evidence suggests proinflammatory cytokines play a role in the pathophysiology of depression. Depressive symptoms are common in patients with plaque psoriasis, a chronic immune-mediated skin disease mediated by proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-17, IL-22, IL-23, and TNF-α.

SUMMARY OF THE INVENTION

[0006] The present invention provides a method for treating depression, anhedonia, or fatigue in a subject comprising administering to the subject an effective amount of a pharmaceutical composition comprising an agent that blocks binding of IL-23 to IL-23 receptor. The IL-23 antibody may be an antibody specific for the p19 unit of IL-23 or an antibody that binds to the p40 subuint shared by IL-12 and IL-23, thus binding to both IL-12 and IL-23. In another embodiment, the agent that blocks binding of IL-23 to IL-23 receptor comprises an isolated antibody or an antigen-binding fragment thereof.

[0007] In another aspect of the invention the pharmaceutical composition comprises an isolated anti-IL23 specific antibody having the guselkumab CDR sequences comprising (i) the heavy chain CDR amino acid sequences of SEQ ID NO: 5, SEQ ID NO: 20, and SEQ ID NO: 44; and (ii) the light chain CDR amino acid sequences of SEQ ID NO: 50, SEQ ID NO: 56, and SEQ ID NO: 73 at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

[0008] In another embodiment, the isolated antibody or an antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region of SEQ ID NO:106 and SEQ ID NO:116, respectively, at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

[0009] One embodiment of the invention is a method for treating depression, anhedonia, or fatigue in a subject comprising administering to the subject an effective amount of a pharmaceutical composition comprising an agent that blocks binding of IL-23 to IL-23 receptor.

[0010] In another embodiment, the isolated antibody or an antigen-binding fragment thereof is administered at a dose of about 25-100mg about every 2-4 weeks.

[0011] In another embodiment, the isolated antibody or an antigen-binding fragment thereof is administered at a dose selected from the group comprising about 100 mg every 2 weeks, about 25 mg every 4 weeks, about 50 mg every 4 weeks, and about 100 mg every 4 weeks.

[0012] In another embodiment, the isolated antibody or an antigen-binding fragment thereof is administered at a dose of about 11 mg/kg every 3 weeks.

[0013] In another embodiment, the isolated antibody or an antigen-binding fragment thereof is administered subcutaneously.

[0014] In another embodiment, the isolated antibody or an antigen-binding fragment thereof is administered intravenously.

BRIEF DESCRIPTION OF THE FIGURES

[0015] **Figure 1** shows the antidepressant effects in patients with high depressive symptoms treated for disorders other than depression in clinical trials (18 trials, 9 compounds, 7 targets).

[0016] **Figure 2** shows the antidepressant effects adjusted for primary disease severity in patients with high depressive symptoms treated for disorders other than depression in clinical trials (18 trials, 9 compounds, 7 targets).

[0017] **Figure 3** shows the HADS Depression score of patients at baseline and weeks 8 and 16 in the psoriasis clinical trial involving guselkumab.

[0018] **Figures 4A and 4B** show the HADS Depression score of patients adjusted for disease severity at baseline and weeks 8 and 16 in the psoriasis clinical trial involving guselkumab.

[0019] **Figure 5** shows the demographics and baseline characteristics of patients in the psoriasis clinical trial involving guselkumab.

DETAILED DESCRIPTION OF THE INVENTION

[0020] All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats.

[0021] The disclosed subject matter may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed subject matter are not limited to those described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed subject matter.

[0022] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed methods are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0023] When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Further, reference to values stated in ranges include each and every value within that range. All ranges are inclusive and combinable. When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise.

[0024] It is to be appreciated that certain features of the disclosed methods which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

Definitions

[0025] As used herein, the singular forms "a," "an," and "the" include the plural.

[0026] Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0027] The term "about" when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term "about" is used to encompass variations of ± 10% or less, variations of ± 5% or less, variations of ± 1% or less, variations of ± 0.5% or less, or variations of ± 0.1% or less from the specified value.

[0028] "Treating" or "treatment" refer to any success or indicia of success in the attenuation or amelioration of an injury, pathology, or condition, including any objective or subjective parameter such as abatement, remission, diminishing of symptoms or making the condition more tolerable to the patient,

slowing in the rate of degeneration or decline, making the final point of degeneration less debilitating, improving a subject's physical or mental well-being, or prolonging the length of survival. The treatment may be assessed by objective or subjective parameters, including the results of a physical examination, neurological examination, or psychiatric evaluations.

[0029] "Depression", also known as "unipolar affective disorder", is characterized by a combination of symptoms such as lowered mood, loss of energy, loss of interest, feeling of physical illness, poor concentration, altered appetite, altered sleep and a slowing down of physical and mental functions resulting in a relentless feeling of hopelessness, helplessness, guilt, and anxiety.

[0030] "Fatigue" refers to a condition of physical and/or mental exhaustion. Fatigue can be subjectively described as feeling weary, tired, exhausted, malaise, listless, lack of energy, or feeling run down.

[0031] "Effective amount" or "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount of an agent that blocks binding of IL-23 to IL-23 receptor may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the agent are outweighed by the therapeutically beneficial effects.

[0032] As used herein, "an agent that blocks binding of IL-23 to IL-23 receptor" refers to an IL-23 antibody which can specifically bind to the p19 subunit of IL-23, to the p40 subunit of IL-23, or both. In some aspects, the agent that blocks binding of IL-23 to IL-23 receptor is an IL-23 antibody or other molecule (e.g. , small molecule, aptamer, scaffolding molecule, etc) which can compete for binding to the p19 subunit of IL-23, to the p40 subunit of IL-23, or both, with the antibody described in the present invention or another IL-23 antibody known in the art. In other aspects, the agent that blocks binding of IL-23 to IL-23 receptor is a small molecule or cyclic peptide IL-23 receptor antagonist. Exemplary cyclic peptide IL-23 receptor antagonists are described in U.S. Patent No. 9,624,268.

[0033] As used herein, an "anti-IL-23 specific antibody," "anti-IL-23 antibody," "antibody portion," or "antibody fragment" and/or "antibody variant" and the like include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of an IL-23 receptor or binding protein, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to, where such antibody modulates, decreases, increases,

antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one IL-23 activity or binding, or with IL-23 receptor activity or binding, *in vitro, in* situ and/or in *vivo*. As a non-limiting example, a suitable anti-IL-23 antibody, specified portion or variant of the present invention can bind at least one IL-23 molecule, or specified portions, variants or domains thereof. A suitable anti-IL-23 antibody, specified portion, or variant can also optionally affect at least one of IL-23 activity or function, such as but not limited to, RNA, DNA or protein synthesis, IL-23 release, IL-23 receptor signaling, membrane IL-23 cleavage, IL-23 activity, IL-23 production and/or synthesis.

[0034] The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian IL-23. For example, antibody fragments capable of binding to IL-23 or portions thereof, including, but not limited to, Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')2 (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, supra).

[0035] Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')2 heavy chain portion can be designed to include DNA sequences encoding the CH1 domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

[0036] As used herein "chimeric" antibodies or "humanized" antibodies or "CDR-grafted" include any combination of the herein described murine CDR's with one or more proteins or peptides derived from a non-murine, preferably, human antibody. In accordance with the invention, chimeric or humanized antibodies are provided wherein the CDR's are derived from the murine CLB-8 antibody capable of binding human IL-23 and at least a portion, or the remainder of the antibody is derived from one or more human antibodies. Thus, the human part of the antibody may include the framework, CL, CH domains (e.g., CH1, CH2, CH3), hinge, (VL, VH)) regions which are substantially non-immunogenic in humans. The regions of the antibody that are derived from human antibodies need not have 100% identity with human antibodies. In a preferred embodiment, as many of the human amino acid residues as possible are

retained in order for the immunogenicity to be negligible, but the human residues may be modified as necessary to support the antigen binding site formed by the CDR's while simultaneously maximizing the humanization of the antibody. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies.

[0037] It is pointed out that a humanized antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when the antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

[0038] As used herein, the term "human antibody" is an antibody with at least fully human frameworks and constant regions (CL, CH domains (e.g., CH1, CH2, CH3), and hinge), and CDRs derived from antigen binding antibodies. Fully human frameworks comprise frameworks that correspond to human germline sequences as well as sequences with somatic mutations. CDRs may be derived from one or more CDRs that bind to IL-23 in the context of any antibody framework. For example, the CDRs of the human antibody of the present invention may be derived from CDRs that bind IL-23 in the context of a mouse antibody framework and then are engineered to bind IL-23 in the context of a fully human framework. Often, the human antibody is substantially non-immunogenic in humans.

[0039] Anti-IL-23 antibodies useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to IL-23 and, optionally and preferably, as having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as the incidence of titrable levels of antibodies to the anti-IL-23 antibody in patients treated with anti-IL-23 antibody as occurring in less than 25% of patients treated, preferably, in less than 10% of patients treated with the recommended dose for the recommended course of therapy during the treatment period.

[0040] "Subject" refers to human and non-human animals, including all vertebrates, e.g., mammals and non-mammals, such as non-human primates, mice, rabbits, sheep, dogs, cats, horses, cows, chickens, amphibians, and reptiles. In many embodiments of the described methods, the subject is a human.

Antibodies of the Present Invention – Production and Generation

[0041] Antibodies that bind to human IL-23 and that comprise the defined heavy or light chain variable region or CDR regions can be prepared using suitable methods, such as phage display (Katsube, Y., et al., Int J Mol. Med, 1(5):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

[0042] A preferred anti-IL-23 antibody is guselkumab (also referred to as CNTO1959) having the heavy chain variable region amino acid sequence of SEQ ID NO: 106 and the light chain variable region amino acid sequence of SEQ ID NO: 116 and having the heavy chain CDR amino acid sequences of SEQ ID NO: 5, SEQ ID NO: 20, and SEQ ID NO: 44; and the light chain CDR amino acid sequences of SEQ ID NO: 50, SEQ ID NO: 56, and SEQ ID NO: 73. Other anti-IL-23 antibodies have sequences listed herein and are described in U.S. Patent No. 7,935,344, the entire contents of which are incorporated herein by reference.

[0043] As stated, the invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Such anti-IL-23 antibodies can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human IL-23 with high affinity (e.g., K_D less than or equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g., charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

[0044] Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given anti-IL-23 antibody, fragment or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

[0045] Amino acids in an anti-IL-23 antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one IL-23 neutralizing activity. Sites that are critical for antibody binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

[0046] Anti-IL-23 antibodies of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 5 to all of the contiguous amino acids of at least one of SEQ ID NOS: 5, 20, 44, 50, 56 and 73.

[0047] An anti-IL-23 antibody can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NOS: 106 and 116.

[0048] In one embodiment, the amino acid sequence of an immunoglobulin chain, or portion thereof (e.g., variable region, CDR) has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence of the corresponding chain of at least one of SEQ ID NOS: 106 and 116. For example, the amino acid sequence of a light chain variable region can be compared with the sequence of SEQ ID NO:116, or the amino acid sequence of a heavy chain CDR3 can be compared with SEQ ID NO: 44. Preferably, 70-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

[0049] Exemplary heavy chain and light chain variable regions sequences are provided in SEQ ID NOS: 106 and 116. The antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in an anti-IL-23 antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220,

230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

[0050] As those of skill will appreciate, the present invention includes at least one biologically active antibody of the present invention. Biologically active antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related and known antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

[0051] In another aspect, the invention relates to antibodies and antigen-binding fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased in vivo serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

[0052] The modified antibodies and antigen-binding fragments of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody. Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example PEG5000 and PEG20,000, wherein the subscript is the average

molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

[0053] Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C12, laurate), n-tetradecanoate (C14, myristate), n-octadecanoate (C18, stearate), n-eicosanoate (C20, arachidate), n-docosanoate (C22, behenate), n-triacontanoate (C30), n-tetracontanoate (C40), cis-Δ9-octadecanoate (C18, oleate), all cis-Δ5,8,11,14-eicosatetraenoate (C20, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

[0054] The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A “modifying agent” as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., Bioconjugate Techniques, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C1-C12 group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, -(CH2)3-, -NH-(CH2)6-NH-, -(CH2)2-NH- and -CH2-O-CH2-CH2-O-CH2-CH2-O-CH-NH-. Modifying agents that comprise a linker moiety can be

produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, et al., WO 92/16221 the entire teachings of which are incorporated herein by reference.)

[0055] The modified antibodies of the invention can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment. The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch et al., Bioconjugate Chem., 3:147-153 (1992); Werlen et al., Bioconjugate Chem., 5:411-417 (1994); Kumaran et al., Protein Sci. 6(10):2233-2241 (1997); Itoh et al., Bioorg. Chem., 24(1): 59-68 (1996); Capellas et al., Biotechnol. Bioeng., 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., Bioconjugate Techniques, Academic Press: San Diego, CA (1996).

[0056] The antibodies of the invention can bind human IL-23 with a wide range of affinities (KD). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human IL-23 with high affinity. For example, a mAb can bind human IL-23 with a KD equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9},10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

[0057] The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, et al., "Antibody-Antigen Interactions," In Fundamental Immunology, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis Immunology, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., KD, Ka,

Kd) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

[0058] Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one IL-23 protein, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

Human Monoclonal Antibodies

[0059] In one aspect of the invention there is provided a method for the treatment or prophylaxis of an IL-23-mediated disorder such as depression and/or fatigue, comprising administering to a patient in need thereof a therapeutically effective amount of an IL-23 antigen binding protein or fragment thereof.

[0060] In one such aspect of the invention as herein described the antigen binding protein or fragment thereof specifically binds to IL-23 and inhibits the binding of IL-23 to the IL-23 receptor (IL-23R).

[0061] In one aspect of the invention there is provided a method for the treatment or prophylaxis of an IL-23-mediated disorder such as depression and/or fatigue comprising administering to a patient in need thereof a therapeutically effective amount of an IL-23 antigen binding protein or fragment thereof wherein the antigen binding protein or fragment thereof comprises one or more of the following CDR's:

i) CDRH1 as set out in SEQ ID NO. 5; or

ii) CDRH2 as set out in SEQ ID NO. 20; or

iii) CDRH3 as set out in SEQ ID NO. 44; or

iv) CDRL1 as set out in SEQ ID NO. 50; or

v) CDRL2 as set out in SEQ ID NO. 56; or

vi) CDRL3 as set out in SEQ ID NO. 73.

[0062] The antigen binding proteins of the invention may comprise heavy chain variable regions and light chain variable regions of the invention which may be formatted into the structure of a natural antibody or functional fragment or equivalent thereof. An antigen binding protein of the invention may therefore comprise the VH regions of the invention formatted into a full-length antibody, a (Fab')2 fragment, a Fab fragment, or equivalent thereof (such as scFV, bitri- or tetra-bodies, Tandabs etc.), when paired with an appropriate light chain.

[0063] In one such aspect of the invention as herein described the antigen binding protein is selected from the group consisting of a dAb, Fab, Fab', $F(ab')_2$, Fv, diabody, triabody, tetrabody, miniantibody, and a minibody.

[0064] In one aspect of the invention there is provided an antigen binding protein comprising an isolated heavy chain variable domain of SEQ ID NO: 106.

[0065] In another aspect of the invention there is provided an antigen binding protein comprising an isolated light chain variable domain SEQ ID NO: 116. For example, in one such aspect the IL-23 antigen binding protein (IL-23 antibody) or fragment thereof is CNTO1959, also known as guselkumab.

[0066] In certain embodiments, the antibody comprises an altered (e.g., mutated) Fc region. For example, in some embodiments, the Fc region has been altered to reduce or enhance the effector functions of the antibody. In some embodiments, the Fc region is an isotype selected from IgM, IgA, IgG, IgE, or other isotype.

[0067] Alternatively or additionally, it may be useful to combine amino acid modifications with one or more further amino acid modifications that alter C1q binding and/or the complement dependent cytotoxicity (CDC) function of the Fc region of an IL-23 binding molecule. The starting polypeptide of particular interest may be one that binds to C1q and displays complement dependent cytotoxicity. Polypeptides with pre-existing C1q binding activity, optionally further having the ability to mediate CDC may be modified such that one or both of these activities are enhanced. Amino acid modifications that alter C1q and/or modify its complement dependent cytotoxicity function are described, for example, in WO0042072, which is hereby incorporated by reference.

[0068] As disclosed above, one can design an Fc region of the human IL-23 antibody of the present invention with altered effector function, e.g., by modifying C1q binding and/or FcγR binding and thereby changing CDC activity and/or ADCC activity. "Effector functions" are responsible for activating or

diminishing a biological activity (e.g., in a subject). Examples of effector functions include, but are not limited to: C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor; BCR), etc. Such effector functions may require the Fc region to be combined with a binding domain (e.g., an antibody variable domain) and can be assessed using various assays (e.g., Fc binding assays, ADCC assays, CDC assays, etc.).

[0069] For example, one can generate a variant Fc region of the human IL-23 antibody with improved C1q binding and improved FcγRIII binding (e.g., having both improved ADCC activity and improved CDC activity). Alternatively, if it is desired that effector function be reduced or ablated, a variant Fc region can be engineered with reduced CDC activity and/or reduced ADCC activity. In other embodiments, only one of these activities may be increased, and, optionally, also the other activity reduced (e.g., to generate an Fc region variant with improved ADCC activity, but reduced CDC activity and vice versa).

[0070] Fc mutations can also be introduced in engineer to alter their interaction with the neonatal Fc receptor (FcRn) and improve their pharmacokinetic properties. A collection of human Fc variants with improved binding to the FcRn have been described (Shields et al., (2001). High resolution mapping of the binding site on human IgG1 for FcγRI, FcγRII, FcγRIII, and FcRn and design of IgG1 variants with improved binding to the FcγR, J. Biol. Chem. 276:6591-6604).

[0071] Another type of amino acid substitution serves to alter the glycosylation pattern of the Fc region of the human IL-23 antibody. Glycosylation of an Fc region is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. The recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain peptide sequences are asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline. Thus, the presence of either of these peptide sequences in a polypeptide creates a potential glycosylation site.

[0072] The glycosylation pattern may be altered, for example, by deleting one or more glycosylation site(s) found in the polypeptide, and/or adding one or more glycosylation site(s) that are not present in the polypeptide. Addition of glycosylation sites to the Fc region of a human IL-23 antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). An exemplary glycosylation variant has an amino acid substitution of residue Asn 297 of the heavy chain. The alteration may also be made by the

addition of, or substitution by, one or more serine or threonine residues to the sequence of the original polypeptide (for O-linked glycosylation sites). Additionally, a change of Asn 297 to Ala can remove one of the glycosylation sites.

[0073] In certain embodiments, the human IL-23 antibody of the present invention is expressed in cells that express beta (1,4)-N-acetylglucosaminyltransferase III (GnT III), such that GnT III adds GlcNAc to the human IL-23 antibody. Methods for producing antibodies in such a fashion are provided in WO/9954342, WO/03011878, patent publication 20030003097A1, and Umana et al., Nature Biotechnology, 17:176-180, Feb. 1999.

[0074] A human anti-IL-23 antibody can be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-IL-23 antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

[0075] Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428, 5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg et al.; Jakobovits et al. WO 98/50433, Jakobovits et al. WO 98/24893, Lonberg et al. WO 98/24884, Lonberg et al. WO 97/13852, Lonberg et al. WO 94/25585, Kucherlapate et al. WO 96/34096, Kucherlapate et al. EP 0463 151 B1, Kucherlapate et al. EP 0710 719 A1, Surani et al. US. Pat. No. 5,545,807, Bruggemann et al. WO 90/04036, Bruggemann et al. EP 0438 474 B1, Lonberg et al. EP 0814 259 A2, Lonberg et al. GB 2 272 440 A, Lonberg et al. Nature 368:856-859 (1994), Taylor et al., Int. Immunol. 6(4)579-591 (1994), Green et al, Nature Genetics 7:13-21 (1994), Mendez et al., Nature Genetics 15:146-156 (1997), Taylor et al., Nucleic Acids Research 20(23):6287-6295 (1992), Tuaillon et al., Proc Natl Acad Sci USA 90(8)3720-3724 (1993), Lonberg et al., Int Rev Immunol 13(1):65-93 (1995) and Fishwald et al., Nat Biotechnol 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

[0076] Screening antibodies for specific binding to similar proteins or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. Antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more

amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278.

[0077] Other systems for generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge Antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge Antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, supra; Ausubel, supra; or Sambrook, supra.

[0078] Antibodies of the present invention can also be prepared using at least one anti-IL-23 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, rabbits and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US Patent Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

[0079] Antibodies of the present invention can additionally be prepared using at least one anti-IL-23 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to, tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's),

including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and references cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to known methods. See also, e.g., Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (Oct., 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944 (1994); and references cited therein.

[0080] The antibodies of the invention can bind human IL-23 with a wide range of affinities (K_D). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human IL-23 with high affinity. For example, a human or human mAb can bind human IL-23 with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13}, 10^{-14}, 10^{-15} or any range or value therein, as determined by surface plasmon resonance or the Kinexa method, as practiced by those of skill in the art.

[0081] The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, et al., "Antibody-Antigen Interactions," In Fundamental Immunology, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis Immunology, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., KD, Kon, Koff) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

[0082] Preferred anti-IL-23 antibodies of the invention have the sequences shown in the Sequence Listing below.

[0083] The isolated antibodies of the present invention comprise the antibody amino acid sequences disclosed herein encoded by any suitable polynucleotide, or any isolated or prepared antibody. Preferably, the human antibody or antigen-binding fragment binds human IL-23 and, thereby, partially or substantially neutralizes at least one biological activity of the protein. An antibody, or specified portion or variant thereof, that partially or preferably substantially neutralizes at least one biological activity of at least one IL-23 protein or fragment can bind the protein or fragment and thereby inhibit activities mediated through the binding of IL-23 to the IL-23 receptor or through other IL-23-dependent or mediated mechanisms. As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit an IL-23-dependent activity by about 20-120%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-IL-23 antibody to inhibit an IL-23-dependent activity is preferably assessed by at least one suitable IL-23 protein or receptor assay, as described herein and/or as known in the art. A human

antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4 (e.g., γ1, γ2, γ3, or γ4). Antibodies of this type can be prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., IgG, IgA, and IgM) transgenes as described herein and/or as known in the art. In another embodiment, the anti-human IL-23 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

[0084] At least one antibody of the present invention can be expressed in a modified form, such as a fusion protein, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

[0085] Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated proteins have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va (www.atcc.org). Preferred host cells include cells of lymphoid origin, such as myeloma and lymphoma cells. Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

[0086] Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to, an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding

sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or proteins of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

Purification of an Antibody

[0087] An anti-IL-23 antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

[0088] Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Sections 17.37-17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, supra, Chapters 12-14, all entirely incorporated herein by reference.

Cloning and Expression in CHO Cells

[0089] The vector pC4 may be used for the expression of IL-23 antibody. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop

resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

[0090] Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., Cell 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLVI. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the IL-23 in a regulated way in mammalian cells (M. Gossen, and H. Bujard, Proc. Natl. Acad. Sci. USA 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

[0091] The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[0092] The DNA sequence encoding the complete IL-23 antibody is used according to known method steps. Isolated nucleic acid encoding a suitable human constant region (i.e., HC and LC regions) is also used in this construct.

[0093] The isolated variable and constant region encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

[0094] Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5 μg of the expression plasmid pC4 is cotransfected with 0.5 μg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an

enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 μg /ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 μg /ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Amino Acid Codes

[0095] The amino acids that make up anti-IL-23 antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three-letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994)

[0096] An anti-IL-23 antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein. Amino acids in an anti-IL-23 antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to, at least one IL-23 neutralizing activity. Sites that are critical for antibody binding can also be identified by structural analysis, such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

[0097] Non-limiting variants that can enhance or maintain at least one of the listed activities include, but are not limited to, any of the above polypeptides, further comprising at least one mutation corresponding to at least one substitution in the residues varied among the disclosed variant amino acid sequences.

[0098] In another aspect, the invention relates to human antibodies and antigen-binding fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased in vivo serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric

group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

[0099] The modified antibodies and antigen-binding fragments of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody. Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example, PEG5000 and PEG20,000, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

[0100] Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C12, laurate), n-tetradecanoate (C14, myristate), n-octadecanoate (C18, stearate), n-eicosanoate (C20, arachidate) , n-docosanoate (C22, behenate), n-triacontanoate (C30), n-tetracontanoate (C40), cis-Δ9-octadecanoate (C18, oleate), all cis-Δ5,8,11,14-eicosatetraenoate (C20, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of

dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably, one to about six, carbon atoms.

[0101] The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups, such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., Bioconjugate Techniques, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example, a divalent C1-C12 group wherein one or more carbon atoms can be replaced by a heteroatom, such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, -(CH2)3-, -NH-(CH2)6-NH-, -(CH2)2-NH- and -CH2-O-CH2-CH2-O-CH2-CH2-O-CH-NH-. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate, as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, et al., WO 92/16221, the entire teachings of which are incorporated herein by reference.)

[0102] The modified antibodies of the invention can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment.

The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch et al., Bioconjugate Chem., 3:147-153 (1992); Werlen et al., Bioconjugate Chem., 5:411-417 (1994); Kumaran et al., Protein Sci. 6(10):2233-2241 (1997); Itoh et al., Bioorg. Chem., 24(1): 59-68 (1996); Capellas et al., Biotechnol. Bioeng., 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., Bioconjugate Techniques, Academic Press: San Diego, CA (1996).

Antibody Compositions Comprising Further Therapeutically Active Ingredients

[0103] The present invention also provides at least one anti-IL-23 antibody composition comprising at least one, at least two, at least three, at least four, at least five, at least six or more anti-IL-23 antibodies thereof, as described herein and/or as known in the art that are provided in a non-naturally occurring composition, mixture or form. Such compositions comprise non-naturally occurring compositions comprising at least one or two full length, C- and/or N-terminally deleted variants, domains, fragments, or specified variants, of the anti-IL-23 antibody amino acid sequence selected from the group consisting of 70-100% of the contiguous amino acids of any of the antibody sequences disclosed herein. Preferred anti-IL-23 antibody compositions include at least one or two full length, fragments, domains or variants as at least one CDR or LBR containing portions of the anti-IL-23 antibody sequence of 70-100% of or specified fragments, domains or variants thereof. Such composition percentages are by weight, volume, concentration, molarity, or molality as liquid or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein.

[0104] The antibody compositions of the invention can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see, e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmcotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

[0105] The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, and miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, and neuromuscular blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators, expectorants or at least one antitussive, and miscellaneous respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbent or at least one antiflatulent, digestive enzyme or at least one gallstone solubilizer, antidiarrheals, laxatives, antiemetics, and antiulcer drugs. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroid, estrogen or at least one progestin, gonadotropin, antidiabetic drug or at least one glucagon, thyroid hormone, thyroid hormone antagonist, pituitary hormone, and parathyroid-like drug. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoid, antitoxin or at least one antivenin, immune serum, and biological response modifier. The ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, and nasal drugs. See, e.g., contents of Nursing 2001 Drug Handbook, supra.

[0106] The at least one cephalosporin can be at least one selected from cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephradine, and loracarbef. (See, e.g., pp. 24-214 of Nursing 2001 Drug Handbook).

[0107] The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, and magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, and sulindac. The at least one narcotic or opioid analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine

hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, and tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, and zolpidem tartrate. The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximde, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, and valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, sertraline hydrochloride, tranylcypromine sulfate, trimipramine maleate, and venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephrobamate, midazolam hydrochloride, and oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluephenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, and trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, modafinil, pemoline, and phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from amantadine hydrochloride, benztropine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, and trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from bupropion hydrochloride, donepezil hydrochloride, droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex,

nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, and zolmitriptan. (See, e.g., pp. 337-530 of Nursing 2001 Drug Handbook.)

[0108] The at least one cholinergic (e.g., parasymathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, and pyridostigmine bromide. The at least one anticholinergic can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, and scopolamine hydrobromide. The at least one adrenergic (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate. The at least one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, and propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, and tizanidine hydrochloride. The at least one neuromuscular blocker can be at least one selected from atracurium besylate, cisatracurium besylate, doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, and vecuronium bromide. (See, e.g., pp. 531-84 of Nursing 2001 Drug Handbook.)

[0109] The at least one corticosteroid can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, and triamcinolone diacetate.

[0110] The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, and tacrolimus. The at least one biological response modifier can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, and sargramostim. (See, e.g., pp. 964-1040 of Nursing 2001 Drug Handbook.)

[0111] The at least one nasal drug can be at least one selected from beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, and xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of Nursing 2001 Drug Handbook.)

[0112] For example, the at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocorisone valerate, mometasone furoate, and triamcinolone acetonide. (See, e.g., pp. 1098-1136 of Nursing 2001 Drug Handbook.)

[0113] Anti-IL-23 antibody compositions of the present invention can further comprise at least one of any suitable and effective amount of a composition or pharmaceutical composition comprising at least one anti-IL-23 antibody contacted or administered to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, etanercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene

inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-39 (e.g., IL-1, IL-2, etc.). Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

[0114] Anti-IL-23 antibody compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the anti-IL-23 antibody, fragment or variant composition as well known in the art or as described herein.

[0115] Pharmaceutical excipients and additives useful in the present composition include, but are not limited to, proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars, such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin, such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

[0116] Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

[0117] Anti-IL-23 antibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts, such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic

acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts, such as citrate.

[0118] Additionally, anti-IL-23 antibody compositions of the invention can include polymeric excipients/additives, such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates, such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

[0119] These and additional known pharmaceutical excipients and/or additives suitable for use in the anti-IL-23 antibody, portion or variant compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents. An exemplary carrier molecule is the mucopolysaccharide, hyaluronic acid, which may be useful for intraarticular delivery.

Formulations

[0120] As noted above, the invention provides for stable formulations, which preferably comprise a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one anti-IL-23 antibody in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, polymers, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as about 0.0015%, or any range, value, or fraction therein. Non-limiting examples include, no preservative, about 0.1-2% m-cresol (e.g., 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), about 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), about 0.001-0.5% thimerosal (e.g., 0.005, 0.01), about 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

[0121] As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one anti-IL-23 antibody with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one anti-IL-23 antibody, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one anti-IL-23 antibody in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

[0122] The at least one anti-IL-23 antibody used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

[0123] The range of at least one anti-IL-23 antibody in the product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

[0124] Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

[0125] Other excipients, e.g., isotonicity agents, buffers, antioxidants, and preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably, the formulations of the present invention have a pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably, sodium phosphate, particularly, phosphate buffered saline (PBS).

[0126] Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants, such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and chelators, such as EDTA and EGTA, can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

[0127] The formulations of the present invention can be prepared by a process which comprises mixing at least one anti-IL-23 antibody and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one anti-IL-23 antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one anti-IL-23 antibody in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the protein and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

[0128] The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-IL-23 antibody that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably, a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

[0129] The present claimed articles of manufacture are useful for administration over a period ranging from immediate to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2°C to about 40°C and retain the biological activity of the protein for extended periods of time, thus allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

[0130] The solutions of at least one anti-IL-23 antibody of the invention can be prepared by a process that comprises mixing at least one antibody in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody in water or buffer is combined in quantities sufficient to provide the protein and, optionally, a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

[0131] The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-IL-23 antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

[0132] The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one anti-IL-23 antibody that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at least one antibody solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

[0133] Recognized devices comprising single vial systems include pen-injector devices for delivery of a solution, such as BD Pens, BD Autojector®, Humaject®, NovoPen®, B-D®Pen, AutoPen®, and OptiPen®, GenotropinPen®, Genotronorm Pen®, Humatro Pen®, Reco-Pen®, Roferon Pen®, Biojector®, Iject®, J-tip Needle-Free Injector®, Intraject®, Medi-Ject®, e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products, Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN, www.medijject.com), and similarly suitable devices. Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution, such as the HumatroPen®. Examples of other devices suitable include pre-filled syringes, SelfDose™ (West Pharmaceuticals, Inc. of Exton, PA) and other patient controlled injectors, auto-injectors, needle free injectors and needle free IV infusion sets.

[0134] The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product

can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one anti-IL-23 antibody in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical product use.

[0135] The formulations of the present invention can be prepared by a process that comprises mixing at least one anti-IL-23 antibody and a selected buffer, preferably, a phosphate buffer containing saline or a chosen salt. Mixing the at least one anti-IL-23 antibody and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

[0136] The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-IL-23 antibody that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

[0137] Other formulations or methods of stabilizing the anti-IL-23 antibody may result in other than a clear solution of lyophilized powder comprising the antibody. Among non-clear solutions are formulations comprising particulate suspensions, said particulates being a composition containing the anti-IL-23 antibody in a structure of variable dimension and known variously as a microsphere, microparticle, nanoparticle, nanosphere, or liposome. Such relatively homogenous, essentially spherical, particulate formulations containing an active agent can be formed by contacting an aqueous phase containing the active agent and a polymer and a nonaqueous phase followed by evaporation of the nonaqueous phase to cause the coalescence of particles from the aqueous phase as taught in U.S. 4,589,330. Porous microparticles can be prepared using a first phase containing active agent and a polymer dispersed in a continuous solvent and removing said solvent from the suspension by freeze-drying or dilution-extraction-precipitation as taught in U.S. 4,818,542. Preferred polymers for such preparations are natural or synthetic copolymers or polymers selected from the group consisting of gelatin

agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic aced, glycolide-L(-) lactide poly(episilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), poly(epsilon-caprolactone-CO-glycolic acid), poly(ß-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate). Particularly preferred polymers are polyesters, such as polyglycolic acid, polylactic aced, glycolide-L(-) lactide poly(episilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), and poly(epsilon-caprolactone-CO-glycolic acid. Solvents useful for dissolving the polymer and/or the active include: water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate. The process of dispersing the active containing phase with a second phase may include pressure forcing said first phase through an orifice in a nozzle to affect droplet formation.

[0138] Dry powder formulations may result from processes other than lyophilization, such as by spray drying or solvent extraction by evaporation or by precipitation of a crystalline composition followed by one or more steps to remove aqueous or nonaqueous solvent. Preparation of a spray-dried antibody preparation is taught in U.S. 6,019,968. The antibody-based dry powder compositions may be produced by spray drying solutions or slurries of the antibody and, optionally, excipients, in a solvent under conditions to provide a respirable dry powder. Solvents may include polar compounds, such as water and ethanol, which may be readily dried. Antibody stability may be enhanced by performing the spray drying procedures in the absence of oxygen, such as under a nitrogen blanket or by using nitrogen as the drying gas. Another relatively dry formulation is a dispersion of a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant as taught in WO 9916419. The stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler. Equipment useful in the commercial manufacture of spray dried medicaments are manufactured by Buchi Ltd. or Niro Corp.

[0139] At least one anti-IL-23 antibody in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Alternative Administration

[0140] Many known and developed modes can be used according to the present invention for administering pharmaceutically effective amounts of at least one anti-IL-23 antibody according to the present invention. While pulmonary administration is used in the following description, other modes of

administration can be used according to the present invention with suitable results. IL-23 antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

Parenteral Formulations and Administration

[0141] Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols, such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent, such as aqueous solution, a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

Alternative Delivery

[0142] The invention further relates to the administration of at least one anti-IL-23 antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one anti-IL-23 antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration particularly in semisolid forms, such as, but not limited to, creams and suppositories; for buccal, or sublingual administration, such as, but not limited to, in the form of tablets or capsules; or intranasally, such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally, such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug

concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement;" Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing proteins and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways, such as electroporation, or to increase the mobility of charged drugs through the skin, such as iontophoresis, or application of ultrasound, such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

Pulmonary/Nasal Administration

[0143] For pulmonary administration, preferably, at least one anti-IL-23 antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one anti-IL-23 antibody can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of antibodies are also known in the art. All such devices can use formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non-aqueous) or solid particles.

[0144] Metered dose inhalers like the Ventolin® metered dose inhaler, typically use a propellent gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like TurbuhalerTM (Astra), Rotahaler® (Glaxo), Diskus® (Glaxo), SpirosTM inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler® powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like AERxTM Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer (Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention.

[0145] Preferably, a composition comprising at least one anti-IL-23 antibody is delivered by a dry powder inhaler or a sprayer. There are several desirable features of an inhalation device for administering at least one antibody of the present invention. For example, delivery by the inhalation device is

advantageously reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g., less than about 10 μm, preferably about 1-5 μm, for good respirability.

Administration of IL-23 Antibody Compositions as a Spray

[0146] A spray including IL-23 antibody composition can be produced by forcing a suspension or solution of at least one anti-IL-23 antibody through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one anti-IL-23 antibody composition delivered by a sprayer have a particle size less than about 10 μm, preferably, in the range of about 1 μm to about 5 μm, and, most preferably, about 2 μm to about 3 μm.

[0147] Formulations of at least one anti-IL-23 antibody composition suitable for use with a sprayer typically include antibody composition in an aqueous solution at a concentration of about 0.1 mg to about 100 mg of at least one anti-IL-23 antibody composition per ml of solution or mg/gm, or any range, value, or fraction therein. The formulation can include agents, such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include sucrose, mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the antibody composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein, such as IL-23 antibodies, or specified portions or variants, can also be included in the formulation.

Oral Formulations and Administration

[0148] Formulations for oral administration rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants, such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Formulations for delivery of hydrophilic agents including proteins and antibodies

and a combination of at least two surfactants intended for oral, buccal, mucosal, nasal, pulmonary, vaginal transmembrane, or rectal administration are taught in U.S. 6,309,663. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant, such as magnesium stearate, paraben, preserving agent, such as sorbic acid, ascorbic acid, alpha.-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

[0149] Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,5,871,753 and used to deliver biologically active agents orally are known in the art.

Mucosal Formulations and Administration

[0150] A formulation for orally administering a bioactive agent encapsulated in one or more biocompatible polymer or copolymer excipients, preferably, a biodegradable polymer or copolymer, affording microcapsules which due to the proper size of the resultant microcapsules results in the agent reaching and being taken up by the folliculi lymphatic aggregati, otherwise known as the "Peyer's patch," or "GALT" of the animal without loss of effectiveness due to the agent having passed through the gastrointestinal tract. Similar folliculi lymphatic aggregati can be found in the bronchei tubes (BALT) and the large intestine. The above-described tissues are referred to in general as mucosally associated lymphoreticular tissues (MALT). For absorption through mucosal surfaces, compositions and methods of administering at least one anti-IL-23 antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. No. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g., suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the

like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration, excipients include sugars, calcium stearate, magnesium stearate, pregelinatined starch, and the like (U.S. Pat. No. 5,849,695).

Transdermal Formulations and Administration

[0151] For transdermal administration, the at least one anti-IL-23 antibody is encapsulated in a delivery device, such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers, such as polyhydroxy acids, such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers, such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides, and combinations thereof (U.S. Pat. No. 5,814,599).

Prolonged Administration and Formulations

[0152] It can be desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid, such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation, such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b), e.g., a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt, such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g., sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulation in a slow degrading, non-toxic, non-antigenic polymer, such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts, such as those described above, can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant formulations, e.g., gas or liquid liposomes, are known in the literature (U.S. Pat. No. 5,770,222 and

"Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

Clinical Experience with Anti-IL-23 Agents

[0153] Several clinical trials using monoclonal antibodies against IL-23 have been conducted in multiple diseases including psoriasis, psoriatic arthritis and Crohn's disease.

[0154] The present invention also provides a method for modulating or treating at least one IL-23 mediated immune related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, asteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-meditated cytotoxicity, type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary billiary cirrhosis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity , contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular

organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic salicylate intoxication, sleep apnea, obesity, heart failure, sinusitis, inflammatory bowel disease, and the like. See, e.g., the Merck Manual, 12th-17th Editions, Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

[0155] The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV neuropathy, meningitis, hepatitis (A,B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis/epidydimitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis/aseptic meningitis, and the like;

[0156] Any of such methods can optionally comprise administering an effective amount of at least one composition or pharmaceutical composition comprising at least one anti-IL-23 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

[0157] Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-IL-23 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such immune diseases or malignant diseases, wherein the administering of said at least one anti-IL-23 antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an IL-18 antibody or

fragment, small molecule IL-18 antagonist or IL-18 receptor binding protein, an IL-1 antibody (including both IL-1 alpha and IL-1 beta) or fragment, a soluble IL-1 receptor antagonist, an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine, radiation therapy, an anti-angiogenic agent, a chemotherapeutic agent, Thalidomide,a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

[0158] The following examples illustrate the invention. These examples should not be construed as to limit the scope of this invention. The examples are included for purposes of illustration and the present invention is limited only by the claims.

Example 1: Clinical trials

[0159] A mega-analysis of Janssen and GlaxoSmithKline Immunology clinical trials (18 trials, 9 compounds, 7 targets) was conducted to assess antidepressant effects in patients with high depressive symptoms. Monoclonal antibodies against IL-6 (sirukumab and siltuximab) and IL-12/23 (ustekinumab) showed significant antidepressant effects relative to placebo. IL-12/23 effects remained significant after adjusting for improvement in the primary disease in the study. See Figures 1 and 2 that show depressive symptom score, including adjusted for disease symptom severity.

[0160] **Study Data**: PSO3002: A phase 3, randomized, placebo- and active comparator- (with TNF-α inhibitor adalimumab) controlled study evaluating the efficacy and safety of guselkumab in patients with moderate to severe plaque psoriasis.

[0161] **Subjects:** 990 of 992 randomized subjects were treated with guselkumab, adalimumab, or placebo. Seventy patients receiving conventional antidepressant agents and 3 patients having missing data on HDS were excluded.

[0162] **Assessment Instruments and Response Criteria:**

PASI: Psoriasis Area and Severity Index

PASI90: Subjects with ≥ 90% improvement in PASI score relative to baseline

Non-responders: Subjects who did not achieve PASI90 response up to week 16 (LOCF).

HDS: Hospital Anxiety and Depression Scale-Depression Score

Baseline HDS≥11: "High Depressive Symptom Cohort"
8 ≤ Baseline HDS < 11: "Borderline to Mild Depressive Symptoms"

Statistical Model: The trajectory of the HDS over time for each treatment arm was estimated using a mixed model for repeated measures (MMRM) approach without and with adjustment for psoriasis disease severity. Treatment, visit (weeks 0/8/16), and treatment*visit interaction were included in the models as fixed effects. Geographically pooled site was included as a covariate. In models adjusted for disease severity, the total PASI score, PASI75 response (with or without ≥75% improvement in the PASI), total PASI score*visit interaction, and total PASI score*PASI75 response were included as additional covariates.

[0163] **Efficacy on Depressive Symptoms:**

[0164] Changes from baseline in least square mean estimates of HDS between the guselkumab and placebo groups were compared at Weeks 8 and 16. Analyses were repeated for psoriasis non-responders, as defined by failure to achieve PASI90 up to week 16 (LOCF). Figure 5 shows the demographics and baseline characteristics of patients. Depression (HDS) scores were significantly higher for patients with greater severity of psoriasis.

[0165] 12.1% (111) of patients had an HDS≥11 at baseline, consistent with prevalence estimates for clinical depression in psoriasis (12.1%). As shown in Figure 3, guselkumab significantly improved depressive symptoms in subjects with high depressive symptoms at baseline compared with placebo at weeks 8 and 16. Similar result was observed for adalimumab at week 16 but not at week 8. Guselkumab

also improved psoriasis over this same time period. Thus, improvement in depressive symptoms may be the indirect result of improvement in psoriasis.

[0166] To test for improvement in depressive symptoms beyond what is due to psoriasis improvement, the study team (i) statistically adjusted the Depression Total Score for disease severity, and (ii) analyzed mood improvements among psoriasis non-responders. Adjusting for psoriasis disease severity, as shown in Figures 4A and 4B, the week 16 effect of guselkumab on depressive symptoms remained significant. Among patients designated as plaque psoriasis non-responders, both the week 8 and week 16 effects remained significant.

[0167] **Key Findings:** Guselkumab treatment is associated with improvements in depressive symptoms in plaque psoriasis patients with moderate-to-severe depressive symptoms, even after adjustment for psoriasis improvements. Notably, IL-23 has been shown to play a major role in mediating neuroinflammation in preclinical models.

[0168] **Limitations:** The PSO3002 trial was not designed or powered for this post-hoc analysis. Further it may not be possible to fully dissociate mood and psoriasis symptoms.

[0169] **Main implications:** These results support further exploration of the role of IL-23 in depression. Further, IL-23 inhibition may be effective for major depressive disorder patients with immune dysregulation.

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<213> Homo sapiens

<400> 62
Gln Gln Thr Ser Asn Thr Pro Phe Thr
1 5

<210> 63
<211> 9
<212> PRT
<213> Homo sapiens

<400> 63
Gln Gln Phe Ile Thr Tyr Leu Pro Thr
1 5

<210> 64
<211> 9
<212> PRT
<213> Homo sapiens

<400> 64
Gln Gln Asp Ala Leu Ser Pro Phe Thr
1 5

<210> 65
<211> 9
<212> PRT
<213> Homo sapiens

<400> 65
Gln Gln Asp Arg Gly Thr Pro Phe Thr
1 5

<210> 66
<211> 9
<212> PRT
<213> Homo sapiens

<400> 66
Gln Gln Ser Leu Asn Ile Pro Phe Thr
1 5

<210> 67
<211> 9
<212> PRT
<213> Homo sapiens

<400> 67
Gln Gln Asp Thr Ser Ser Pro Phe Thr
1 5

<210> 68
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized human sequence

<220>
<221> unsure
<222> (3)
<223> Where Xaa can be T, F, D, or S

<220>
<221> unsure
<222> (4)
<223> Where Xaa can be S, I, A, T, R, or L

<220>
<221> unsure
<222> (5)
<223> Where Xaa can be N, T, L, S, or G

<220>
<221> unsure
<222> (6)
<223> Where Xaa can be T, Y, S, or I

<220>
<221> unsure
<222> (7)
<223> Where Xaa can be P or L

<220>
<221> unsure

<222> (8)
<223> Where Xaa can be F or P

<400> 68
Gln Gln Xaa Xaa Xaa Xaa Xaa Xaa Phe Thr
1 5 10

<210> 69
<211> 11
<212> PRT
<213> Homo sapiens

<400> 69
Gln Thr Tyr Ala Ser Leu Gly Pro Gly Glu Val
1 5 10

<210> 70
<211> 9
<212> PRT
<213> Homo sapiens

<400> 70
Gln Gln Tyr Ser Ser Glu Pro Val Thr
1 5

<210> 71
<211> 9
<212> PRT
<213> Homo sapiens

<400> 71
Ser Ser Trp Thr Pro Ser Ser Val Val
1 5

<210> 72
<211> 11
<212> PRT
<213> Homo sapiens

<400> 72
Ser Ser Trp Thr Asp Thr Pro Asn Met Ile Val
1 5 10

<210> 73
<211> 11
<212> PRT
<213> Homo sapiens

<400> 73

Ala Ser Trp Thr Asp Gly Leu Ser Leu Val Val
1 5 10

<210> 74
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized human sequence

<220>
<221> unsure
<222> (1)
<223> Where Xaa can be S or A

<220>
<221> unsure
<222> (6)
<223> Where Xaa can be T or G

<220>
<221> unsure
<222> (7)
<223> Where Xaa can be P or L

<220>
<221> unsure
<222> (8)
<223> Where Xaa can be S or N

<220>
<221> unsure
<222> (9)
<223> Where Xaa can be S, M, or L

<220>
<221> unsure
<222> (10)
<223> Where Xaa can be I or V

<400> 74
Xaa Ser Trp Thr Asp Xaa Xaa Xaa Xaa Xaa Val
1 5 10

<210> 75
<211> 11
<212> PRT
<213> Homo sapiens

<400> 75
Ser Ser Tyr Asp Thr Asn Lys Pro Leu Val Val
1 5 10

<210> 76
<211> 11
<212> PRT
<213> Homo sapiens

<400> 76
Gly Ser Tyr Asp Val Tyr Gly Arg Phe Tyr Val
1 5 10

<210> 77
<211> 11
<212> PRT
<213> Homo sapiens

<400> 77
Ser Ser Tyr Tyr Phe Tyr Leu Gln Arg Ile Val
1 5 10

<210> 78
<211> 11
<212> PRT
<213> Homo sapiens

<400> 78
Gln Thr Tyr Tyr Phe Ser Tyr Ser Gly Pro Val
1 5 10

<210> 79
<211> 11
<212> PRT
<213> Homo sapiens

<400> 79
Gly Ser Trp Asp Pro Ile Phe Ser Tyr Glu Val
1 5 10

<210> 80
<211> 117
<212> PRT
<213> Homo sapiens

<400> 80
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Met Phe Gly Tyr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Ile Tyr Ala Gly Met Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 81
<211> 117
<212> PRT
<213> Homo sapiens

<400> 81
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Val Phe Gly Phe Thr His Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Ile Tyr Ala Gly Met Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 82
<211> 108
<212> PRT
<213> Homo sapiens

<400> 82
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Gly Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Gly Ser Ile Ser
85 90 95
Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 83
<211> 108
<212> PRT

<213> Homo sapiens

<400> 83
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Gly Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser His Ile Ser
85 90 95
Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 84
<211> 108
<212> PRT
<213> Homo sapiens

<400> 84
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Gly Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser His Leu Ile
85 90 95
Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 85
<211> 108
<212> PRT
<213> Homo sapiens

<400> 85
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Gly Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

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Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Ala His Ile Leu
                85                  90                  95
Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 86
<211> 127
<212> PRT
<213> Homo sapiens

<400> 86

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
            20                  25                  30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Gly Ile Ile Pro Ile Phe Gly His Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
            100                 105                 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
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<210> 87
<211> 127
<212> PRT
<213> Homo sapiens

<400> 87

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
            20                  25                  30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Ile Pro Pro Ile Gly Asn Ala Trp Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
            100                 105                 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
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<210> 88
<211> 127
<212> PRT

<213> Homo sapiens

<400> 88
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ser Pro Gly Thr Gly Ile Asn Ala Tyr Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
100 105 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 89
<211> 126
<212> PRT
<213> Homo sapiens

<400> 89
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Asn Ala His Leu Gly Gly Thr Trp Tyr Ala Gln Lys Phe Gln
50 55 60
Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met
65 70 75 80
Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met Met
100 105 110
Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 90
<211> 127
<212> PRT
<213> Homo sapiens

<400> 90
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile Asp Pro Asn Phe Gly Gly Ala Tyr Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
100 105 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 91
<211> 127
<212> PRT
<213> Homo sapiens

<400> 91
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Leu Ile Asp Pro Val Phe Gly Gly Ala Tyr Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
100 105 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 92
<211> 127
<212> PRT
<213> Homo sapiens

<400> 92
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Leu Ile Asp Pro Met Phe Gly Gly Ala Tyr Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Lys Lys Gly Met Tyr Gly Gly Trp Thr Tyr Pro Leu Met
100 105 110
Met Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 93
<211> 108
<212> PRT
<213> Homo sapiens

<400> 93
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Ser Asn Thr Pro
85 90 95
Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 94
<211> 108
<212> PRT
<213> Homo sapiens

<400> 94

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Ser Asn Thr Pro
85 90 95
Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 95
<211> 108
<212> PRT
<213> Homo sapiens

<400> 95
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Ile Thr Tyr Leu
85 90 95
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 96
<211> 108
<212> PRT
<213> Homo sapiens

<400> 96
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Ala Leu Ser Pro
85 90 95

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

<210> 97
<211> 108
<212> PRT
<213> Homo sapiens

<400> 97
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Arg Gly Thr Pro
85 90 95
Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 98
<211> 108
<212> PRT
<213> Homo sapiens

<400> 98
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Tyr Ala Ser Arg Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Leu Asn Ile Pro
85 90 95
Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 99
<211> 116
<212> PRT
<213> Homo sapiens

<400> 99
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30
Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Arg Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Glu Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg His Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 100
<211> 110
<212> PRT
<213> Homo sapiens

<400> 100
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
20 25 30

Tyr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Gly Asn Thr His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Ala Ser Leu Gly
85 90 95
Pro Gly Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 101
<211> 121
<212> PRT
<213> Homo sapiens

<400> 101
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 Thr Phe Ser Ser Tyr
20 25 30
Trp Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Phe Trp Ser Phe Gly Asn Tyr Phe Ala Asn Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 102
<211> 107
<212> PRT
<213> Homo sapiens

<400> 102
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Phe Tyr Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Glu Pro Val
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 103
<211> 117
<212> PRT
<213> Homo sapiens

<400> 103
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 104
<211> 117
<212> PRT
<213> Homo sapiens

<400> 104
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Asp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 105
<211> 117
<212> PRT
<213> Homo sapiens

<400> 105
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

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 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser
        115
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<210> 106
<211> 117
<212> PRT
<213> Homo sapiens

<400> 106

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser
        115
```

<210> 107
<211> 117
<212> PRT
<213> Homo sapiens

<400> 107

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asp Pro Val Ser Ser Trp Thr Lys Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 108
<211> 117
<212> PRT
<213> Homo sapiens

<400> 108
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ser Pro Ser Gly Ser Thr Thr Trp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 109
<211> 117
<212> PRT
<213> Homo sapiens

<400> 109
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Phe Ile Ser Pro Asp Gly Ser His Thr Trp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 110

<211> 117
<212> PRT
<213> Homo sapiens

<400> 110
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ser Pro Thr Gly Ser Val Thr Trp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 111
<211> 117
<212> PRT
<213> Homo sapiens

<400> 111
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ser Pro Thr Gly Ser Ser Thr Trp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 112
<211> 117
<212> PRT
<213> Homo sapiens

<400> 112
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ser Pro Thr Gly Ser Ala Thr Trp Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser
115

<210> 113
<211> 109
<212> PRT
<213> Homo sapiens

<400> 113
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Thr Pro Ser
85 90 95
Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 114
<211> 111
<212> PRT
<213> Homo sapiens

<400> 114
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Thr Asp Thr
85 90 95
Pro Asn Met Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 115
<211> 111
<212> PRT
<213> Homo sapiens

<400> 115
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Thr Asp Gly
85 90 95
Leu Ser Leu Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 116
<211> 111
<212> PRT
<213> Homo sapiens

<400> 116

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
20 25 30
Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80
Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Thr Asp Gly
85 90 95
Leu Ser Leu Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 117
<211> 121
<212> PRT
<213> Homo sapiens

<400> 117
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 Thr Phe Ser Ser Phe
20 25 30

```
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Asn Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 118
<211> 123
<212> PRT
<213> Homo sapiens

<400> 118

```
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 Thr Phe Ser Ser Phe
            20                  25                  30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Asn Ile Glu His Lys Phe Met Gly Tyr Thr Thr Tyr Tyr Ala Ala
    50                  55                  60
Gly Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
            100                 105                 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 119
<211> 123
<212> PRT
<213> Homo sapiens

<400> 119

```
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 Thr Phe Ser Ser Phe
            20                  25                  30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ser Ile Glu His Lys Tyr Thr Gly Tyr Thr Thr Tyr Tyr Ala Ala
    50                  55                  60
Pro Val 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
```

Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 120
<211> 123
<212> PRT
<213> Homo sapiens

<400> 120
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Asn Ile Glu His Lys Tyr Thr Ser Tyr Thr Thr Tyr Tyr Ala Ala
50 55 60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 121
<211> 123
<212> PRT
<213> Homo sapiens

<400> 121
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Asn Ile Glu His Lys Tyr Leu Asn Tyr Ala Thr Tyr Tyr Ala Ala
50 55 60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 122
<211> 123
<212> PRT

<213> Homo sapiens

<400> 122
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Asn Ile Glu His Lys Tyr Leu Gly Tyr Ala Thr Val Tyr Ala Ala
50 55 60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 123
<211> 123
<212> PRT
<213> Homo sapiens

<400> 123
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Glu His Lys Tyr Leu Ser Tyr Ala Thr Tyr Tyr Ala Ala
50 55 60
Gly Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 124
<211> 123
<212> PRT
<213> Homo sapiens

<400> 124
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu His Lys Tyr Leu Ser Tyr Thr Thr Phe Tyr Ala Ala
50 55 60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 125
<211> 123
<212> PRT
<213> Homo sapiens

<400> 125
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Glu His Lys Tyr Leu Ser Tyr Thr Thr His Tyr Ala Ala
50 55 60
Ser Val 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

Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 126
<211> 123
<212> PRT
<213> Homo sapiens

<400> 126
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 Thr Phe Ser Ser Phe
20 25 30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Glu His Lys Tyr Leu Ser Tyr Thr Thr Leu Tyr Ala Ala
50 55 60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
100 105 110

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


<210> 127
<211> 123
<212> PRT
<213> Homo sapiens

<400> 127
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 Thr Phe Ser Ser Phe
            20                  25                  30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Glu His Lys Tyr Leu Ser Tyr Ala Thr Leu Tyr Ala Ala
    50                  55                  60
Ser Val 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
Tyr Cys Ala Arg Tyr Trp Gly Thr Pro Tyr Leu Met Gln Phe Asp Asn
            100                 105                 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 128
<211> 111
<212> PRT
<213> Homo sapiens

<400> 128
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Thr Asn
                85                  90                  95
Lys Pro Leu Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> 129
<211> 111
<212> PRT
<213> Homo sapiens

<400> 129
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
```

```
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Tyr Phe Tyr
                85                  90                  95
Leu Gln Arg Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 130
<211> 111
<212> PRT
<213> Homo sapiens

<400> 130

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Tyr Phe Ser
                85                  90                  95
Tyr Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 131
<211> 111
<212> PRT
<213> Homo sapiens

<400> 131

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Asp Val Tyr
                85                  90                  95
Gly Arg Phe Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 132
<211> 111
<212> PRT
<213> Homo sapiens

<400> 132
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Pro Ile
85 90 95
Phe Ser Tyr Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 133
<211> 381
<212> DNA
<213> Homo sapiens

<400> 133
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agcaactaca tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatggggatc agccctggca ccggtatcaa cgcatactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagcaag 300
aagggcatgt acggcggctg gacctacccc ctgatgatgt tcgacctgtg gggccagggc 360
accctggtga ccgtgagcag c 381

<210> 134
<211> 381
<212> DNA
<213> Homo sapiens

<400> 134
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcagcag cgtgaaggtg 60
agctgcaagg ccagcggcgg caccttcagc agcaactaca tcagctgggt gcgccaggcc 120
cccggccagg gcctggagtg gatgggcatc agccccggca ccggcatcaa cgcctactac 180
gcccagaagt tccagggccg cgtgaccatc accgccgacg agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc ccgcagcaag 300
aagggcatgt acggcggctg gacctacccc ctgatgatgt tcgacctgtg gggccagggc 360
accctggtga ccgtgagcag c 381

<210> 135
<211> 381
<212> DNA
<213> Homo sapiens

<400> 135
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60
agctgcaaag cctccggagg cacttttttct tctaattata tttcttgggt gcgccaagcc 120
cctgggcagg gtctcgagtg gatgggcatt tctcctggta ctggtattaa tgcttattat 180
gctcagaagt ttcagggtcg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgttctaag 300
aagggtatgt atggtggttg gacttatcct cttatgatgt ttgatctttg gggccaaggc 360
accctggtga cggttagctc a 381

<210> 136
<211> 324
<212> DNA
<213> Homo sapiens

<400> 136
gagatcgtgc tgacccagag ccccgccacc ctgagcctga gccccggcga gcgcgccacc 60
ctgagctgcc gcgccagcca gagcgtgagc agcaactacc tggcctggta ccagcagaag 120
cccggccagg ccccccgcct gctgatctac tacgccagcc gccgcgccac cggcgtgccc 180
gcccgcttca gcggcagcgg cagcggcacc gacttcaccc tgaccatcag cagcctggag 240
cccgaggact tcgccgtgta ctactgccag cagaccagca acacccccct caccttcggc 300
cagggcacca aggtggagat caag 324

<210> 137
<211> 324
<212> DNA
<213> Homo sapiens

<400> 137
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaactact tagcctggta ccaacagaaa 120
cctggccagg ctcccaggct cctcatctat tacgcatccc gcagggccac tggcgtgcca 180
gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctagag 240
cctgaagatt ttgcagttta ttactgtcag cagacttcta atactccttt tacctttggc 300
cagggtacga aagttgaaat taaa 324

<210> 138
<211> 324
<212> DNA
<213> Homo sapiens

<400> 138
gagatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagcca gtctgtttct tctaattatc tggcttggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatttat tatgcttctc gtcgtgcaac tggggtcccg 180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcggtgta ttattgccag cagacttcta atactccttt tacctttggc 300
cagggtacga aagttgaaat taaa 324

<210> 139
<211> 351
<212> DNA
<213> Homo sapiens

<400> 139
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttagc aactactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atcgacccta gcaactctta caccagatac 180

agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagatggtac 300
tacaagccct tcgacgtgtg gggccagggc accctggtga ccgtgagcag c 351

<210> 140
<211> 351
<212> DNA
<213> Homo sapiens

<400> 140
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60
agctgcaagg gcagcggcta cagcttcagc aactactgga tcggctgggt gcgccagatg 120
cccggcaagg gcctggagtg gatgggcatc atcgacccca gcaacagcta cacccgctac 180
agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccgctggtac 300
tacaagccct tcgacgtgtg gggccagggc accctggtga ccgtgagcag c 351

<210> 141
<211> 351
<212> DNA
<213> Homo sapiens

<400> 141
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttccttttct aattattgga ttggttgggt gcgccagatg 120
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Pro Leu Val Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr
    50   55   60
Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln
65   70   75   80
Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly
                85   90   95

Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu
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Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
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145   150   155   160
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Claims

1. A method for treating depression, anhedonia, or fatigue in a subject comprising administering to the subject an effective amount of a pharmaceutical composition comprising an agent that blocks binding of IL-23 to IL-23 receptor.

2. The method of claim 1, wherein the subject has depressed mood, anhedonia, or fatigue.

3. The method of claim 1, wherein the subject has psoriasis.

4. The method of claim 1, wherein the agent that blocks binding of IL-23 to IL-23 receptor comprises an isolated antibody or an antigen-binding fragment thereof.

5. The method according to claim 4, wherein the isolated antibody or an antigen-binding fragment thereof comprises the following complementarity determining regions (CDRs):
i) CDRH1 having the amino acid sequence of SEQ ID NO: 5; and
ii) CDRH2 having the amino acid sequence of SEQ ID NO: 20; and
iii) CDRH3 having the amino acid sequence of SEQ ID NO: 44; and
iv) CDRL1 having the amino acid sequence of SEQ ID NO: 50; and
v) CDRL2 having the amino acid sequence of SEQ ID NO: 56; and
vi) CDRL3 having the amino acid sequence of SEQ ID NO: 73.

6. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region having the amino acid sequences of SEQ ID NO: 106 and SEQ ID NO: 116, respectively.

7. The method of claim 6, wherein the isolated antibody or an antigen-binding fragment thereof is in a pharmaceutical composition at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition, wherein the diluent is water at standard state.

8. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof is administered at a dose of 25-100mg every 2-8 weeks.

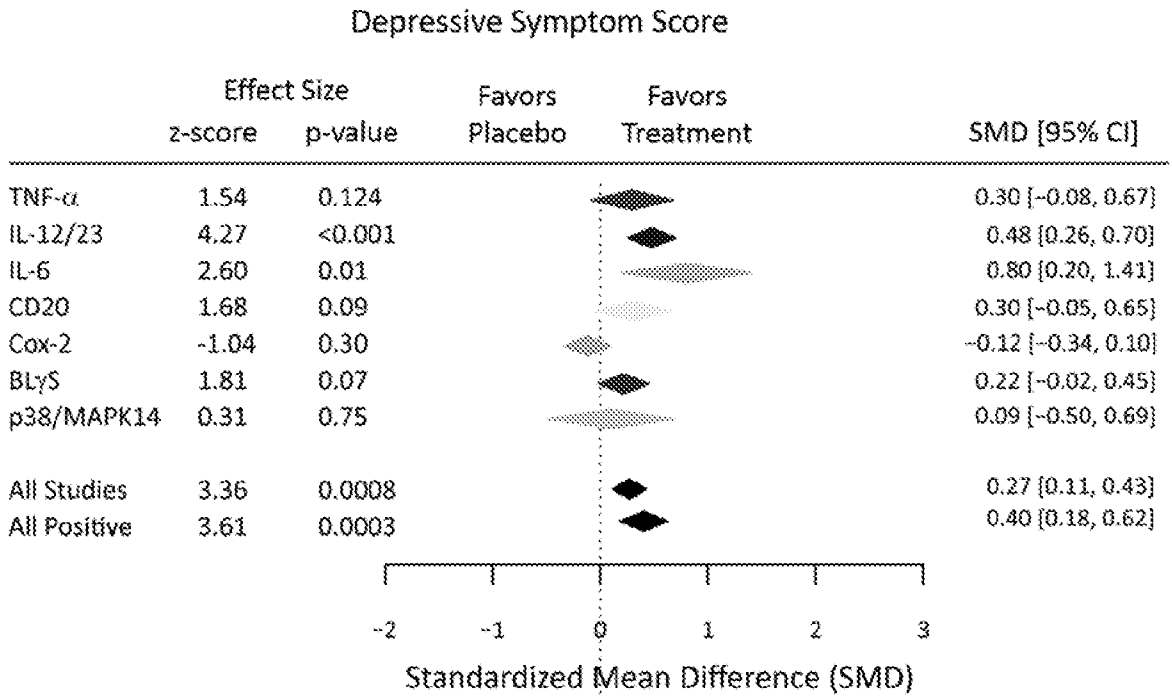
9. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof is administered at a dose selected from the group comprising 100 mg every 2 weeks, 25 mg every 4 weeks, 50 mg every 4 weeks, 100 mg every 4 weeks, 25 mg every 8 weeks, 50 mg every 8 weeks and 100 mg every 8 weeks.

10. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof is administered at a dose of 11mg/kg every 3 weeks.

11. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof is administered subcutaneously.

12. The method of claim 4, wherein the isolated antibody or an antigen-binding fragment thereof is administered intravenously.

Figure 1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Effect Size
z-score
p-value
Favors Placebo
Favors Treatment
SMD [95% CI]
TNF-α 1.54 0.124 0.30 [-0.08, 0.67]
IL-12/23 4.27 <0.001 0.48 [0.26, 0.70]
IL-6 2.60 0.01 0.80 [0.20, 1.41]
CD20 1.68 0.09 0.30 [-0.05, 0.65]
Cox-2 -1.04 0.30 -0.12 [-0.34, 0.10]
BLyS 1.81 0.07 0.22 [-0.02, 0.45]
p38/MAPK14 0.31 0.75 0.09 [-0.50, 0.69]
All Studies 3.36 0.0008 0.27 [0.11, 0.43]
All Positive 3.61 0.0003 0.40 [0.18, 0.62]
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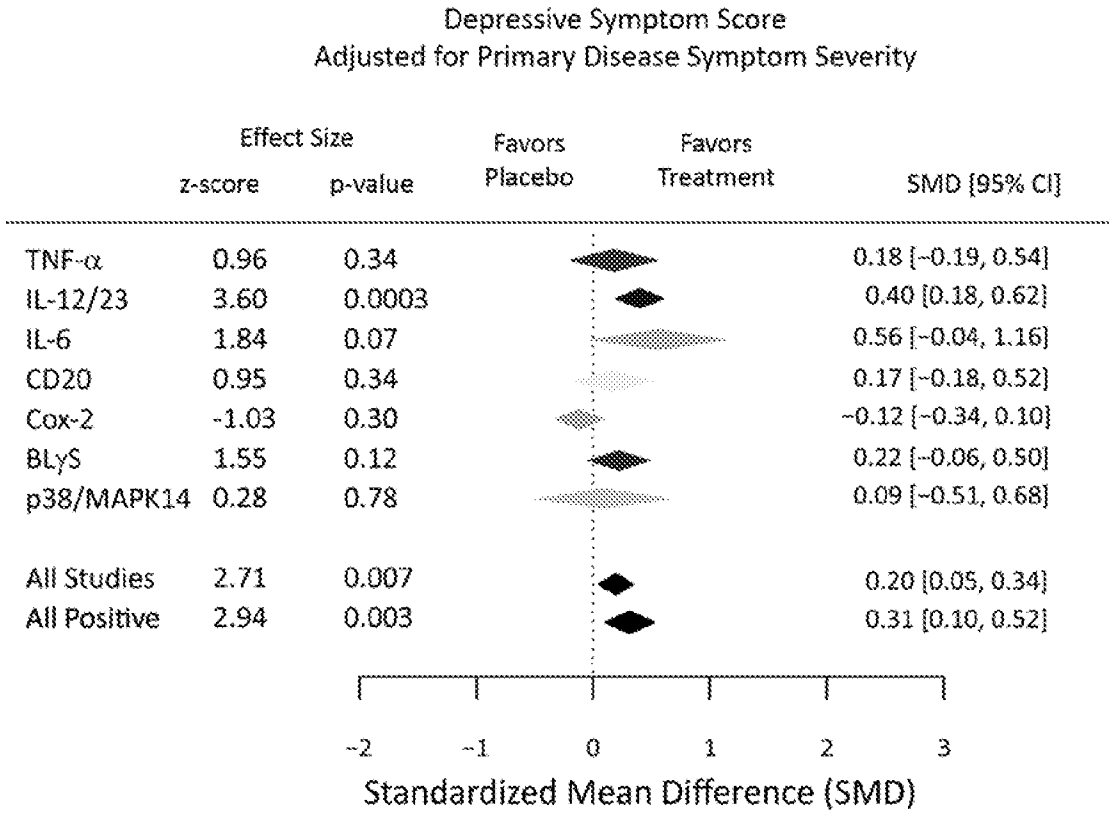
2
3
Standardized Mean Difference (SMD)

Figure 2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Adjusted for Primary Disease Symptom Severity
Effect Size
z-score
p-value
Favors Placebo
Favors Treatment
SMD [95% CI]
TNF-α 0.96 0.34 0.18 [-0.19, 0.54]
IL-12/23 3.60 0.0003 0.40 [0.18, 0.62]
IL-6 1.84 0.07 0.56 [-0.04, 1.16]
CD20 0.95 0.34 0.17 [-0.18, 0.52]
Cox-2 -1.03 0.30 -0.12 [-0.34, 0.10]
BLyS 1.55 0.12 0.22 [-0.06, 0.50]
p38/MAPK14 0.28 0.78 0.09 [-0.51, 0.68]
All Studies 2.71 0.007 0.20 [0.05, 0.34]
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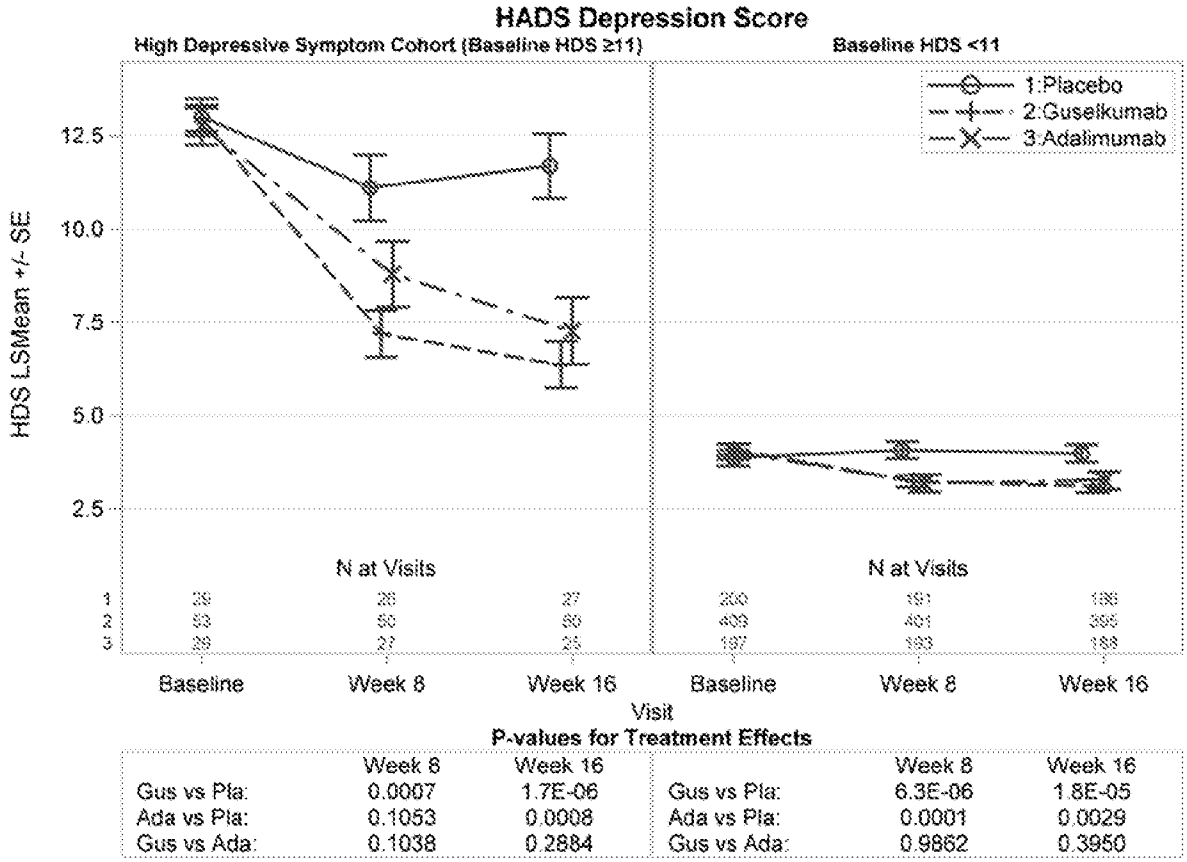
Standardized Mean Difference (SMD)

Figure 3

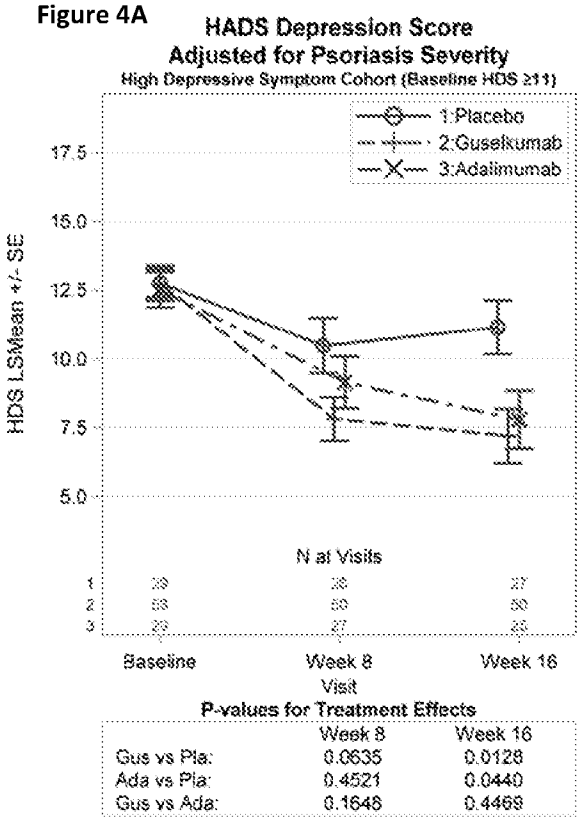


P-values for Treatment Effects

	Week 8	Week 16		Week 8	Week 16
Gus vs Pla:	0.0007	1.7E-06	Gus vs Pla:	6.3E-06	1.8E-05
Ada vs Pla:	0.1053	0.0008	Ada vs Pla:	0.0001	0.0029
Gus vs Ada:	0.1038	0.2884	Gus vs Ada:	0.9862	0.3950

Figures 4A and 4B

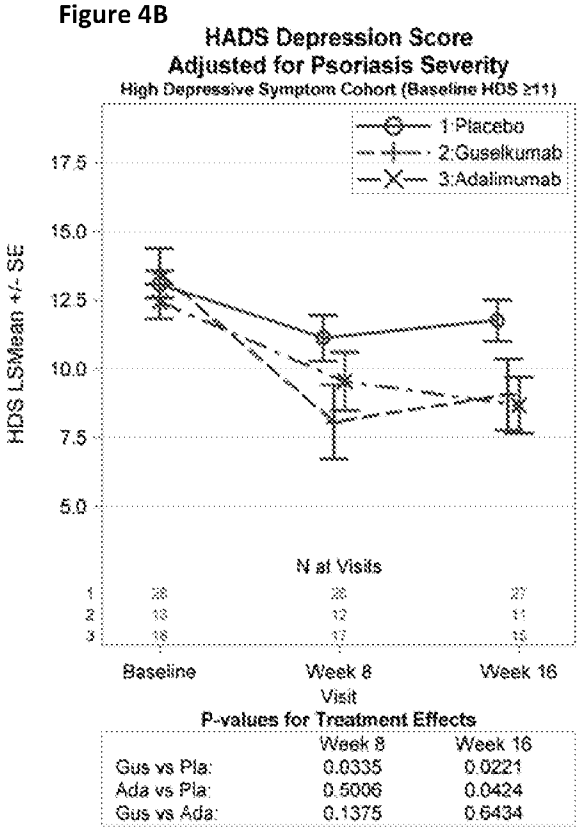
Figure 4A



P-values for Treatment Effects

	Week 8	Week 16
Gus vs Pla:	0.0635	0.0128
Ada vs Pla:	0.4521	0.0440
Gus vs Ada:	0.1648	0.4469

Figure 4B



P-values for Treatment Effects

	Week 8	Week 16
Gus vs Pla:	0.0335	0.0221
Ada vs Pla:	0.5006	0.0424
Gus vs Ada:	0.1375	0.6434

Figure 5

	HDS ≥ 11 (N=111)	8 ≤ HDS < 11 (N=133)	HDS < 8 (N=673)	p-value
Age, Years	42.4 (10.8)	44 (10.9)	43.4 (12.7)	0.54
Male Sex	70 (63.1%)	92 (69.2%)	489 (72.7%)	0.1
Race Asian	23 (20.7%)	23 (17.3%)	86 (12.8%)	0.23
Black or AA		3 (2.3%)	13 (1.9%)	
White	86 (77.5%)	105 (78.9%)	560 (83.2%)	
Other	2 (1.8%)	2 (1.5%)	14 (2.1%)	
BMI, kg/m^2	29.6 (6.2)	30.3 (6.9)	29.3 (6.3)[1]	0.08
PASI Total Score	24.7 (10.6)	22.3 (8.5)	21.3 (8.2)	**0.0029**
CRP, mg/L	6 (8.6)[2]	6.1 (11.9)[3]	6 (16.5)[4]	0.23

Mean (SD) is shown for Age, BMI, PASI Total Score, CRP, and P-values are from Kruskal-Wallis test.
N (%) is shown for Sex, Race, P-values are from chi-square tests.
AA: African American. [1]N=672; [2]N=109; [3]N=131; [4]N=662.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/053892

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395; A61P 25/00; A61P 37/00; C07K 16/24; C12N 15/13 (2019.01)
CPC - A61K 2039/505; C07K 16/244; C07K 2317/56; C07K 2317/76 (2019.08)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/133.1; 424/145.1; 424/158.1; 530/388.23 (keyword delimited)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2011/0287028 A1 (BENSON et al) 24 November 2011 (24.11.2011) entire document	1-6, 8-12 ---------- 7
Y	US 2018/0094052 A1 (JANSSEN BIOTECH, INC.) 05 April 2018 (05.04.2018) entire document	7
P, X	GORDON et al. "Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study," Eur Acad Dermatol Venereol, 18 July 2018 (18.07.2018), Vol. 32, Pgs. 1940-1949. entire document	1-12
A	US 2017/0291942 A1 (JANSSEN BIOTECH, INC.) 12 October 2017 (12.10.2017) entire document	1-12
A	US 2015/0147337 A1 (MERCK SHARP & DOHME CORP.) 28 May 2015 (28.05.2015) entire document	1-12
A	WO 2017/189959 A1 (VOYAGER THERAPEUTICS, INC.) 02 November 2017 (02.11.2017) entire document	1-12

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2019	21 OCT 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774