Anti-IL-23 Antibodies

Technical Field of the Invention

This invention generally relates to anti-IL-23p19 antibodies for diagnostic and therapeutic use. More specifically, humanized anti-IL-23p19 antibodies and methods of use for the treatment of various diseases or disorders are disclosed. Pharmaceutical compositions and kits comprising such compounds are also disclosed.

Background of the Invention

Higher eukaryotes have evolved an intricate response to pathogens that is initiated by the innate immune response and followed by the adaptive immune response. Together these two mechanisms not only eradicate pathogens that infect the organism but also establish a long term immunological response against future exposures. Deficiencies in these responses can result in increased susceptibility to infections and/or alterations of the adaptive immune response leading to chronic inflammation and autoimmunity. IL-12, a heterodimeric cytokine consisting of a p40 and a p35 protein subunit, has long been considered the hallmark cytokine of the innate immune response with major influence on adaptive immunity. However, data from investigation of this cytokine's biological role led to confusing results. For example, while p40-deficient mice were resistant to Collagen Induced Arthritis (CIA) and Experimental Autoimmune Encephalomyelitis (EAE), p35-deficient mice were susceptible to both and even displayed exacerbated disease. Such conundrums began to be resolved with the discovery in the late 1990's of a new member of the IL-12 cytokine family with a distinct role in the immune response – IL-23.

IL-23 is composed of a common subunit (p40) with IL-12 and a unique p19 subunit. Despite this shared p40 subunit, the roles for IL-23 and IL-12 are quite different. IL-12 is important for Th1 responses via promotion of Th1 cell differentiation, proliferation and activation. In contrast, IL-23 supports the development and maintenance of a recently defined set of $CD4^+$ T helper cells termed Th17 cells due to their ability to produce IL-17 and related cytokines. There is mounting evidence that IL-23 is involved

in chronic autoimmune inflammation and the modulation of IL-23 activity could provide promising therapies against autoimmune diseases.

There is therefore a need for antagonist molecules against IL-23 with beneficial pharmacological properties, which can be used as therapeutic agents to treat diseases, in particular immunological and autoimmune diseases in humans.

Accordingly, one aim of the present invention is to provide anti-IL-23 antagonist molecules, in particular anti-IL-23 antagonist molecules which have high binding affinity to IL-23.

A further aim of the present invention is to provide anti-IL-23 antagonist molecules, which have high specificity for IL-23.

A further aim of the present invention is to provide anti-IL-23 antagonists, which have high blocking activity for the association of IL-23 and its receptor.

A further aim of the present invention is to provide anti-IL-23 antagonists, which have potent cellular activity.

A further aim of the present invention is to provide anti-IL-23 antagonists, which have a favorable bioavailability.

A further aim of the present invention is to provide anti-IL-23 antagonists, which have favorable biophysical properties.

Further aims of the present invention include combinations of any of the aims set forth above.

Summary of the Invention

The present invention addresses the above needs and provides antibodies that bind to the p19 subunit of the IL-23 protein. In one aspect, an antibody of the present invention binds to human IL-23 with high affinity. In another aspect, an antibody of the present invention inhibits the IL-23 stimulated production of IL-17 from mouse splenocytes. In another aspect, an antibody of the present invention does not bind to nor antagonize IL-12, which is a closely related family member to IL-23.

In one embodiment, the present invention provides anti-IL-23p19 antibodies that are derived from mouse hybridomas, for example monoclonal antibodies. In one embodiment, the present invention provides full length anti-IL-23p19 antibodies. In

another embodiment, the present invention provides anti-IL-23p19 humanized antibodies, for example humanized monoclonal anti-IL-23p19 antibodies, for example full length humanized monoclonal anti-IL-23p19 antibodies. In one aspect, a humanized antibody of the present invention binds to human IL-23 with high affinity. In another aspect, a humanized antibody of the present invention also binds to cynomolgus IL-23 with high affinity. In a further aspect, a humanized antibody of the present invention inhibits IL-23-induced STAT3 phosphorylation in DB cells. In another aspect, a humanized antibody of the present invention antagonizes the action of IL-23 by binding to the p19 subunit of IL-23, for example as measured by the inhibition of cytokines such as IL-17 and IL-22, whose production is stimulated by IL-23. In a further aspect, a humanized antibody of the present invention has a favorable pharmacokinetic (PK) profile. In a further aspect, a humanized antibody of the present invention has favorable biophysical properties, such as quality, stability or solubility, for example as defined by the percentage of antibody in monomer form.

Further embodiments encompass DNA molecules encoding antibodies of the present invention, expression vectors and host cells comprising such DNA molecules, and methods of making antibodies of the present invention. The present invention further provides therapeutic uses for the antibodies of the present invention, in particular against immunological and autoimmune diseases.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a light chain CDR1 (L-CDR1) sequence of SEQ ID NO:1, 4, 6, 7, 8, 11, 15, 18, 19, 22, 27 or 30; a light chain CDR2 (L-CDR2) sequence of SEQ ID NO:2, 5, 9, 12, 16, 20, 23, 25, 28 or 31; a light chain CDR3 (L-CDR3) sequence of SEQ ID NO:3, 10, 13, 14, 17, 21, 24, 26, 29, or 32; a heavy chain CDR1 (H-CDR1) sequence of SEQ ID NO:33, 36, 38, 40, 43, 45, 48, 51, 54, 57, 60, 63, 66, 67, 68, 69, 77 or 80; a heavy chain CDR2 (H-CDR2) sequence of SEQ ID NO:34, 39, 41, 46, 49, 52, 55, 58, 61, 64, 70, 72, 73, 75, 78 or 81; and a heavy chain CDR3 (H-CDR3) sequence of SEQ ID NO:35, 37, 42, 44, 47, 50, 53, 56, 59, 62, 65, 71, 74, 76, 79 or 82. In one embodiment, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises a light chain variable region comprising a

L-CDR1 listed above, a L-CDR2 listed above and a L-CDR3 listed above, and a heavy chain variable region comprising a H-CDR1 listed above, a H-CDR2 listed above and a H-CDR3 listed above.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 33, 34, and 35, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:4, 5, 3, 36, 34 and 37, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 38, 39 and 35, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:6, 2, 3, 40, 41 and 42, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 3, 43, 41 and 44, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 46 and 47, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 48, 49 and 50, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:11, 12, 13, 51, 52 and 53, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 14, 54, 55 and 56, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:15, 16, 17, 57, 58 and 59, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:18, 16, 17, 60, 61 and 62, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:19, 20, 21, 63, 66, 67 or 68, 64 and 65, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 23, 24, 69, 70 and 71, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 25, 26, 55, 72 and 71, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 73 and 74, respectively; or a L-

CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:27, 28, 29, 45, 75 and 76, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 77, 78 and 79, respectively; or a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:30, 31, 32, 80, 81 and 82, respectively. In one embodiment, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises a light chain variable region comprising a L-CDR1, L-CDR2 and L-CDR3 combination listed above, and a heavy chain variable region comprising a H-CDR1, H-CDR2 and H-CDR3 combination listed above.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:84 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:121; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:86 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:123; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:88 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:125; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:90 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:127; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:91 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:128; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:93 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:130; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:95 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:132; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:97 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:134; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:99 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:136; or a light

chain variable region comprising the amino acid sequence of SEQ ID NO:101 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:138; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:103 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:140; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:105 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:142; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:107 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:144; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:109 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:146; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:111 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:148; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:113 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:150; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:115 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:152; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:117 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:154; or a light chain variable region comprising the amino acid sequence of SEQ ID NO:119 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:156.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:158, 160, 162 and 164 and a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:166, 168, 170 and 172.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment

thereof has a K_D for IL-23 of less than 40pM, or a K_D for IL-23 of less than 20pM, or K_D for IL-23 of less than 10pM or K_D for IL-23 of less than 1pM.

In a further embodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that binds to human IL-23p19 at an epitope consisting of amino acid residues 108 to 126 and amino acid residues 137 to 151 of SEQ ID NO: 181.

In a further embodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with an antibody of the present invention. In one enbodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176. In one enbodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:178. In one enbodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176. In one enbodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO: 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 178.

In one embodiment, the anti-IL-23p19 antibody is a humanized antibody. In one embodiment, the anti-IL-23p19 antibody is a monoclonal antibody. In one embodiment,

the anti-IL-23p19 antibody is a full length antibody. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody. In one embodiment the antigen-binding fragment is a Fab, $F(ab')_2$, or single chain Fv fragment. In one embodiment, the antigen-binding fragment comprises a light chain variable region and a heavy chain variable region.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*: the amino acid sequence of SEQ ID NO:63, 66, 67 or 68 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*: the amino acid sequence of SEQ ID NO:66 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 63, 66, 67 or 68 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

In one embodiment, the present invention further provides an anti-IL-23p19 or antigen-binding fragment thereof antibody, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:66 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of any one of SEQ ID NO:158, 160, 162 or 164; and a heavy chain variable region comprising the amino acid sequence any one of SEQ ID NO:166, 168, 170 or 172.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of

SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

In one embodiment, the present invention further provides an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

In one embodiment, the anti-IL-23p19 antibody is a humanized antibody. In one embodiment, the anti-IL-23p19 antibody is a monoclonal antibody. In one embodiment, the anti-IL-23p19 antibody is a full length antibody. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal anti-IL-23p19 antibody, for example a full length humanized monoclonal antibody. In one embodiment, the antigen-binding fragment is a Fab, $F(ab')_2$, or single chain Fv fragment. In one embodiment, the antigen-binding fragment comprises a light chain variable region and a heavy chain variable region.

In one embodiment, the present invention further provides an antibody comprising the amino acid sequence SEQ ID NO:166 or 168 linked to a human IgG1, IgG2, IgG3, IgG4, IgM, IgA or IgE heavy chain constant region. An antibody comprising the amino acid sequence of SEQ ID NO: 166 or 168 linked to a human IgG1 heavy chain constant region. An antibody comprising the amino acid sequence of SEQ ID NO:158 or 160 linked to a human kappa or lambda light chain constant region. An antibody comprising the amino acid sequence of SEQ ID NO: 158 or 160 linked to a human kappa light chain constant region.

In one embodiment, the present invention further provides an antibody comprising the amino acid sequence of SEQ ID NO:166 or 168 linked to a human IgG1 heavy chain constant region; and the amino acid sequence of SEQ ID NO:158 or 160 linked to a human kappa light chain constant region.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence selected from the group consisting of any one of SEQ ID NO:158, 160, 162 and 164 and a heavy chain variable region comprising the amino acid sequence selected from the group consisting of any one of SEQ ID NO:166, 168, 170 and 172.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 or 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176 or 178.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:178.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176.

In one embodiment, the present invention further provides a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO: 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 178.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:160 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:160 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:166 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:166. In one embodiment, the anti-IL-23p19 antibody is a

humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:160 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:160 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:168 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:168. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:158 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:158 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:166 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:166. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:158 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions

of the variable domain light chain amino acid sequence of SEQ ID NO:158 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:168 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:168. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized by a K_D for human IL-23 equal or less than 1 pM. In one aspect, there is no shift in binding on-rate in 50% human serum.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it blocks IL-23 binding to human IL-23R/Fc in vitro.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it does not bind to human IL-12.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it inhibits human IL-23 induced IL-17 production in mouse splenocytes with IC_{50}'s equal or less than 20 pM.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it inhibits human IL-23 induced STAT3 phosphorylation in human DB cells with IC_{50}'s equal or less than 40 pM.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it has no predicted activity in ADCC/CDC.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it has a K_D equal or less than_1 pM for cynomolgus monkey IL-23.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it has no cross reactivity to mouse or rat IL-23.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it inhibits human IL-23 induced IL-17 and IL-22 production in a mouse ear at 80% or greater inhibition of both cytokines at 1 mg/kg.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized by a melting temperature of 83°C as determined by differential scanning calorimetry.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized by solubility equal or greater than 100 mg/ml, as measured by UV spectroscopy and monitored by turbidity.

In a further aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it is present in at least 90% monomer form, or in at least 92% monomer form, or in at least 95% monomer form in a buffer.

In a further aspect, a humanized anti-IL-23p19 antibody of the present invention may be further characterized in that it remains in at least 90% monomer form, or in at least 92% monomer form, or in at least 95% monomer form in a buffer for one month or for four months.

In one aspect, the humanized anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

Further embodiments encompass a DNA molecule encoding a variable light chain region above, a DNA molecule encoding a variable heavy chain region above, a DNA molecule encoding a light chain region above, or a DNA molecule encoding a heavy chain region above.

Further embodiments encompass an expression vector containing a DNA molecule above. In one embodiment, an expression vector comprises a DNA molecule encoding the constant heavy chain and/or the constant light chain, respectively, linked to the DNA molecule encoding the variable heavy chain and/or the variable light chain, respectively. Further embodiments encompass a host cell carrying one or more expression vectors above. In one embodiment, a host is a mammalian cell.

Further embodiments encompass a method for producing an antibody or antigen-binding fragment thereof above comprising transfecting a mammalian host cell with

one or more of the vectors above, cultivating the host cell and recovering and purifying the antibody or antigen-binding fragment thereof.

Further embodiments encompass a method for producing an antibody or antigen-binding fragment thereof above comprising obtaining a mammalian host cell comprising one or more of the vectors above, and cultivating the host cell. In one embodiment, the method further comprises recovering and purifying the antibody or antigen-binding fragment thereof.

In one embodiment, the present invention further provides an antibody or antigen-binding fragment thereof above for use in medicine. In one embodiment, the use is the treatment of an inflammatory disease, of an autoimmune disease, of a respiratory disease, of a metabolic disorder or of cancer. In one embodiment, the use is for the treatment of psoriasis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, or ankylosing spondylitis. In one embodiment, the use is for the treatment of psoriasis. In one embodiment, the use is for the treatment of inflammatory bowel disease.

In one embodiment, the present invention further provides a pharmaceutical composition comprising an antibody molecule or antigen-binding fragment above and a pharmaceutically acceptable carrier.

In one embodiment, the present invention further provides a method for treating an inflammatory disease, an autoimmune disease, a respiratory disease, a metabolic disorder or cancer comprising administering to a subject in need thereof, for example a patient, an effective amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof above, or a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof. In one embodiment, the antibody or antigen-binding fragment is administered by a parenteral route of administration, or is administered intravenously or subcutaneously. In one embodiment, the antibody or antigen-binding fragment is administered subcutaneously. In one embodiment, the disease is

psoriasis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, or ankylosing spondylitis. In one embodiment, the disease is psoriasis. In one embodiment, the disease is inflammatory bowel disease.

In one embodiment, the present invention further provides a method for inhibiting the binding of IL-23 to the IL-23 receptor on a mammalian cell, comprising administering to the cell an antibody molecule or antigen-binding fragment above, whereby signaling mediated by the IL-23 receptor is inhibited.

In one embodiment, the present invention further provides a method for treating a subject having an IL-23-associated disorder, comprising administering to the subject an antibody or antigen-binding fragment above, which antibody or antigen-binding fragment binds to human IL-23.

In one embodiment, the present invention further provides a method for detecting and/or quantifying IL-23 levels in a biological sample by contacting the sample with an antibody or antigen binding fragment above and detecting binding of the antibody or fragment thereof with IL-23p19. This information can be used to diagnose an IL-23-associated disorder. Thus, methods are provided for diagnosing an IL-23-associated disorder or for determining if a subject has an increased risk of developing an IL-23-associated disorder, wherein the method comprises contacting a biological sample from a subject with an antibody or antigen binding fragment above and detecting binding of the antibody or antigen binding fragment to IL-23p19 to determine the expression or concentration of IL-23.

In one embodiment, the present invention further provides a method for inhibiting the binding of IL-23 to the IL-23 receptor on a cell, comprising administering to the cell or cellular environment an antibody or antigen-binding fragment above, whereby signaling mediated by the IL-23 receptor is inhibited.

Brief Description of the Figures

Figure 1: Alignment of mouse and humanized variable regions. Figure 1a: Anti-IL-23p19 6B8 Engineered Vk regions. Figure 1b: Anti-IL-23p19 6B8 Engineered VH regions.

The numbering of the amino acids is by the standard Kabat numbering scheme. Regular font = Human; italic/underlined font = Murine; shadowed font = Synthetic; bold/italic/underlined = CDR.

Figure 2: Competition binding assay of human of IL-23 binding to IL-23R/Fc.

Detailed Description

The p19 subunit of IL-23 (also referred to herein as "IL-23p19" and "p19 subunit") is a 189 amino acid polypeptide containing a 21 aa leader sequence (Oppmann et al. Immunity 13:715 (2000), SEQ ID NO: 181). The biological activity of the molecule is only detected when it is partnered with the IL-12p40 subunit to form IL-23. IL-23 is predominantly expressed by activated dendritic cells (DCs) and phagocytic cells. The receptor for IL-23 was found to be composed of the IL-12Rβ1 subunit of IL-12 receptor partnered with a unique subunit called IL-23R (Parham et al. J. Immunol. 168:5699 (2002)). Expression of the receptor is detected primarily on memory T cells and NK cells. Thus, expression of this cytokine:receptor pair appears to be restricted to specific populations of immune cells. While it was first thought that IL-12 and IL-23 would share many functions, the data has shown the picture to be different. Whereas IL-12 has a predominant role in the production of Th1 cells, IL-23 was found to be critically involved in the production and maintenance of a recently recognized Th cell subset termed Th17 (Kikly et al. Curr. Opin. Immunol. 18:670 (2006), Kastelein et al. Ann. Rev. Immunol. 25:221 (2007)). These cells produce IL-17A, IL-17F, IL-22 and other pro-inflammatory cytokines such as IL-6 and TNF-α. As described below, animal model studies on the role of these Th17 cells show their importance as a driving force in chronic inflammation and autoimmunity.

The present invention provides antibodies that bind to the p19 subunit of the IL-23, in particular human IL-23p19. The present invention also relates to humanized antibodies that recognize the p19 subunit of IL-23. In specific embodiments, the sequence of these humanized antibodies has been identified based on the sequences of certain lead mouse antibodies.

The lead mouse antibodies of the present invention were derived from mouse hybridomas. The immunization of the mice is carried out using different techniques. For example, antibodies that are specific for human IL-23p19 proteins or fragments thereof can be raised against an immunogenic antigen such as an isolated IL-23p19 protein, an isolated IL-23 protein, an isolated hybrid IL-23 protein, and/or a portion thereof of any of the above (including synthetic peptides). For example, a hybrid IL-23 protein comprising a mouse IL-23p40 subunit and a human IL-23p19 subunit is used to immunize mice. Preparation of immunogenic antigens and monoclonal antibody production can be performed using any suitable technique known in the art.

The lead mouse antibodies were selected based on their high affinity to human IL-23. Accordingly, in one aspect, the present invention provides an antibody that binds to human IL-23 with high affinity. Selected mouse antibodies were humanized to result in humanized antibodies. The humanized antibodies of the present invention bind to human IL-23 with high affinity. Accordingly, in another aspect, the present invention provides a humanized antibody that binds to human IL-23 with high affinity. Accordingly, in one embodiment, the present invention provides an anti-IL-23p19 antibody having a K_D of less than 40pM. In a further embodiment, the present invention provides an anti-IL-23p19 antibody having a K_D of less than 20pM. In a further embodiment, the present invention provides an anti-IL-23p19 antibody having a K_D less than 10pM. In a further embodiment, the present invention provides an anti-IL-23p19 antibody having a K_D less than 1pM.

In another aspect, an antibody of the present invention binds to IL-23p19 with high affinity in the absence of human serum or in the presence of 50% human serum.

In a further aspect, a humanized antibody of the present invention also binds to cynomolgus monkey IL-23 with high affinity.

In another aspect, an antibody of the present invention binds to IL-23, but does not bind to IL-12. In a further aspect, an antibody of the present invention does not interfere with the biological activity of IL-12, which is a closely related family member to IL-23.

In another aspect, an antibody of the present invention inhibits the IL-23 stimulated production of IL-17 from mouse splenocytes.

In a further aspect, a humanized antibody of the present invention inhibits IL-23-induced STAT3 phosphorylation in DB cells.

In a further aspect, a humanized antibody of the present invention antagonizes the action of IL-23 by binding to the p19 subunit of IL-23, as measured by the inhibition of cytokines such as IL-17 and IL-22, whose production is stimulated by IL-23, and detected by the reduction in the levels of these cytokines.

In a further aspect, a humanized antibody of the present invention has a favorable pharmacokinetic profile (PK) profile, as exemplified by in vivo half life in cynomolgus monkeys.

In a further aspect, a humanized monoclonal anti-IL-23p19 antibody of the present invention has favorable biophysical properties, for example quality, stability, or solubility.

In one aspect, the anti-IL-23p19 antibody is a humanized antibody. In one aspect, the anti-IL-23p19 antibody is a monoclonal antibody. In one aspect, the anti-IL-23p19 antibody is a full length antibody. In one aspect, the anti-IL-23p19 antibody is a humanized monoclonal antibody, for example a full length humanized monoclonal antibody.

An antibody or antigen-binding fragment thereof of the present invention recognizes specific "IL-23p19 antigen epitope" or " IL-23p19 epitope". As used herein these terms refer to a molecule (e.g., a peptide) or a fragment of a molecule capable of immunoreactivity with an anti-IL-23p19 antibody and, for example, include an IL-23p19 antigenic determinant recognized by the any of the antibodies having a light chain/heavy chain sequence combination of SEQ ID NO:84/121, 86/123, 88/125, 90/127, 91/128, 93/130, 95/132, 97/134, 99/136, 101/138, 103/140, 105/142, 107/144,

109/146, 111/148, 113/150, 115/152, 117/154, 119/156, 160/166, 160/168, 158/166 or 158/168. IL-23p19 antigen epitopes can be included in proteins, protein fragments, peptides or the like. The epitopes are most commonly proteins, short oligopeptides, oligopeptide mimics (i.e., organic compounds that mimic antibody binding properties of the IL-23p19 antigen), or combinations thereof. The minimum size of a peptide or polypeptide epitope for an antibody is thought to be about four to five amino acids. Peptide or polypeptide epitopes contain for example at least seven amino acids or for example at least nine amino acids or for example between about 15 to about 20 amino acids. Since an antibody can recognize an antigenic peptide or polypeptide in its tertiary form, the amino acids comprising an epitope need not be contiguous, and in some cases, may not even be on the same peptide chain. Epitopes may be determined by various techniques known in the art, such as X-ray crystallography, Hydrogen/Deuterium Exchange Mass Spectrometry (HXMS), site-directed mutagenesis, alanine scanning mutagenesis, and peptide screening methods.

The generalized structure of antibodies or immunoglobulin is well known to those of skill in the art. These molecules are heterotetrameric glycoproteins, typically of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains and are typically referred to as full length antibodies. Each light chain is covalently linked to a heavy chain by one disulfide bond to form a heterodimer, and the heterotrameric molecule is formed through a covalent disulfide linkage between the two identical heavy chains of the heterodimers. Although the light and heavy chains are linked together by one disulfide bond, the number of disulfide linkages between the two heavy chains varies by immunoglobulin isotype. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at the amino-terminus a variable domain (V_H), followed by three or four constant domains (C_{H1}, C_{H2}, C_{H3}, and C_{H4}), as well as a hinge region between C_{H1} and C_{H2}. Each light chain has two domains, an amino-terminal variable domain (V_L) and a carboxy-terminal constant domain (C_L). The V_L domain associates non-covalently with the V_H domain, whereas the C_L domain is commonly covalently linked to the C_{H1} domain via a disulfide bond. Particular amino acid residues are believed to form an interface between the light and

heavy chain variable domains (Chothia et al., 1985, J. Mol. Biol. 186:651-663). Variable domains are also referred herein as variable regions.

Certain domains within the variable domains differ extensively between different antibodies i.e., are "hypervariable." These hypervariable domains contain residues that are directly involved in the binding and specificity of each particular antibody for its specific antigenic determinant. Hypervariability, both in the light chain and the heavy chain variable domains, is concentrated in three segments known as complementarity determining regions (CDRs) or hypervariable loops (HVLs). CDRs are defined by sequence comparison in Kabat et al., 1991, In: Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., whereas HVLs (also referred herein as CDRs) are structurally defined according to the three-dimensional structure of the variable domain, as described by Chothia and Lesk, 1987, J. Mol. Biol. 196: 901-917. These two methods result in slightly different identifications of a CDR. As defined by Kabat, CDR-L1 is positioned at about residues 24-34, CDR-L2, at about residues 50-56, and CDR-L3, at about residues 89-97 in the light chain variable domain; CDR-H1 is positioned at about residues 31-35, CDR-H2 at about residues 50-65, and CDR-H3 at about residues 95-102 in the heavy chain variable domain. The exact residue numbers that encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody. The CDR1, CDR2, CDR3 of the heavy and light chains therefore define the unique and functional properties specific for a given antibody.

The three CDRs within each of the heavy and light chains are separated by framework regions (FR), which contain sequences that tend to be less variable. From the amino terminus to the carboxy terminus of the heavy and light chain variable domains, the FRs and CDRs are arranged in the order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The largely β-sheet configuration of the FRs brings the CDRs within each of the chains into close proximity to each other as well as to the CDRs from the other chain. The resulting conformation contributes to the antigen binding site (see Kabat et al.,

1991, NIH Publ. No. 91-3242, Vol. I, pages 647-669), although not all CDR residues are necessarily directly involved in antigen binding.

FR residues and Ig constant domains are not directly involved in antigen binding, but contribute to antigen binding and/or mediate antibody effector function. Some FR residues are thought to have a significant effect on antigen binding in at least three ways: by noncovalently binding directly to an epitope, by interacting with one or more CDR residues, and by affecting the interface between the heavy and light chains. The constant domains are not directly involved in antigen binding but mediate various Ig effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and antibody dependent cellular phagocytosis (ADCP).

The light chains of vertebrate immunoglobulins are assigned to one of two clearly distinct classes, kappa (κ) and lambda (λ), based on the amino acid sequence of the constant domain. By comparison, the heavy chains of mammalian immunoglobulins are assigned to one of five major classes, according to the sequence of the constant domains: IgA, IgD, IgE, IgG, and IgM. IgG and IgA are further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of the classes of native immunoglobulins are well known.

The terms, "antibody", "anti-IL-23p19 antibody", "humanized anti-IL-23p19 antibody", "humanized anti-IL-23p19 epitope antibody", and "variant humanized anti-IL-23p19 epitope antibody" specifically encompass monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments such as variable domains and other portions of antibodies that exhibit a desired biological activity, e.g., IL-23p19 binding.The term "monoclonal antibody" (mAb) refers to an antibody that is highly specific, being directed against a single antigenic determinant, an "epitope". Therefore, the modifier "monoclonal" is indicative of antibodies directed to the identical epitope and is not to be construed as requiring production of the antibody by any particular method. It

should be understood that monoclonal antibodies can be made by any technique or methodology known in the art; including e.g., the hybridoma method (Kohler et al., 1975, Nature 256:495), or recombinant DNA methods known in the art (see, e.g., U.S. Pat. No. 4,816,567), or methods of isolation of monoclonal recombinantly produced using phage antibody libraries, using techniques described in Clackson et al., 1991, Nature 352: 624-628, and Marks et al., 1991, J. Mol. Biol. 222: 581-597.

The term "monomer" refers to a homogenous form of an antibody. For example, for a full-length antibody, monomer means a monomeric antibody having two identical heavy chains and two identical light chains.

Chimeric antibodies consist of the heavy and light chain variable regions of an antibody from one species (e.g., a non-human mammal such as a mouse) and the heavy and light chain constant regions of another species (e.g., human) antibody and can be obtained by linking the DNA sequences encoding the variable regions of the antibody from the first species (e.g., mouse) to the DNA sequences for the constant regions of the antibody from the second (e.g. human) species and transforming a host with an expression vector containing the linked sequences to allow it to produce a chimeric antibody. Alternatively, the chimeric antibody also could be one in which one or more regions or domains of the heavy and/or light chain is identical with, homologous to, or a variant of the corresponding sequence in a monoclonal antibody from another immunoglobulin class or isotype, or from a consensus or germline sequence. Chimeric antibodies can include fragments of such antibodies, provided that the antibody fragment exhibits the desired biological activity of its parent antibody, for example binding to the same epitope (see, e.g., U.S. Pat. No. 4,816,567; and Morrison et al., 1984, Proc. Natl. Acad. Sci. USA 81: 6851-6855).

The terms, "antibody fragment", "anti-IL-23p19 antibody fragment", "anti-IL-23p19 epitope antibody fragment", "humanized anti-IL-23p19 antibody fragment", "humanized anti-IL-23p19 epitope antibody fragment", "variant humanized anti-IL-23p19 epitope antibody fragment" refer to a portion of a full length anti-IL-23p19 antibody, in which a variable region or a functional capability is retained, for example, specific IL-23p19 epitope binding. Examples of antibody fragments include, but are not limited to, a Fab,

Fab', $F(ab')_2$, Fd, Fv, scFv and scFv-Fc fragment, a diabody, a linear antibody, a single-chain antibody, a minibody, a diabody formed from antibody fragments, and multispecific antibodies formed from antibody fragments.

Full length antibodies can be treated with enzymes such as papain or pepsin to generate useful antibody fragments. Papain digestion is used to produces two identical antigen-binding antibody fragments called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment. The Fab fragment also contains the constant domain of the light chain and the C_{H1} domain of the heavy chain. Pepsin treatment yields a $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen.

Fab' fragments differ from Fab fragments by the presence of additional residues including one or more cysteines from the antibody hinge region at the C-terminus of the C_{H1} domain. $F(ab')_2$ antibody fragments are pairs of Fab' fragments linked by cysteine residues in the hinge region. Other chemical couplings of antibody fragments are also known.

"Fv" fragment contains a complete antigen-recognition and binding site consisting of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. In this configuration, the three CDRs of each variable domain interact to define an antigen-biding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody.

A "single-chain Fv" or "scFv" antibody fragment is a single chain Fv variant comprising the V_H and V_L domains of an antibody where the domains are present in a single polypeptide chain. The single chain Fv is capable of recognizing and binding antigen. The scFv polypeptide may optionally also contain a polypeptide linker positioned between the V_H and V_L domains in order to facilitate formation of a desired three-dimensional structure for antigen binding by the scFv (see, e.g., Pluckthun, 1994, In The Pharmacology of monoclonal Antibodies, Vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315).

A "diabody" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (V.sub.H) connected to a light

chain variable domain (V.sub.L) in the same polypeptide chain (V.sub.H-V.sub.L or V.sub.L-V.sub.H). Diabodies are described more fully in, e.g., Holliger et al. (1993) Proc. Natl. Acad. Sci. USA 90: 6444-6448.

Other recognized antibody fragments include those that comprise a pair of tandem Fd segments (V_H-C_{H1}-V_H-C_{H1}) to form a pair of antigen binding regions. These "linear antibodies" can be bispecific or monospecific as described in, for example, Zapata et al. 1995, Protein Eng. 8(10):1057-1062.

A "humanized antibody" or a "humanized antibody fragment" is a specific type of chimeric antibody which includes an immunoglobulin amino acid sequence variant, or fragment thereof, which is capable of binding to a predetermined antigen and which, comprises one or more FRs having substantially the amino acid sequence of a human immunoglobulin and one or more CDRs having substantially the amino acid sequence of a non-human immunoglobulin. This non-human amino acid sequence often referred to as an "import" sequence is typically taken from an "import" antibody domain, particularly a variable domain. In general, a humanized antibody includes at least the CDRs or HVLs of a non-human antibody, inserted between the FRs of a human heavy or light chain variable domain. The present invention describes specific humanized anti-IL-23p19 antibodies which contain CDRs derived from the mouse monoclonal antibodies or humanized CDRs shown in Tables 3 and 4 inserted between the FRs of human germline sequence heavy and light chain variable domains. It will be understood that certain mouse FR residues may be important to the function of the humanized antibodies and therefore certain of the human germline sequence heavy and light chain variable domains residues are modified to be the same as those of the corresponding mouse sequence.

In another aspect, a humanized anti-IL-23p19 antibody comprises substantially all of at least one, and typically two, variable domains (such as contained, for example, in Fab, Fab', F(ab')2, Fabc, and Fv fragments) in which all, or substantially all, of the CDRs correspond to those of a non-human immunoglobulin, and specifically herein, all of the CDRs are mouse or humanized sequences as detailed in Tables 1 through 4 herein below and all, or substantially all, of the FRs are those of a human immunoglobulin

consensus or germline sequence. In another aspect, a humanized anti- IL-23p19 antibody also includes at least a portion of an immunoglobulin Fc region, typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include one or more of the C_{H1}, hinge, C_{H2}, C_{H3}, and/or C_{H4} regions of the heavy chain, as appropriate.

A humanized anti-IL-23p19 antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2. For example, the constant domain can be a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the isotype is typically IgG_1. Where such cytotoxic activity is not desirable, the constant domain may be of another isotype, e.g., IgG_2. An alternative humanized anti-IL-23p19 antibody can comprise sequences from more than one immunoglobulin class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. In specific embodiments, the present invention provides antibodies that are IgG1 antibodies and more particularly, are IgG1 antibodies in which there is a knock-out of effector functions.

The FRs and CDRs, or HVLs, of a humanized anti-IL-23p19 antibody need not correspond precisely to the parental sequences. For example, one or more residues in the import CDR, or HVL, or the consensus or germline FR sequence may be altered (e.g., mutagenized) by substitution, insertion or deletion such that the resulting amino acid residue is no longer identical to the original residue in the corresponding position in either parental sequence but the antibody nevertheless retains the function of binding to IL-23p19. Such alteration typically will not be extensive and will be conservative alterations. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental consensus or germline FR and import CDR sequences, more often at least 90%, and most frequently greater than 95%, or greater than 98% or greater than 99%.

Immunoglobulin residues that affect the interface between heavy and light chain variable regions ("the V_L-V_H interface") are those that affect the proximity or orientation of the two chains with respect to one another. Certain residues that may be involved in interchain interactions include V_L residues 34, 36, 38, 44, 46, 87, 89, 91, 96, and 98 and V_H residues 35, 37, 39, 45, 47, 91, 93, 95, 100, and 103 (utilizing the numbering system set forth in Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987)). U.S. Pat. No. 6,407,213 also discusses that residues such as V_L residues 43 and 85, and V_H residues 43 and 60 also may be involved in this interaction. While these residues are indicated for human IgG only, they are applicable across species. Important antibody residues that are reasonably expected to be involved in interchain interactions are selected for substitution into the consensus sequence.

The terms "consensus sequence" and "consensus antibody" refer to an amino acid sequence which comprises the most frequently occurring amino acid residue at each location in all immunoglobulins of any particular class, isotype, or subunit structure, e.g., a human immunoglobulin variable domain. The consensus sequence may be based on immunoglobulins of a particular species or of many species. A "consensus" sequence, structure, or antibody is understood to encompass a consensus human sequence as described in certain embodiments, and to refer to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular class, isotype, or subunit structure. Thus, the consensus sequence contains an amino acid sequence having at each position an amino acid that is present in one or more known immunoglobulins, but which may not exactly duplicate the entire amino acid sequence of any single immunoglobulin. The variable region consensus sequence is not obtained from any naturally produced antibody or immunoglobulin. Kabat et al., 1991, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., and variants thereof. The FRs of heavy and light chain consensus sequences, and variants thereof, provide useful sequences for the preparation of humanized anti-IL-23p19 antibodies. See, for example, U.S. Pat. Nos. 6,037,454 and 6,054,297.

Human germline sequences are found naturally in the human population. A combination of those germline genes generates antibody diversity. Germline antibody sequences for the light chain of the antibody come from conserved human germline kappa or lambda v-genes and j-genes. Similarly the heavy chain sequences come from germline v-, d- and j-genes (LeFranc, M-P, and LeFranc, G, "The Immunoglobulin Facts Book" Academic Press, 2001).

As used herein, "variant", "anti- IL-23p19 variant", "humanized anti- IL-23p19 variant", or "variant humanized anti- IL-23p19" each refers to a humanized anti-IL-23p19 antibody having at least a light chain variable murine CDR from any of the sequences as shown in Table 1 or a heavy chain murine CDR sequence derived from the murine monoclonal antibody as shown in Table 2. Variants include those having one or more amino acid changes in one or both light chain or heavy chain variable domains, provided that the amino acid change does not substantially impair binding of the antibody to IL-23p19. Exemplary humanized antibodies produced herein include those designated as Antibody A, Antibody B, Antibody C and Antibody D, and the various light chains and heavy chains of the same are shown in SEQ ID Nos:174 and 180, and SEQ ID Nos:176 and 178, respectively.

An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of the antibody's natural environment are those materials that may interfere with diagnostic or therapeutic uses of the antibody, and can be enzymes, hormones, or other proteinaceous or nonproteinaceous solutes. In one aspect, the antibody will be purified to at least greater than 95% isolation by weight of antibody.

An isolated antibody includes an antibody in situ within recombinant cells in which it is produced, since at least one component of the antibody's natural environment will not be present. Ordinarily however, an isolated antibody will be prepared by at least one purification step in which the recombinant cellular material is removed.

The term "antibody performance" refers to factors that contribute to antibody recognition of antigen or the effectiveness of an antibody in vivo. Changes in the amino acid sequence of an antibody can affect antibody properties such as folding,

and can influence physical factors such as initial rate of antibody binding to antigen (k_a), dissociation constant of the antibody from antigen (k_d), affinity constant of the antibody for the antigen (Kd), conformation of the antibody, protein stability, and half life of the antibody.

The term "epitope tagged" when used herein, refers to an anti-IL-23p19 antibody fused to an "epitope tag". An "epitope tag" is a polypeptide having a sufficient number of amino acids to provide an epitope for antibody production, yet is designed such that it does not interfere with the desired activity of the humanized anti-IL-23p19 antibody. The epitope tag is usually sufficiently unique such that an antibody raised against the epitope tag does not substantially cross-react with other epitopes. Suitable tag polypeptides generally contain at least 6 amino acid residues and usually contain about 8 to 50 amino acid residues, or about 9 to 30 residues. Examples of epitope tags and the antibody that binds the epitope include the flu HA tag polypeptide and its antibody 12CA5 (Field et al., 1988 Mol. Cell. Biol. 8: 2159-2165; c-myc tag and 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto (Evan et al., 1985, Mol. Cell. Biol. 5(12):3610-3616; and Herpes simplex virus glycoprotein D (gD) tag and its antibody (Paborsky et al. 1990, Protein Engineering 3(6): 547-553). In certain embodiments, the epitope tag is a "salvage receptor binding epitope". As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (such as IgG_1, IgG_2, IgG_3, or IgG_4) that is responsible for increasing the in vivo serum half-life of the IgG molecule.

In some embodiments, the antibodies of the present invention may be conjugated to a cytotoxic agent. This is any substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (such as I^{131}, I^{125}, Y^{90}, and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant, or animal origin, and fragments thereof. Such cytotoxic agents can be coupled to the humanized antibodies of the present invention using standard procedures, and used, for example, to treat a patient indicated for therapy with the antibody.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. There are numerous examples of chemotherapeutic agents that could be conjugated

with the therapeutic antibodies of the present invention. Examples of such chemotherapeutic agents include alkylating agents such a thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan, and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide, and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin, and bizelesin synthetic analogues); cryptophycines (particularly cryptophycin 1 and cryptophycin 8); dolastatin, auristatins, (including analogues monomethyl-auristatin E and monomethyl-auristatin F); duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine; trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calichemicin gamma1I and calicheamicin phi1, see for example, Agnew, Chem. Intl. Ed. Engl., 33:183-186; dynemicin, including dynemicin A; bisphosphonates, such as clodronate; esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (Adriamycin™) (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, and deoxydoxorubicin), epirubucin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycine, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such a methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-

mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adranals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; democolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone, mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitabronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and doxetaxel (TAXOTERE®, Rhone-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine (Gemzar™); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine Navelbine™); novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids, or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including Nolvadex™), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston™); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate (Megace™), exemestane, formestane, fadrozole, vorozole (Rivisor™), letrozole

(Femara™), and anastrozole (Arimidex™); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids, or derivatives of any of the above. Any one or more of these agents may be conjugated to the humanized antibodies of the present invention to provide a useful therapeutic agent for the treatment of various disorders.

The antibodies also may be conjugated to prodrugs. A "prodrug" is a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active form. See, for example, Wilman, 1986, "Prodrugs in Cancer Chemotherapy", In Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast and Stella et al., 1985, "Prodrugs: A Chemical Approach to Targeted Drug Delivery, In: "Directed Drug Delivery, Borchardt et al., (ed.), pp. 247-267, Humana Press. Useful prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs, and optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs that can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form include, but are not limited to, those chemotherapeutic agents described above.

For diagnostic as well as therapeutic monitoring purposes, the antibodies of the invention also may be conjugated to a label, either a label alone or a label and an additional second agent (prodrug, chemotherapeutic agent and the like). A label, as distinguished from the other second agents refers to an agent that is a detectable compound or composition and it may be conjugated directly or indirectly to a humanized antibody of the present invention. The label may itself be detectable (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable. Labeled humanized anti-IL-23p19 antibody can be prepared and used in various applications including in vitro and in vivo diagnostics.

The antibodies of the present invention may be formulated as part of a liposomal preparation in order to affect delivery thereof in vivo. A "liposome" is a small vesicle composed of various types of lipids, phospholipids, and/or surfactant. Liposomes are useful for delivery to a mammal of a compound or formulation, such as a humanized anti-IL-23p19 antibody disclosed herein, optionally, coupled to or in combination with one or more pharmaceutically active agents and/or labels. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

Certain aspects of the present invention related to isolated nucleic acids that encode one or more domains of the humanized antibodies of the present invention. An "isolated" nucleic acid molecule is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the antibody nucleic acid. An isolated nucleic acid molecule is distinguished from the nucleic acid molecule as it exists in natural cells.

In various aspects of the present invention one or more domains of the humanized antibodies will be recombinantly expressed. Such recombinant expression may employ one or more control sequences, i.e., polynucleotide sequences necessary for expression of an operably linked coding sequence in a particular host organism. The control sequences suitable for use in prokaryotic cells include, for example, promoter, operator, and ribosome binding site sequences. Eukaryotic control sequences include, but are not limited to, promoters, polyadenylation signals, and enhancers. These control sequences can be utilized for expression and production of humanized anti-IL-23p19 antibody in prokaryotic and eukaryotic host cells.

A nucleic acid sequence is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, a nucleic acid presequence or secretory leader is operably linked to a nucleic acid encoding a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked

to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers are optionally contiguous. Linking can be accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers can be used.

As used herein, the expressions "cell", "cell line", and "cell culture" are used interchangeably and all such designations include the progeny thereof. Thus, "transformants" and "transformed cells" include the primary subject cell and cultures derived therefrom without regard for the number of transfers.

The term "mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domesticated and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, and the like. Preferably, the mammal is human.

A "disorder", as used herein, is any condition that would benefit from treatment with a humanized anti-IL-23p19 antibody described herein. This includes chronic and acute disorders or diseases including those pathological conditions that predispose the mammal to the disorder in question. Non-limiting examples or disorders to be treated herein include inflammatory, angiogenic, autoimmune and immunologic disorders, respiratory disorders, cancer, hematological malignancies, benign and malignant tumors, leukemias and lymphoid malignancies.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia.

As used herein, the term "IL-23-associated disorder" or "IL-23-associated disease" refers to a condition in which IL-23 activity contributes to the disease and typically where IL-23 is abnormally expressed. An IL-23-associated disorder includes diseases and disorders of the immune system, such as autoimmune disorders and inflammatory disorders. Such conditions include, but are not limited to, rheumatoid arthritis (RA),

systemic lupus erythematosus (SLE), scleroderma, Sjogren's syndrome, multiple sclerosis, psoriasis, psoriatic arthritis, inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease), pulmonary inflammation, asthma, idiopathic thrombocytopenic purara (ITP) and ankylosing spondylitis.

The term "intravenous infusion" refers to introduction of an agent into the vein of an animal or human patient over a period of time greater than approximately 15 minutes, generally between approximately 30 to 90 minutes.

The term "intravenous bolus" or "intravenous push" refers to drug administration into a vein of an animal or human such that the body receives the drug in approximately 15 minutes or less, generally 5 minutes or less.

The term "subcutaneous administration" refers to introduction of an agent under the skin of an animal or human patient, preferable within a pocket between the skin and underlying tissue, by relatively slow, sustained delivery from a drug receptacle. Pinching or drawing the skin up and away from underlying tissue may create the pocket.

The term "subcutaneous infusion" refers to introduction of a drug under the skin of an animal or human patient, preferably within a pocket between the skin and underlying tissue, by relatively slow, sustained delivery from a drug receptacle for a period of time including, but not limited to, 30 minutes or less, or 90 minutes or less. Optionally, the infusion may be made by subcutaneous implantation of a drug delivery pump implanted under the skin of the animal or human patient, wherein the pump delivers a predetermined amount of drug for a predetermined period of time, such as 30 minutes, 90 minutes, or a time period spanning the length of the treatment regimen.

The term "subcutaneous bolus" refers to drug administration beneath the skin of an animal or human patient, where bolus drug delivery is less than approximately 15 minutes; in another aspect, less than 5 minutes, and in still another aspect, less than 60 seconds. In yet even another aspect, administration is within a pocket between the skin and underlying tissue, where the pocket may be created by pinching or drawing the skin up and away from underlying tissue.

The term "therapeutically effective amount" is used to refer to an amount of an active agent that relieves or ameliorates one or more of the symptoms of the disorder being treated. In another aspect, the therapeutically effective amount refers to a target serum concentration that has been shown to be effective in, for example, slowing disease progression. Efficacy can be measured in conventional ways, depending on the condition to be treated.

The terms "treatment" and "therapy" and the like, as used herein, are meant to include therapeutic as well as prophylactic, or suppressive measures for a disease or disorder leading to any clinically desirable or beneficial effect, including but not limited to alleviation or relief of one or more symptoms, regression, slowing or cessation of progression of the disease or disorder. Thus, for example, the term treatment includes the administration of an agent prior to or following the onset of a symptom of a disease or disorder thereby preventing or removing one or more signs of the disease or disorder. As another example, the term includes the administration of an agent after clinical manifestation of the disease to combat the symptoms of the disease. Further, administration of an agent after onset and after clinical symptoms have developed where administration affects clinical parameters of the disease or disorder, such as the degree of tissue injury or the amount or extent of metastasis, whether or not the treatment leads to amelioration of the disease, comprises "treatment" or "therapy" as used herein. Moreover, as long as the compositions of the invention either alone or in combination with another therapeutic agent alleviate or ameliorate at least one symptom of a disorder being treated as compared to that symptom in the absence of use of the humanized anti-IL-23p19 antibody composition, the result should be considered an effective treatment of the underlying disorder regardless of whether all the symptoms of the disorder are alleviated or not.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

Antibodies

In one aspect, described and disclosed herein are anti-IL-23 antibodies, in particular humanized anti-IL-23p19 antibodies, and compositions and articles of manufacture comprising one or more anti-IL-23 antibody, in particular one or more humanized anti-IL-23p19 antibody of the present invention. Also described are binding agents that include an antigen-binding fragment of an anti-IL-23 antibody, in particular a humanized anti-IL-23p19 antibody. The humanized anti-IL-23p19 antibodies and binding agents can inhibit the production of Th17 associated cytokines, which contribute to chronic autoimmune and inflammatory diseases. The humanized anti-IL-23p19 antibodies and binding agents can thus be used in the treatment of a variety of diseases or disorders. A humanized anti-IL-23p19 antibody and an IL-23p19 binding agent each includes at least a portion that specifically recognizes an IL-23p19 epitope (i.e., an antigen-binding fragment).

In the initial characterization mouse antibodies were selected based on IL-23p19 binding characterization.

Accordingly in one aspect, an antibody of the present invention has a K_D for IL-23, in particular human IL-23, of less than 100pM. In another aspect, an antibody of the present invention has a K_D of less than 40pM. In another aspect, an antibody of the present invention has a K_D of less than 20pM. In another aspect, an antibody of the present invention has a K_D of less than 10pM. In another aspect, a monoclonal antibody of the present invention has a K_D of less than 1pM.

The selected mouse antibodies have the following light chain variable regions and heavy chain variable regions as shown in Table 1 and 2:

Table 1: Anti-IL-23p19 Mouse Leads - VK Sequences

2D1vk	GACATTGTGCTGACCCAATCTCCAGGTTCTTTGGCTGTGTCTCTAGGGCAG AGGGCCACCATATCCTGCAGAACCAGTGAAAGTGTTTATAGTTATGGCCAA AATTTTATACACTGGTACCAGCAGAAACCAGGACAGCCACCCAAACTCCTC ATCTATCGTGCATCCAACCTGGAATCTGGGATCCCTGCCAGGTTCAGTGGC AGTGGGTCTAGGACAGACTTCACCCTCACCATGAATCCTGTGGAGGCTGAT GATGTTGCAACCTATTACTGTCAGCAAACTAATGAGGATCCGTACACGTTC GGAGGGGGGACCAAGCTGGAAATAAGA (SEQ ID NO:83)
	DIVLTQSPGSLAVSLGQRATISCRTSESVYSYGQNFIHWYQQKPGQPPKLL IYRASNLESGIPARFSGSGSRTDFTLTMNPVEADDVATYYCQQTNEDPYTF GGGTKLEIR (SEQ ID NO:84)
6B8Vk	GACATTGTGATGACCCAGTCTCACAAATTCTTGTCCACATCAGTGGGAGAC AGGGTCACCATCACTTGCAAGGCCAGTCGGGATGTGGCTATTGCTGTAGCC TGGTATCAACAGAAACCAGGGCAATCTCCTAAACTACTTCTTTTCTGGGCA TCCACCCGACACACTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCTCGG ACAGATTTCACTCTCACCATTAGCAATGTGCAGTCTGAAGACTTGGCAGAT TATTTCTGTCACCAATATAGCAGCTATCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAAAG (SEQ ID NO:85)
	DIVMTQSHKFLSTSVGDRVTITCKASRDVAIAVAWYQQKPGQSPKLLLFWA STRHTGVPDRFTGSGSRTDFTLTISNVQSEDLADYFCHQYSSYPFTFGSGT KLEIK (SEQ ID NO:86)
9D12-Vk	GACATTGCGCTGACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTGGGGCAG AGGGCCACCATATCCTGCAGAGCCAGTGAAACTATTAATTTTTATGGCACT AGTTTTATGCACTGGTACCAGCAGAAACCAGGACAGTCACCCAAACTCCTC ATCTATCGTGCATCCAACCTAGAATCTGGGATCCCTGCCAGGTTCAGTGGC AGTGGGTCTAGGACAGACTTCACCCTCACCATTAATCCTGTGGAGGCTGAT GATGTTGCAACCTATTACTGTCAGCAAACTAATGAGGATCCGTACACGTTC GGAGGGGGGACTAAGTTGGAAATAAAA (SEQ ID NO:87)
	DIALTQSPASLAVSLGQRATISCRASETINFYGTSFMHWYQQKPGQSPKLL IYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATYYCQQTNEDPYTF GGGTKLEIK (SEQ ID NO:88)
15C11vk	GATGTTGTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGAT CAAGCCTCCATCTCTTGCAGATCTAGTCAGAGCCTTGTACACAGTAATGGA AACACCTATTTACATTGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTC CTGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGT

	GGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAACAGAGTGGAGGCT GAGGATCTGGGAGTTTATTTCTGCTCTCAAAGTACACATGTTCCGTACACG TTCGGAGGGGGGACCCAGCTGGAAATAAAA (SEQ ID NO:89)
	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKL LIYKVSNRFSGVPDRFSGSGSGTDFTLKINRVEAEDLGVYFCSQSTHVPYT FGGGTQLEIK (SEQ ID NO:90)
15F1vk	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLHWYQQRSHESPRLLIKYA SQSISGIPSRFSGSGSGSDFTLTINSVEPEDVGVYYCQNGHSFPFTFGSGT KLEIK (SEQ ID NO:91)
18D3vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTTTCCTGCAGGGCCAGTCAGAGTATTAGCGACTACTTATAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATTTGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCACTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCGACAGTGTGGAACCTGATGATGTTGGAGTC TTTTTCTGTCAAAATGGTCACAGCTTTCCGTTCACGTTCGGAGGGGGGACC AAGCTGGAAATAAAA (SEQ ID NO:92)
	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLYWYQQKSHESPRLLIKFA SQSISGIPSRFTGSGSGSDFTLSIDSVEPDDVGVFFCQNGHSFPFTFGGGT KLEIK (SEQ ID NO:93)
18C4vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCGAGTACTTACAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATATGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCAACAGTGTGGAACCTGAAGATGTTGGAGTG TATTACTGTCAAAATGGTCACAGCTTTCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAAAA (SEQ ID NO:94)
	DIVMTQSPATLSVTPGDRVSLSCRASQSISEYLHWYQQKSHESPRLLIKYA SQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSFPFTFGSGT KLEIK (SEQ ID NO:95)
18E5vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCGACTACTTATAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATTTGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCACTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCGACAGTGTGGAACCTGATGATGTTGGAGTC TTTTTCTGTCAAAATGGTCACAGCTTTCCGTTCACGTTCGGAGGGGGGACC AAGCTGGAAATAAAA (SEQ ID NO:96)

	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLYWYQQKSHESPRLLIKFA SQSISGIPSRFTGSGSGSDFTLSIDSVEPDDVGVFFCQNGHSFPFTFGGGT KLEIK (SEQ ID NO:97)
20E8vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCGAGTATTTACAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATATGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCAACAGTGTGGAACCTGAAGATGTTGGAGTT TATTACTGTCAAAATGGTCACAGCTTTCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAAAA (SEQ ID NO:98)
	DIVMTQSPATLSVTPGDRVSLSCRASQSISEYLHWYQQKSHESPRLLIKYA SQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSFPFTFGSGT KLEIK (SEQ ID NO:99)
22E2vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTCTCCTGCAGGGCCAGCCAGAGTATTAGCGTCTACTTACAC TGGTATCAACAAAAATCACCTGAGTCTCCAAGGCTTCTCATCAAATATGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCAACAGTGTGGAACCTGAAGATGTTGGAGTT TATTACTGTCAAAATGGTCACAGCTTTCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAAAA (SEQ ID NO:100)
	DIVMTQSPATLSVTPGDRVSLSCRASQSISVYLHWYQQKSPESPRLLIKYA SQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSFPFTFGSGT KLEIK (SEQ ID NO:101)
24A54vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAAAT AGAGTCTCTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCGACTACTTACAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATATGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG TCAAATTTCACTCTCAGTATCAACAGTGTGGAACCTGAAGATGTTGGAGTG TATTATTGTCAAAATGGTCACAGCTTTCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAAAA (SEQ ID NO:102)
	DIVMTQSPATLSVTPGNRVSLSCRASQSISDYLHWYQQKSHESPRLLIKYA SQSISGIPSRFSGSGSGSNFTLSINSVEPEDVGVYYCQNGHSFPFTFGSGT KLEIK (SEQ ID NO:103)
26F7Vk	GACATTGTGCTGACACAGTCTCCTGCTTCCTTAGCTGTTTCTCTGGGGCAG AGGGCCACCATCTCATGCAGGGCCAGCAAAAGTGTCAGATTCTCTGACTAT TTTTATATGCACTGGTACCAACAGAAACCAGGACAGCCACCCAAACTCCTC ATCTACCTTGCATCCAACCTAGAATCTGGGGTCCCTGCCAGGTTCAGTGGC

	AGTGGGTCTGGGACAGACTTCACCCTCAACATCCATCCTGTGGAGGAGGAG GATGCTGCAACCTATTACTGTCAGAACAGTAGGGAGCTTCCGTACACGTTC GGAGGGGGGACCAAGCTGGAGATAAAA (SEQ ID NO:104)
	DIVLTQSPASLAVSLGQRATISCRASKSVRFSDYFYMHWYQQKPGQPPKLL IYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQNSRELPYTF GGGTKLEIK (SEQ ID NO:105)
27G8vk	GACATTGTGTTGACACAGTCTCCTGCTTCCTTAGCTGTATCTCTGGGGCAG AGGGCCACCATCTCATGCAGGGCCAGCAAAAGTGTCAGTACATCTGGCTAT AGTTATATACACTGGTACCAACAGAAACCGGGACAGCCACCCAAATTCCTC ATCTATCTTGCATCCAACCTAGATTCTGGGGTCCCTGCCAGGTTCAGTGGC AGTGGGTCTGGGACAGACTTCACCCTCAACATCCATCCTGTGGAGGAGGAG GATGCTGCAACCTATTACTGTCAGCACAGTAGGGAGCTTCCGTACACGTTC GGAGGGGGGACCAAGCTGGAAATAAAA (SEQ ID NO:106)
	DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYIHWYQQKPGQPPKFL IYLASNLDSGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPYTF GGGTKLEIK (SEQ ID NO:107)
31H9vk	GACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGAT AGAGTCTCTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCGACTACTTACAC TGGTATCAACAAAAATCACATGAGTCTCCAAGGCTTCTCATCAAATATGCT TCCCAATCCATCTCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG TCAGATTTCACTCTCAGTATCAACAGTGTGGAACCTGAAGATGTTGGAGTG TATTACTGTCAAAATGGTCACAGCTTTCCGTACACGTTCGGAGGGGGGACC AAGCTGGAAATAAAA (SEQ ID NO:108)
	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLHWYQQKSHESPRLLIKYA SQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSFPYTFGGGT KLEIK (SEQ ID NO:109)
34G3Vk	GATGTTGTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGAT CAAGCCTCCATCTCTTGCAGATCTAGTCAGAGCCTTGTACACAGTAATGGA AACACCTATTTACATTGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTC CTGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCCGACAGGTTCAGT GGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCT GAGGATCTGGGAGTTTATTTCTGCTCTCAAAGTACACATGTTCCGTACACG TTCGGAGGGGGGACCAAGCTGGAAATAAAT (SEQ ID NO:110)
	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKL LIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPYT FGGGTKLEIN (SEQ ID NO:111)

34D9Vk	GACATTATGATGACCCAGTCTCACAAATTCATGTCCACATCAGTAGGAGAC AGGGTCAGCATCACCTGCAAGGCCAGTCAGGATGTGGGTAATGCTGTGGTC TGGTATCAACAAAAACCAGGGCAATCTCCTAAACTACTGATTTACTGGGCA TCCACCCGGCACATTGGAGTCCCTGATCGCTTCACAGGCAGTGGATCTGGG ACAGATTTCACTCTCACCATTACCAATGTGCAGTCTGAAGACTTGGCAGAT TATTTCTGTCAGCAATATAGCAGCTATCTCACGTTCGGTGCTGGGACCAAG CTGGAGCTGAAA (SEQ ID NO:112)
	DIMMTQSHKFMSTSVGDRVSITCKASQDVGNAVVWYQQKPGQSPKLLIYWA STRHIGVPDRFTGSGSGTDFTLTITNVQSEDLADYFCQQYSSYLTFGAGTK LELK (SEQ ID NO:113)
43F5vk	GATGTTGTGATGACCCAATCTCCACTCTCCCTGCCTGTCAGTCTTGGAGAT CAAGCCTCCATCTCTTGCAGATCTAGTCAGAGCCTTGTACACAGTAATGGA AACACCTATCTACATTGGTACCTGCTGAAGCCAGGCCAGTCTCCAAAGCTC CTGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGT GGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCT GAGGATCTGGGAGTTTATTTCTGCTCTCAAAGTACACATGTTCCGTACACG TTCGGAGGGGGGACCAAGCTGGAAATAAAA (SEQ ID NO:114)
	DVVMTQSPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLLKPGQSPKL LIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPYT FGGGTKLEIK (SEQ ID NO:115)
73H10Vk	GACATCCAGATGACTCAGTCTCCAGTTTTCCTGTCTGCATCTGTGGGAGAA ACTGTCACCATCACATGTCGAGCAAGTGAGAATATTGACAGTTATTTAGCA TGGTATCAGCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTTTGCTGCA CGAAACTTAGCAGATGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGGC ACACAGTATTCTCTCAAGATCAACAGAATGCAGTCTGAAGATGTTGCGAGA TACTACTGTCAACATTATTATAGTACTCCATTCACGTTCGGCTCGGGGACA AAGTTGGAAATAGAA (SEQ ID NO:116)
	DIQMTQSPVFLSASVGETVTITCRASENIDSYLAWYQQKQGKSPQLLVFAA RNLADGVPSRFSGSGSGTQYSLKINRMQSEDVARYYCQHYYSTPFTFGSGT KLEIE (SEQ ID NO:117)
74H3Vk	GACATCCAGATGACTCAGTCGCCAGCTTCCCTGTCTGCATCTGTGGGAGAA ACTGTCATCTTCACATGTCGAGCAAGTGAGAATATTGACAGTTATTTAGCA TGGTATCAGCAGAAACAGGGAAAATCTCCTCAGCTCCTGGTCTATGCTGCA ACAAACTTAGCAGATGGTGTGCCATCAAGGTTCAGTGGCAGTGGATCAGGC ACACAGTATTCTCTCAAGATCAACAGCCTGCAGTCTGAAGATGTTGCGAGA TATTACTGTCTACATTATTATAGTACTCCATTCACGTTCGGCTCGGGGACA GAGTTGGAAATAAAA (SEQ ID NO:118)

	DIQMTQSPASLSASVGETVIFTCRASENIDSYLAWYQQKQGKSPQLLVYAA TNLADGVPSRFSGSGSGTQYSLKINSLQSEDVARYYCLHYYSTPFTFGSGT ELEIK (SEQ ID NO:119)

Table 2: Anti-IL-23p19 Mouse Leads - VH Sequences

2D1vh	CAGGTGCAGCTGAAGGAGTCAGGACCTGGCCTGGTGGCGCCCTCACAGAGC CTGTCCATCACATGCACTGTCTCTGGGTTCTCATTAACCACCTATGCTATA AGCTGGGTTCGCCAGTCACCAGGAAAGGGTCTGGAGTGGCTTGGAGTCATA TGGACTGGTGGAGGCACAAAATATAATTCAGCTCTCAAATCCAGACTGAGC ATCAGCAAAGACAACTCCAAGAGTCAAGTTTTCTTAAAAATGAACAGTCTG CAAACTGATGACACAGCCAGGTACTACTGTGCCAGAAAGGACTATAATTAC GGGGGTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:120)
	QVQLKESGPGLVAPSQSLSITCTVSGFSLTTYAISWVRQSPGKGLEWLGVI WTGGGTKYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTARYYCARKDYNY GGAMDYWGQGTSVTVSS (SEQ ID NO:121)
6B8VH	CAGGTTCAGCTGCAACAGTCTGACGCTGAGTTGGTGAAACCTGGCACTTCA GTGAAGACATCCTGCAAAATTTCTGGCAACACCTTCACTGACCAAACTATT CACTGGATGAAGCAGAGGCCTGAACAGGGCCTGGAATGGATTGGATATATT TATCCTAGAGATGATAGTCCTAAGTACAATGAGAACTTCAAGGGCAAGGCC ACATTGACTGCAGACAAATCCTCCAGCACAGCCTACATGCAGCTCAACAGT CTGACATCTGAGGACTCTGCAGTCTATTTCTGTGCAATCCCAGACAGGTCA GGCTACGCCTGGTTTATTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCT TCA (SEQ ID NO:122)
	QVQLQQSDAELVKPGTSVKTSCKISGNTFTDQTIHWMKQRPEQGLEWIGYI YPRDDSPKYNENFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCAIPDRS GYAWFIYWGQGTLVTVSS (SEQ ID NO:123)
9D12VH	CAGGTGCAGCTGAAGGAGTCAGGACCTGTCCTGGTGGCGCCCTCACAGAGC CTGTCCATCACATGCACTGTCTCTGGGTTCTCATTAAACAACTTTGCTATA AGTTGGGTTCGTCAGCCACCAGGAAAGGGTCTGGAGTGGCTTGGAGCAATA TGGACTGGTGGAGGCACAAATTATAATTCAGCTCTCAAATCCAGACTGAGC ATCAGCAAAGACAACTCCAAGAGTCAAGTTTTCTTAAAAATGAACAGTCTG CAAACTGATGACACAGCCAGGTATTATTGTGTCAGAAAGGACTATAGTTAC GGGGGTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:124)
	QVQLKESGPVLVAPSQSLSITCTVSGFSLNNFAISWVRQPPGKGLEWLGAI WTGGGTNYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTARYYCVRKDYSY GGAMDYWGQGTSVTVSS (SEQ ID NO:125)

15C11vh	GAGGTCCAGCTGCAACAGTCTGGACCTGTGCTGGTGAAGCCTGGGGCTTCA GTGAAGATGTCCTGTAAGGCTTCTGGATACACATTCACTGACTACTATATG AACTGGGTGAAGCAGAGCCATGGAAAGAGCCTTGAGTGGATTGGAGTTATT ATTCCTTACAACGGTGGTACTAGCTACAACCAGAAGTTCAAGGGCAAGGCC ACATTGACTGTTGACAAGTCCTCCAGCACAGCCTACATGGAGCTCAACAGC CTGACATCTGAGGACTCTGCAGTCTATTACTGTGCACGAGATGGTCACCGC TGGTACTTCGATGTCTGGGGCACAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:126)
	EVQLQQSGPVLVKPGASVKMSCKASGYTFTDYYMNWVKQSHGKSLEWIGVI IPYNGGTSYNQKFKGKATLTVDKSSSTAYMELNSLTSEDSAVYYCARDGHR WYFDVWGTGTTVTVSS (SEQ ID NO:127)
15F1vh	EVQLQQSGPELVKPGASVKMSCKASGYTFTCCIMHWVKQKPGQGLEWIGYI NPYNDGTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARRWDE AYWGQGTLVTVSA (SEQ ID NO:128)
18D3vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTCAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTCGCTATCTTATT CACTGGGTGAAACAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATT AATCCTTACAATGATGGTACTAAATACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTACCTCTAACTGGGACCTC GACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA (SEQ ID NO:129)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTRYLIHWVKQKPGQGLEWIGYI NPYNDGTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCTSNWDL DYWGQGTTLTVSS (SEQ ID NO:130)
18C4vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAAGTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCCTCTGGATACACATTCACTAGTTCTGTTATA CACTGGGTGAAGCAGAAGGCTGGGCAGGGCCTTGAGTGGATTGGATATATC AATCCCTATAATGATGGTACTAAGTACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAGATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTACAAGACGGTTGGACGAG GCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:131)
	EVQLQQSGPEVVKPGASVKMSCKASGYTFTSSVIHWVKQKAGQGLEWIGYI NPYNDGTKYNEKFKGKATLTSDRSSSTAYMELSSLTSEDSAVYYCTRRLDE AYWGQGTLVTVSA (SEQ ID NO:132)

18E5vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTGCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTCGCTATCTTATT CACTGGGTGAAGCAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATT AATCCTTACAATGATGGTACTAAATATAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTACCTCTAATTGGGACCTC GACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA (SEQ ID NO:133)
	EVQLQQSGPELVKPGAAVKMSCKASGYTFTRYLIHWVKQKPGQGLEWIGYI NPYNDGTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCTSNWDL DYWGQGTTLTVSS (SEQ ID NO:134)
20E8vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAACTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCCTCTGGATACACATTCACTAGTTCTGTTATG CACTGGGTGAAGCAGAAGGCTGGGCAGGGCCTTGAGTGGATTGGATATATC AATCCCTATAATGATGGTACTCAGTACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATTTTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTACAAGACGGTTGGACGAG GCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:135)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTSSVMHWVKQKAGQGLEWIGYI NPYNDGTQYNEKFKGKATLTSDKFSSTAYMELSSLTSEDSAVYYCTRRLDE AYWGQGTLVTVSA (SEQ ID NO:136)
22E2vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTAGCTCTATTATT CACTGGGTGAAGCAGAGGCCTGGGCAGGGCCTTGAGTGGATTGGATATATT AATCCTTACGATGATGTTACTAAGTACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTGCAAGACGGTGGGACGAG TCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:137)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTSSIIHWVKQRPGQGLEWIGYI NPYDDVTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARRWDE SYWGQGTLVTVSA (SEQ ID NO:138)
24A5vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACTTTCACTACCTCTATTATG CACTGGGTGAAACAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATT AATCCTTACGATGATGTTACTAAGTACAATGAAAAGTTCAAAGGCAAGGCC

	ACATTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCAGTCTATTACTGTGTAAGACGGTGGGACGAG GCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:139)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTTSIMHWVKQKPGQGLEWIGYI NPYDDVTKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCVRRWDE AYWGQGTLVTVSA (SEQ ID NO:140)
26F7VH	GAGGTCCAGCTGCAACAATCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCA GTGAAGATATCCTGTAAGGCTTCTGGATACACGTTTACTGACTACTACATG AACTGGGTGAGGCAGAGCCATGGAGAGAGCCTTGAGTGGATTGGAGATTTT AATCATAACAATGATGTTATTACTTACAACCCGAAGTTCAAGGGCAAGGTC ACATTGACTGTAGAGAAGTCTTCCACCACAGCCTACATGGAGCTCCGCAGC CTGTCATCTGAGGACTCTGCAGTCTATTACTGTGCAAGGGGGCTACGAGGC TACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:141)
	EVQLQQSGPELVKPGASVKISCKASGYTFTDYYMNWVRQSHGESLEWIGDF NHNNDVITYNPKFKGKVTLTVEKSSTTAYMELRSLSSEDSAVYYCARGLRG YYAMDYWGQGTSVTVSS (SEQ ID NO:142)
27G8vh	CAGGTTCAGCTGCAACAGTCTGACGCTGAGTTGGTGAAACCTGGAGCTTCA GTGAAGATATCCTGCAAGGTTTCTGGCTACACCTTCACTGACCATACTATT CACTGGATGAAGCAGAGGCCTGAACAGGGCCTGGAATGGATTGGATATATT TATCCTAGAGATGGTTATCCTAAGTTCAATGAGAAGTTCAAGGGCAAGGCC ACATTGACTGCAGACAAATCCTCCAGCACAGCCTACATGCAGCTCAACAGC CTGACATCTGAGGACTCTGCAGTCTATTTCTGTGCAAGACGGCCCCCTTAC TATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCGCCGTCTCCTCA (SEQ ID NO:143)
	QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWIGYI YPRDGYPKFNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCARRPPY YAMDYWGQGTSVAVSS (SEQ ID NO:144)
31H9vh	GAGGTCCAACTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTAGGTATCTTATG CACTGGGTGAAGCAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGTTATATT AATCCTTACAATGATGGTACTAATTACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTTCCCTTAACTGGGACTAT GCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:145)

	EVQLQQSGPELVKPGASVKMSCKASGYTFTRYLMHWVKQKPGQGLEWIGYI NPYNDGTNYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCSLNWDY AYWGQGTLVTVSA (SEQ ID NO:146)
34G3VH	GAGTTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGCGCTTCA GTGAAGATATCCTGCAAGGCTTCTGGTTACTCATTCACTGACTACAACATG AACTGGGTGAAGCAGAGCAAAGGAAAGAGCCTTGAGTGGATTGGAGTAATT ATTCCTAACTATGGTTTTACTAGCTACAATCAGAACTTCAAGGGCAAGGCC ACTTTGACTGTAGACCAGTCTTCCAGCACAGCCCACATGCAGCTCAACAGT GTGACATCTGAGGACTCTGCAGTCTATTACTGTGTAAGAGATGGGGGAATA CTCCTCTGGTATCTCGATGTCTGGGGCACAGGGACCACGGTCACCGTCTCC TCA (SEQ ID NO:147)
	EFQLQQSGPELVKPGASVKISCKASGYSFTDYNMNWVKQSKGKSLEWIGVI IPNYGFTSYNQNFKGKATLTVDQSSSTAHMQLNSVTSEDSAVYYCVRDGGI LLWYLDVWGTGTTVTVSS (SEQ ID NO:148)
34D9VH7	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCA GTGAAGATACCCTGCAAGGCTTCTGGATACACATTCACTGACTACAACATG GACTGGGTGAAGAAGAGCCATGGAAAGAGCCTTGAGTGGATTGGAGATATC AATCCTCACAATGGTGGTACTATCTACAACCAGAAGTTCAAGGGCAAGGCC ACATTGACTGTAGACAAGTCCTCCAGCACAGCCCACATGGAGCTCCGCAGC CTGACATCTGAGGACACTGCAGTCTATTACTGTGCAAGAAATTACTACGGT AGTAGTTACGGCTGGTACTTCGATGTCTGGGGCACAGGGACCACGGTCACC GTCTCGTCA (SEQ ID NO:149)
	EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWVKKSHGKSLEWIGDI NPHNGGTIYNQKFKGKATLTVDKSSSTAHMELRSLTSEDTAVYYCARNYYG SSYGWYFDVWGTGTTVTVSS (SEQ ID NO:150)
43F5vh	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCA GTGAAGATTTCCTGCAGGGCTTCTGGTTACTCATTCACTGGCTACTACATG AACTGGGTGAAGCAAAGTCCTGAAAAGAGCCTTGAGTGGATTGGAGAGATT ATTCCTACCACTGGTGGTACTTCCTACAACCAGAAGTTCAAGGCCAAGGCC ACATTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAGCTCAAGAGC CTGACATCTGAGGACTCTGCAGTCTATTACTGTGCAAGAGAGAGCGGTGGG TTCTACTGGTACTTCGATGTCTGGGGCACAGGGACCACGGTCACCGTCTCC TCA (SEQ ID NO:151)
	EVQLQQSGPELVKPGASVKISCRASGYSFTGYYMNWVKQSPEKSLEWIGEI IPTTGGTSYNQKFKAKATLTVDKSSSTAYMQLKSLTSEDSAVYYCARESGG FYWYFDVWGTGTTVTVSS (SEQ ID NO:152)

73H10VH	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTAGGTATGTTATG CACTGGGTGAAGCAGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATT AATCCTTACAATGATGTTACTAAGTACAATGAGAAGTTCAAAGGCAAGGCC ACACTGACTTCAGACAGATCCTCCAGCACAGCCTACATGAAACTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTATTGTGCAAGAAACTGGGACGTT CCTTACTGGGGCCAAGGGACTCTGATCACTGTCTCTGCA (SEQ ID NO:153)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTRYVMHWVKQKPGQGLEWIGYI NPYNDVTKYNEKFKGKATLTSDRSSSTAYMKLSSLTSEDSAVYYCARNWDV PYWGQGTLITVSA (SEQ ID NO:154)
74H3VH	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCA GTGAAGATGTCCTGCAAGGCTTCTGGATACACATTCACTAGGTATCTTATG CACTGGGTGAAGCAGAAGCCTGGACAGGGCCTTGAGTGGATTGGATATATT AATCCTTACAATGATGGTACTAAGTACAATGAGAGGTTCAAAGGCAAGGCC ACACTGACTTCAGACAAATCCTCCAGCACAGCCTACATGGAGCTCAGCAGC CTGACCTCTGAGGACTCTGCGGTCTATTACTGTGCAAGAAACTGGGACGTA CCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA (SEQ ID NO:155)
	EVQLQQSGPELVKPGASVKMSCKASGYTFTRYLMHWVKQKPGQGLEWIGYI NPYNDGTKYNERFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARNWDV PYWGQGTLVTVSA (SEQ ID NO:156)

Human framework sequences were selected for each of the mouse leads based on the framework homology, CDR structure, conserved canonical residues, conserved interface packing residues and other parameters.

The mouse light chain and heavy chain CDRs of the various mouse antibodies are shown in Table 3 and Table 4, respectively. Table 4 also shows three heavy chains CDRs derived from the mouse antibody 6B8 through the humanization process.

Table 3: LIGHT CHAIN CDR sequences

	L-CDR1	L-CDR2	L-CDR3
18C4	RASQSISEYLH (SEQ ID NO:1)	YASQSIS (SEQ ID NO:2)	QNGHSFPFT (SEQ ID NO:3)
18E5	RASQSISDYLY (SEQ ID NO:4)	FASQSIS (SEQ ID NO:5)	QNGHSFPFT (SEQ ID NO:3)
18D3	RASQSISDYLY (SEQ ID NO:4)	FASQSIS (SEQ ID NO:5)	QNGHSFPFT (SEQ ID NO:3)
20E8	RASQSISEYLH (SEQ ID NO:1)	YASQSIS (SEQ ID NO:2)	QNGHSFPFT (SEQ ID NO:3)
22E2	RASQSISVYLH (SEQ ID NO:6)	YASQSIS (SEQ ID NO:2)	QNGHSFPFT (SEQ ID NO:3)
24A5	RASQSISDYLH (SEQ ID NO:7)	YASQSIS (SEQ ID NO:2)	QNGHSFPFT (SEQ ID NO:3)
15C11	RSSQSLVHSNGNTYLH (SEQ ID NO:8)	KVSNRFS (SEQ ID NO:9)	SQSTHVPYT (SEQ ID NO:10)
43F5	RSSQSLVHSNGNTYLH (SEQ ID NO:8)	KVSNRFS (SEQ ID NO:9)	SQSTHVPYT (SEQ ID NO:10)
27G8	RASKSVSTSGYSYIH (SEQ ID NO:11)	LASNLDS (SEQ ID NO:12)	QHSRELPYT (SEQ ID NO:13)
31H9	RASQSISDYLH (SEQ ID NO:7)	YASQSIS (SEQ ID NO:2)	QNGHSFPYT (SEQ ID NO:14)
2D1	RTSESVYSYGQNFIH (SEQ ID NO:15)	RASNLES (SEQ ID NO:16)	QQTNEDPYT (SEQ ID NO:17)
9D12	RASETINFYGTSFMH (SEQ ID NO:18)	RASNLES (SEQ ID NO:16)	QQTNEDPYT (SEQ ID NO:17)
6B8	KASRDVAIAVA (SEQ ID NO:19)	WASTRHT (SEQ ID NO:20)	HQYSSYPFT (SEQ ID NO:21)
73H10	RASENIDSYLA (SEQ ID NO:22)	AARNLAD (SEQ ID NO:23)	QHYYSTPFT (SEQ ID NO:24)

74H3	RASENIDSYLA (SEQ ID NO:22)	AATNLAD (SEQ ID NO:25)	LHYYSTPFT (SEQ ID NO:26)
35H8	RSSQSLVHSNGNTYLH (SEQ ID NO:8)	KVSNRFS (SEQ ID NO:9)	SQSTHVPYT (SEQ ID NO:10)
26F7	RASKSVRFSDYFYMH (SEQ ID NO:27)	LASNLES (SEQ ID NO:28)	QNSRELPYT (SEQ ID NO:29)
34G3	RSSQSLVHSNGNTYLH (SEQ ID NO:8)	KVSNRFS (SEQ ID NO:9)	SQSTHVPYT (SEQ ID NO:10)
34D9	KASQDVGNAVV (SEQ ID NO:30)	WASTRHI (SEQ ID NO:31)	QQYSSYLT (SEQ ID NO:32)

Table 4: HEAVY CHAIN CDR sequences

	H-CDR1	H-CDR2	H-CDR3
18C4	GYTFTSSVIH (SEQ ID NO:33)	YINPYNDGTKYNEKFKG (SEQ ID NO:34)	RLDEAY (SEQ ID NO:35)
18E5	GYTFTRYLIH (SEQ ID NO:36)	YINPYNDGTKYNEKFKG (SEQ ID NO:34)	NWDLDY (SEQ ID NO:37)
18D3	GYTFTRYLIH (SEQ ID NO:36)	YINPYNDGTKYNEKFKG (SEQ ID NO:34)	NWDLDY (SEQ ID NO:37)
20E8	GYTFTSSVMH (SEQ ID NO:38)	YINPYNDGTQYNEKFKG (SEQ ID NO:39)	RLDEAY (SEQ ID NO:35)
22E2	GYTFTSSIIH (SEQ ID NO:40)	YINPYDDVTKYNEKFKG (SEQ ID NO:41)	RWDESY (SEQ ID NO:42)
24A5	GYTFTTSIMH (SEQ ID NO:43)	YINPYDDVTKYNEKFKG (SEQ ID NO:41)	RWDEAY (SEQ ID NO:44)
15C11	GYTFTDYYMN (SEQ ID NO:45)	VIIPYNGGTSYNQKFKG (SEQ ID NO:46)	DGHRWYFDV (SEQ ID NO:47)
43F5	GYSFTGYYMN (SEQ ID NO:48)	EIIPTTGGTSYNQKFKA (SEQ ID NO:49)	ESGGFYWYFDV (SEQ ID NO:50)
27G8	GYTFTDHTIH (SEQ ID NO:51)	YIYPRDGYPKFNEKFKG (SEQ ID NO:52)	RPPYYAMDY (SEQ ID NO:53)
31H9	GYTFTRYLMH (SEQ ID NO:54)	YINPYNDGTNYNEKFKG (SEQ ID NO:55)	NWDYAY (SEQ ID NO:56)
2D1	GFSLTTYAIS (SEQ ID NO:57)	VIWTGGGTKYNSALKS (SEQ ID NO:58)	KDYNYGGAMDY (SEQ ID NO:59)
9D12	GFSLNNFAIS (SEQ ID NO:60)	AIWTGGGTNYNSALKS (SEQ ID NO:61)	KDYSYGGAMDY (SEQ ID NO:62)
6B8	GNTFTDQTIH (SEQ ID NO:63)	YIYPRDDSPKYNENFKG (SEQ ID NO:64)	PDRSGYAWFIY (SEQ ID NO:65)
Hu_6B8-2	GYTFTDQTIH (SEQ ID NO:66)	YIYPRDDSPKYNENFKG (SEQ ID NO:64)	PDRSGYAWFIY (SEQ ID NO:65)
Hu_6B8-5	GFTFTDQTIH (SEQ ID NO:67)	YIYPRDDSPKYNENFKG (SEQ ID NO:64)	PDRSGYAWFIY (SEQ ID NO:65)

Hu_6B8 -36/65	GGTFTDQTIH (SEQ ID NO:68)	YIYPRDDSPKYNENFKG (SEQ ID NO:64)	PDRSGYAWFIY (SEQ ID NO:65)
73H10	GYTFTRYVMH (SEQ ID NO:69)	YINPYNDVTKYNEKFKG (SEQ ID NO:70)	NWDVPY (SEQ ID NO:71)
74H3	GYTFTRYLMH (SEQ ID NO:54)	YINPYNDGTKYNERFKG (SEQ ID NO:72)	NWDVPY (SEQ ID NO:71)
35H8	GYTFTDYYMN (SEQ ID NO:45)	VIIPYNGGISYNQKFKG (SEQ ID NO:73)	NDYDWYFDV (SEQ ID NO:74)
26F7	GYTFTDYYMN (SEQ ID NO:45)	DFNHNNDVITYNPKFKG (SEQ ID NO:75)	GLRGYYAMDY (SEQ ID NO:76)
34G3	GYSFTDYNMN (SEQ ID NO:77)	VIIPNYGFTSYNQNFKG (SEQ ID NO:78)	DGGILLWYLDV (SEQ ID NO:79)
34D9	GYTFTDYNMD (SEQ ID NO:80)	DINPHNGGTIYNQKFKG (SEQ ID NO:81)	NYYGSSYGWYFDV (SEQ ID NO:82)

The CDRs listed above in Tables 3 and 4 are defined using the Chothia numbering system (Al-Lazikani et al., (1997) JMB 273,927-948).

Fabs that showed better or equal binding as compared to the chimeric parent Fab were selected for conversion to IgG. 6B8 was converted to an IgG1KO format. IgG1KO (knock-out of effector functions) has two mutations in the Fc region, Leu234Ala and Leu235Ala, which reduce effector function such as FcγR and complement binding. The IgG format is described in the literature (see for example Hezareh et al. (2001) Journal of Virology 75: 12161-12168). Example 1 describes the humanization process in further detail. The results of such humanization resulted in humanized antibody sequences. A representative number of humanized light chain and heavy chain variable regions derived from mouse antibody 6B8 are provided and shown in Tables 5 and 6. An alignment between the humanized light chain and heavy chain variable regions derived from mouse antibody 6B8 and the chain and heavy chain variable regions from mouse antibody 6B8 is shown in Figure 1.

Selected combination of humanized light chain and heavy chain variable regions derived from mouse antibody 6B8 resulted in Antibodies A, B, C and D:

Antibody A: 6B8-IgG1KO-2 with IgK-66 (heavy chain variable region 6B8CVH-02 and light chain variable region 6B8CVK-66);

Antibody B: 6B8-IgG1KO-5 with IgK-66 (heavy chain variable region 6B8CVH-05 and light chain variable region 6B8CVK-66);

Antibody C: 6B8-IgG1KO-2 with IgK-65 (heavy chain variable region 6B8CVH-02 and light chain variable region 6B8CVK-65);

Antibody D: 6B8-IgG1KO-5 with IgK-65 (heavy chain variable region 6B8CVH-05 and light chain variable region 6B8CVK-65).

Antibodies A, B, C and D have the heavy and light chain sequences shown in Table 7.

Table 5: Humanized 6B8-VK Sequences

6B8CVK-65	Gacatccagatgacccagagcccaagcagcctgagcgccagcgtggg cgaccgcgtgaccatcacctgcaaggccagccgcgacgtggccatcg ccgtggcctggtaccagcagaagccaggcaaggtgccaaagctgctg ctgttctgggccagcacccgccacaccggcgtgccagaccgcttcag cggcagcggcagcggcaccgacttcaccctgaccatcagcagcctgc agccagaggacctggccgactactactgccaccagtacagcagctac ccattcaccttcggccagggcaccaagctggagatcaag (SEQ ID NO:157)
	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLL LFWASTRHTGVPDRFSGSGSGTDFTLTISSLQPEDLADYYCHQYSSY PFTFGQGTKLEIK (SEQ ID NO:158)
6B8CVK-66	Gacatccagatgacccagagcccaagcagcctgagcgccagcgtggg cgaccgcgtgaccatcacctgcaaggccagccgcgacgtggccatcg ccgtggcctggtaccagcagaagccaggcaaggtgccaaagctgctg atctactgggccagcacccgccacaccggcgtgccaagccgcttcag cggcagcggcagccgcaccgacttcaccctgaccatcagcagcctgc agccagaggacgtggccgactacttctgccaccagtacagcagctac ccattcaccttcggcagcggcaccaagctggagatcaag (SEQ ID NO:159)
	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLL IYWASTRHTGVPSRFSGSGSRTDFTLTISSLQPEDVADYFCHQYSSY PFTFGSGTKLEIK (SEQ ID NO:160)
6B8CVK-67	Gacatccagatgacccagagcccaagcagcctgagcgccagcgtggg cgaccgcgtgaccatcacctgcaaggccagccgcgacgtggccatcg ccgtggcctggtaccagcagaagccaggcaaggtgccaaagctgctg ctgtactgggccagcacccgccacaccggcgtgccaagccgcttcag cggcagcggcagccgcaccgacttcaccctgaccatcagcagcctgc agccagaggacgtggccacctactactgccaccagtacagcagctac ccattcaccttcggcagcggcaccaagctggagatcaag (SEQ ID NO:161)
	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLL LYWASTRHTGVPSRFSGSGSRTDFTLTISSLQPEDVATYYCHQYSSY PFTFGSGTKLEIK (SEQ ID NO:162)

6B8CVK-78	Gacatccagatgacccagagcccaagcagcctgagcgccagcgtggg cgaccgcgtgaccatcacctgcaaggccagccgcgacgtggccatcg ccgtggcctggtaccagcagaagccaggcaaggtgccaaagctgctg ctgttctgggccagcacccgccacaccggcgtgccagaccgcttcag cggcagcggcagccgcaccgacttcaccctgaccatcagcagcctgc agccagaggacctggccgactactactgccaccagtacagcagctac ccattcaccttcggcagcggcaccaagctggagatcaag (SEQ ID NO:163)
	DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQQKPGKVPKLL LFWASTRHTGVPDRFSGSGSRTDFTLTISSLQPEDLADYYCHQYSSY PFTFGSGTKLEIK (SEQ ID NO:164)

Table 6: Humanized 6B8-VH Sequence

6B8CVH-02	Caggtgcagctggtgcagagcggcgccgaggtgaagaagccaggcag cagcgtgaaggtgagctgcaaggccagcggctacaccttcaccgacc agaccatccactggatgcgccaggccccaggccagggcctggagtgg atcggctacatctacccacgcgacgacagcccaaagtacaacgagaa cttcaagggcaaggtcaccatcaccgccgacaagagcaccagcaccg cctacatggagctgagcagcctgcgcagcgaggacaccgccgtgtac tactgcgccatcccagaccgcagcggctacgcctggttcatctactg gggccagggcaccctggtgaccgtgagcagc (SEQ ID NO:165)
	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWMRQAPGQGLEW IGYIYPRDDSPKYNENFKGKVTITADKSTSTAYMELSSLRSEDTAVY YCAIPDRSGYAWFIYWGQGTLVTVSS (SEQ ID NO:166)
6B8CVH-05	Caggtgcagctggtgcagagcggcgccgaggtgaagaagccaggcag cagcgtgaaggtgagctgcaaggccagcggcttcaccttcaccgacc agaccatccactgggtgcgccaggccccaggccagggcctggagtgg atgggctacatctacccacgcgacgacagcccaaagtacaacgagaa cttcaagggcaaggtcaccctgaccgccgacaagagcaccagcaccg cctacatggagctgagcagcctgcgcagcgaggacaccgccgtgtac tactgcgccatcccagaccgcagcggctacgcctggttcatctactg gggccagggcaccctggtgaccgtgagcagc (SEQ ID NO:167)
	QVQLVQSGAEVKKPGSSVKVSCKASGFTFTDQTIHWVRQAPGQGLEW MGYIYPRDDSPKYNENFKGKVTLTADKSTSTAYMELSSLRSEDTAVY YCAIPDRSGYAWFIYWGQGTLVTVSS (SEQ ID NO:168)
6B8CVH-36	Caggtgcagctggtgcagagcggcgccgaggtgaagaagccaggcag cagcgtgaagaccagctgcaaggccagcggcggcaccttcaccgacc agaccatccactgggtgcgccagcgcccaggccagggcctggagtgg atgggctacatctacccacgcgacgacagcccaaagtacaacgagaa cttcaagggccgcgtcaccatcaccgccgacaagagcaccagcaccg cctacatggagctgagcagcctgcgcagcgaggacaccgccgtgtac tactgcgccatcccagaccgcagcggctacgcctggttcatctactg gggccagggcaccctggtgaccgtgagcagc (SEQ ID NO:169)
	QVQLVQSGAEVKKPGSSVKTSCKASGGTFTDQTIHWVRQRPGQGLEW MGYIYPRDDSPKYNENFKGRVTITADKSTSTAYMELSSLRSEDTAVY YCAIPDRSGYAWFIYWGQGTLVTVSS (SEQ ID NO:170)

6B8CVH-65	Caggtgcagctggtgcagagcggcgccgaggtgaagaagccaggcag cagcgtgaaggtgagctgcaaggccagcggcggcaccttcaccgacc agaccatccactgggtgcgccaggccccaggccagggcctggagtgg atgggctacatctacccacgcgacgacagcccaaagtacaacgagaa tttcaagggccgcgtcaccctgaccgccgacaagagcaccagcaccg cctacatggagctgagcagcctgcgcagcgaggacaccgccgtgtac ttctgcgcccgcccagaccgcagcggctacgcctggttcatctactg gggccagggcaccctggtgaccgtgagcagc (SEQ ID NO:171)
	QVQLVQSGAEVKKPGSSVKVSCKASGGTFTDQTIHWVRQAPGQGLEW MGYIYPRDDSPKYNENFKGRVTLTADKSTSTAYMELSSLRSEDTAVY FCARPDRSGYAWFIYWGQGTLVTVSS (SEQ ID NO:172)

Table 7: Heavy and Light Chain DNA and Amino Acid Sequences for Antibodies A, B, C, and D

Antibody A	IgK light Chain #66	Gacatccagatgacccagagcccaagcagcctgagcg ccagcgtgggcgaccgcgtgaccatcacctgcaaggc cagccgcgacgtggccatcgccgtggcctggtaccag cagaagccaggcaaggtgccaaagctgctgatctact gggccagcacccgccacaccggcgtgccaagccgctt cagcggcagcggcagccgcaccgacttcaccctgacc atcagcagcctgcagccagaggacgtggccgactact tctgccaccagtacagcagctacccattcaccttcgg cagcggcaccaagctggagatcaagcgtactgtggct gcaccatctgtcttcatcttcccgccatctgatgagc agttgaaatctggaactgcctctgttgtgtgcctgct gaataacttctatcccagagaggccaaagtacagtgg aaggtggataacgccctccaatcgggtaactcccagg agagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagac tacgagaaacacaaagtctacgcctgcgaagtcaccc atcagggcctgagctcgcccgtcacaaagagcttcaa caggggagagtgt (SEQ ID NO:173)
		DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQ QKPGKVPKLLIYWASTRHTGVPSRFSGSGSRTDFTLT ISSLQPEDVADYFCHQYSSYPFTFGSGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:174)
	IgG1 KO Heavy Chain #2	Caggtgcagctggtgcagagcggcgccgaggtgaaga agccaggcagcagcgtgaaggtgagctgcaaggccag cggctacaccttcaccgaccagaccatccactggatg cgccaggccccaggccagggcctggagtggatcggct acatctacccacgcgacgacagcccaaagtacaacga gaacttcaagggcaaggtcaccatcaccgccgacaag

		agcaccagcaccgcctacatggagctgagcagcctgc gcagcgaggacaccgccgtgtactactgcgccatccc agaccgcagcggctacgcctggttcatctactggggc cagggcaccctggtgaccgtgagcagcgcctccacca agggcccatcggtcttcccctggcaccctcctccaa gagcacctctgggggcacagcggccctgggctgcctg gtcaaggactacttccccgaaccggtgacggtgtcgt ggaactcaggcgccctgaccagcggcgtgcacacctt cccggctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggca cccagacctacatctgcaacgtgaatcacaagcccag caacaccaaggtcgacaagagagttgagcccaaatct tgtgacaaaactcacacatgcccaccgtgcccagcac cagaagctgctgggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggacc cctgaggtcacatgcgtcgtggtggacgtgagccacg aagaccctgaggtcaagttcaactggtacgtggacgg cgtggaggtgcataatgccaagacaaagccgcgggag gagcagtacaacagcacgtaccgtgtggtcagcgtcc tcaccgtcctgcaccaggactggctgaatggcaagga gtacaagtgcaaggtctccaacaaagccctcccagcc cccatcgagaaaaccatctccaaagccaaagggcagc cccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgc ctggtcaaaggcttctatcccagcgacatcgccgtgg agtgggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctccttc ttcctctacagcaagctcaccgtggacaagagcaggt ggcagcaggggaacgtcttctcatgctccgtgatgca tgaggctctgcacaaccactacacgcagaagagcctc tccctgtctccgggt (SEQ ID NO:175)
		QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDQTIHWM RQAPGQGLEWIGYIYPRDDSPKYNENFKGKVTITADK STSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL

		VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG (SEQ ID NO:176)
Antibody B	IgK light Chain #66	(SEQ ID NO:173)
		(SEQ ID NO:174)
	IgG1KO Heavy Chain #5	caggtgcagctggtgcagagcggcgccgaggtgaaga agccaggcagcagcgtgaaggtgagctgcaaggccag cggcttcaccttcaccgaccagaccatccactgggtg cgccaggccccaggccagggcctggagtggatgggct acatctacccacgcgacgacagcccaaagtacaacga gaacttcaagggcaaggtcaccctgaccgccgacaag agcaccagcaccgcctacatggagctgagcagcctgc gcagcgaggacaccgccgtgtactactgcgccatccc agaccgcagcggctacgcctggttcatctactggggc cagggcaccctggtgaccgtgagcagcgcctccacca agggcccatcggtcttcccccctggcaccctcctccaa gagcacctctgggggcacagcggccctgggctgcctg gtcaaggactacttccccgaaccggtgacggtgtcgt ggaactcaggcgccctgaccagcggcgtgcacacctt cccggctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggca cccagacctacatctgcaacgtgaatcacaagcccag

		caacaccaaggtcgacaagagagttgagcccaaatct tgtgacaaaactcacacatgcccaccgtgcccagcac cagaagctgctggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggacc cctgaggtcacatgcgtcgtggtggacgtgagccacg aagaccctgaggtcaagttcaactggtacgtggacgg cgtggaggtgcataatgccaagacaaagccgcgggag gagcagtacaacagcacgtaccgtgtggtcagcgtcc tcaccgtcctgcaccaggactggctgaatggcaagga gtacaagtgcaaggtctccaacaaagccctcccagcc cccatcgagaaaaccatctccaaagccaaagggcagc cccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgc ctggtcaaaggcttctatcccagcgacatcgccgtgg agtgggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctccttc ttcctctacagcaagctcaccgtggacaagagcaggt ggcagcaggggaacgtcttctcatgctccgtgatgca tgaggctctgcacaaccactacacgcagaagagcctc tccctgtctccgggt (SEQ ID NO:177)
		QVQLVQSGAEVKKPGSSVKVSCKASGFTFTDQTIHWV RQAPGQGLEWMGYIYPRDDSPKYNENFKGKVTLTADK STSTAYMELSSLRSEDTAVYYCAIPDRSGYAWFIYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG (SEQ ID NO:178)

Antibody C	IgK light Chain #65	Gacatccagatgacccagagcccaagcagcctgagcg ccagcgtgggcgaccgcgtgaccatcacctgcaaggc cagccgcgacgtggccatcgccgtggcctggtaccag cagaagccaggcaaggtgccaaagctgctgctgttct gggccagcacccgccacaccggcgtgccagaccgctt cagcggcagcggcagcggcaccgacttcaccctgacc atcagcagcctgcagccagaggacctggccgactact actgccaccagtacagcagctacccattcaccttcgg ccagggcaccaagctggagatcaagcgtactgtggct gcaccatctgtcttcatcttcccgccatctgatgagc agttgaaatctggaactgcctctgttgtgtgcctgct gaataacttctatcccagagaggccaaagtacagtgg aaggtggataacgccctccaatcgggtaactcccagg agagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagac tacgagaaacacaaagtctacgcctgcgaagtcaccc atcagggcctgagctcgcccgtcacaaagagcttcaa caggggagagtgt (SEQ ID NO:179)
		DIQMTQSPSSLSASVGDRVTITCKASRDVAIAVAWYQ QKPGKVPKLLLFWASTRHTGVPDRFSGSGSGTDFTLT ISSLQPEDLADYYCHQYSSYPFTFGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:180)
	IgG1KO Heavy Chain #2	(SEQ ID NO:175)
		(SEQ ID NO:176)

Antibody D	IgK light Chain #65	(SEQ ID NO:179)
		(SEQ ID NO:180)
	IgG1KO Heavy Chain #5	(SEQ ID NO:177)
		(SEQ ID NO:178)

Light chains and heavy chain variable regions of Antibodies A, B, C, and D are underlined in Table 7 above.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention has at least one of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, 4, 5, 6, 7, 8, 9, 10, or 11 of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- K_D for human IL-23 ≤ 1 pM (no shift in binding on-rate in 50% human serum)
- Blocks IL-23 binding to human IL-23R/Fc in vitro
- No binding to human IL-12
- Inhibits human IL-23 induced IL-17 production in mouse splenocytes with IC_{50}'s ≤ 20 pM
- Inhibits human IL-23 induced STAT3 phosphorylation in human DB cells with IC_{50}'s ≤ 40 pM
- No predicted activity in ADCC/CDC
- K_D ≤1 pM for cynomolgus monkey IL-23
- No cross reactivity to mouse or rat IL-23
- Inhibits human IL-23 induced IL-17 and IL-22 production in mouse ear (≥80% inhibition of both cytokines at 1 mg/kg)
- Stability 83°C (melting temperature 83°C as determined by differential scanning calorimetry)
- Solubility ≥100 mg/ml (as measured by UV spectroscopy and monitored by turbidity)
- Subcutaneous administration of 1.0 mg/kg in three cynomolgus monkeys shows sustained ≥ 10 nM exposure for approximately 28 days with a bioavailability of approximately 70%.

By no predicted activity in ADCC/DC, it is meant herein that a humanized anti-IL-23p19 antibody of the present invention has reduced affinity to Fc receptor and therefore is predicted not to have activity in ADCC/CDC.

In one aspect, a humanized anti-IL-23p19 antibody of the present invention has at least one of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, 4, 5, 6, 7, 8, 9, or 10 of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- K_D for human IL-23 ≤ 1 pM (no shift in binding on-rate in 50% human serum)
- Blocks IL-23 binding to human IL-23R/Fc in vitro
- No binding to human IL-12
- Inhibits human IL-23 induced IL-17 production in mouse splenocytes with IC_{50}'s ≤ 20 pM
- Inhibits human IL-23 induced STAT3 phosphorylation in human DB cells with IC_{50}'s ≤ 40 pM
- No predicted activity in ADCC/CDC
- K_D ≤1 pM for cynomolgus monkey IL-23
- No cross reactivity to mouse or rat IL-23
- Inhibits human IL-23 induced IL-17 and IL-22 production in mouse ear (≥80% inhibition of both cytokines at 1 mg/kg)
- Stability 83°C (melting temperature 83°C as determined by differential scanning calorimetry)
- Solubility ≥100 mg/ml (as measured by UV spectroscopy and monitored by turbidity).

In a further aspect, a humanized antibody of the present invention has at least one of the following binding properties (properties A). In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- K_D for human IL-23 ≤ 1 pM (no shift in binding on-rate in 50% human serum)
- No binding to human IL-12
- K_D ≤1 pM for cynomolgus monkey IL-23
- No cross reactivity to mouse or rat IL-23.

In particular, a humanized antibody of the present invention has a K_D for human IL-23 ≤ 1 pM (no shift in binding on-rate in 50% human serum) and no binding to human IL-12.

In a further aspect, a humanized antibody of the present invention has at least one of the following functional properties (properties B). In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- Blocks IL-23 binding to human IL-23R/Fc in vitro
- Inhibits human IL-23 induced IL-17 production in mouse splenocytes with IC_{50}'s ≤ 20 pM
- Inhibits human IL-23 induced STAT3 phosphorylation in human DB cells with IC_{50}'s ≤ 40 pM
- Inhibits human IL-23 induced IL-17 and IL-22 production in mouse ear (≥80% inhibition of both cytokines at 1 mg/kg).

In a further aspect, a humanized antibody of the present invention has at least one of the following properties (properties C). In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- No predicted activity in ADCC/CDC
- Stability 83°C (melting temperature 83°C as determined by differential scanning calorimetry)
- Solubility ≥100 mg/ml (as measured by UV spectroscopy and monitored by turbidity)
- Subcutaneous administration of 1.0 mg/kg in three cynomolgus monkeys shows sustained ≥ 10 nM exposure for approximately 28 days with a bioavailability of approximately 70%.

In a further aspect, a humanized antibody of the present invention has at least one of the following properties (properties C). In a further aspect, a humanized anti-IL-23p19

antibody of the present invention has any combination of at least two of the properties below. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has all the properties below.

- No predicted activity in ADCC/CDC
- Stability 83°C (melting temperature 83°C as determined by differential scanning calorimetry)
- Solubility ≥100 mg/ml (as measured by UV spectroscopy and monitored by turbidity).

In a further aspect, a humanized antibody of the present invention has at least one property A, at least one property B and at least one property C. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention has any combination of at least two, or at least 3, of the properties A, B, and C.

In some aspects, the humanized antibody displays blocking activity, whereby it decreases the binding of IL-23 to IL-23 receptor by at least 45%, by at least 50%, by at least 55%, by at least 60%, by at least 65%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, or by at least 95%. The ability of an antibody to block binding of IL-23 to the IL-23 receptor can be measured using competitive binding assays known in the art. Alternatively, the blocking activity of an antibody can be measured by assessing the biological effects of IL-23, such as the production of IL-17 and IL-22 to determine if signaling mediated by the IL-23 receptor is inhibited.

In a further aspect, the present invention provides a humanized anti-IL-23p19 antibody having favorable biophysical properties. In one aspect, a humanized anti-IL-23p19 antibody of the present invention is present in at least 90% monomer form, or in at least 92% monomer form, or in at least 95% monomer form in a buffer. In a further aspect, a humanized anti-IL-23p19 antibody of the present invention remains in at least 90% monomer form, or in at least 92% monomer form, or in at least 95% monomer form in a buffer for one month or for four months.

In one aspect, a humanized antibody of the present invention is Antibody A, Antibody B, Antibody C or Antibody D. Accordingly, in one embodiment, a humanized antibody of the

present invention comprises the light chain sequence of SEQ ID NO:174 and the heavy chain sequence of SEQ ID NO:176 (Antibody A). In another embodiment, a humanized antibody of the present invention comprises the light chain sequence of SEQ ID NO:174 and the heavy chain sequence of SEQ ID NO:178 (Antibody B). In another embodiment, a humanized antibody of the present invention comprises the light chain sequence of SEQ ID NO:180 and the heavy chain sequence of SEQ ID NO:176 (Antibody C). In another embodiment, a humanized antibody of the present invention comprises the light chain sequence of SEQ ID NO:180 and the heavy chain sequence of SEQ ID NO:178 (Antibody D).

In a further embodiment, a humanized antibody of the present invention consists of the light chain sequence of SEQ ID NO:174 and the heavy chain sequence of SEQ ID NO:176 (Antibody A). In a further embodiment, a humanized antibody of the present invention consists of the light chain sequence of SEQ ID NO:174 and the heavy chain sequence of SEQ ID NO:178 (Antibody B). In a further embodiment, a humanized antibody of the present invention consists of the light chain sequence of SEQ ID NO:180 and the heavy chain sequence of SEQ ID NO:176 (Antibody C). In a further embodiment, a humanized antibody of the present invention consists of the light chain sequence of SEQ ID NO:180 and the heavy chain sequence of SEQ ID NO:178 (Antibody D).

In some embodiments, the humanized anti-IL-23p19 antibodies, including antigen-binding fragments thereof, such as heavy and light chain variable regions, comprise an amino acid sequence of the residues derived from Antibody A (light chain sequence = SEQ ID NO:174; heavy chain sequence = SEQ ID NO:176), Antibody B (light chain sequence = SEQ ID NO:174; heavy chain sequence = SEQ ID NO:178), Antibody C (light chain sequence = SEQ ID NO:180; heavy chain sequence = SEQ ID NO:176) or Antibody D (light chain sequence = SEQ ID NO:180; heavy chain sequence = SEQ ID NO:178).

In a further embodiment, the present invention provides an anti-IL-23p19 antibody or an antigen-binding fragment thereof that binds to human IL-23p19 at an epitope consisting of amino acid residues 108 to 126 and amino acid residues 137 to 151 of SEQ ID NO: 181.

In a further embodiment, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with an antibody of the present invention, for example Antibody A, Antibody B, Antibody C or Antibody D described herein. The ability of an antibody or antigen-binding fragment to competitively bind to IL-23p19 can be measured using competitive binding assays known in the art.

The humanized anti-IL-23p19 antibodies optionally include specific amino acid substitutions in the consensus or germline framework regions. The specific substitution of amino acid residues in these framework positions can improve various aspects of antibody performance including binding affinity and/or stability, over that demonstrated in humanized antibodies formed by "direct swap" of CDRs or HVLs into the human germline framework regions.

In some embodiments, the present invention describes other monoclonal antibodies with a light chain variable region having the amino acid sequence set forth in of SEQ ID NO: 84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119. In some embodiments, the present invention describes other monoclonal antibodies with a heavy chain variable region having the amino acid sequence set forth in of SEQ ID NO: 121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156 (see Tables 1 and 2 above). The CDR sequence of these mouse antibodies are shown in Tables 3 and 4. Placing such CDRs into FRs of the human consensus heavy and light chain variable domains will yield useful humanized antibodies of the present invention.

In particular, the present invention provides monoclonal antibodies with the combinations of light chain variable and heavy chain variable regions of SEQ ID NO:84/121, 86/123, 88/125, 90/127, 91/128, 93/130, 95/132, 97/134, 99/136, 101/138, 103/140, 105/142, 107/144, 109/146, 111/148, 113/150, 115/152, 117/154 or 119/156. Such variable regions can be combined with human constant regions.

In some embodiments, the present invention describes other humanized antibodies with light chain variable region sequences having the amino acid sequence set forth in of

SEQ ID NO:158, 160, 162 or 164. In some embodiments, the present invention describes other humanized antibodies with heavy chain variable region sequences having the amino acid sequence set forth in of SEQ ID NO:166, 168, 170 or 172 (see Tables 5 and 6 above). The CDR sequences of these antibodies are shown in Tables 3 and 4. In particular, the present invention provides monoclonal antibodies with the combinations of light chain variable and heavy chain variable regions of SEQ ID NO: 160/166, 160/168, 158/166 or 158/168. Such variable regions can be combined with human constant regions.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:160 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:160 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:166 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:166. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:160 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:160 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:168 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:168. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:158 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:158 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:166 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:166. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody.

In a further embodiment, the present invention relates to an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a humanized light chain variable domain comprising the CDRs of SEQ ID NO:158 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:158 and a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:168 and framework regions having an amino acid sequence at least 90% identical, at least 93% identical or at least 95% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:168. In one embodiment, the anti-IL-23p19 antibody is a humanized monoclonal antibody.

In some specific embodiments, the humanized anti-IL-23p19 antibodies disclosed herein comprise at least a heavy or a light chain variable domain comprising the CDRs or HVLs of the murine monoclonal antibodies or humanized antibodies as shown in Tables 1 through 6 above and the FRs of the human germline heavy and light chain variable domains.

The CDRs of these sequences are shown in Tables 3 and 4. Accordingly, in one aspect, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a light chain CDR1 (L-CDR1) sequence of SEQ ID NO:1, 4,

6, 7, 8, 11, 15, 18, 19, 22, 27 or 30; a light chain CDR2 (L-CDR2) sequence of SEQ ID NO:2, 5, 9, 12, 16, 20, 23, 25, 28 or 31; a light chain CDR3 (L-CDR3) sequence of SEQ ID NO:3, 10, 13, 14, 17, 21, 24, 26, 29, or 32; a heavy chain CDR1 (H-CDR1) sequence of SEQ ID NO:33, 36, 38, 40, 43, 45, 48, 51, 54, 57, 60, 63, 66, 67, 68, 69, 77 or 80; a heavy chain CDR2 (H-CDR2) sequence of SEQ ID NO:34, 39, 41, 46, 49, 52, 55, 58, 61, 64, 70, 72, 73, 75, 78 or 81; and a heavy chain CDR3 (H-CDR3) sequence of SEQ ID NO:35, 37, 42, 44, 47, 50, 53, 56, 59, 62, 65, 71, 74, 76, 79 or 82. In one aspect, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises a light chain variable region comprising a L-CDR1 listed above, a L-CDR2 listed above and a L-CDR3 listed above, and a heavy chain variable region comprising a H-CDR1 listed above, a H-CDR2 listed above and a H-CDR3 listed above.

In a further aspect, the present invention provides an anti-IL-23p19 antibody or antigen-binding fragment thereof comprising:

a) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 33, 34, and 35, respectively; or

b) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:4, 5, 3, 36, 34 and 37, respectively; or

c) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 38, 39 and 35, respectively; or

d) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:6, 2, 3, 40, 41 and 42, respectively; or

e) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 3, 43, 41 and 44, respectively; or

f) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 46 and 47, respectively; or

g) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 48, 49 and 50, respectively; or

h) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:11, 12, 13, 51, 52 and 53, respectively; or

i) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 14, 54, 55 and 56, respectively; or

j) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:15, 16, 17, 57, 58 and 59, respectively; or

k) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:18, 16, 17, 60, 61 and 62, respectively; or

l) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:19, 20, 21, 63, 66, 67 or 68, 64 and 65, respectively; or

m) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 23, 24, 69, 70 and 71, respectively; or

n) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 25, 26, 55, 72 and 71, respectively; or

o) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 73 and 74, respectively; or

p) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:27, 28, 29, 45, 75 and 76, respectively; or

q) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 77, 78 and 79, respectively; or

r) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:30, 31, 32, 80, 81 and 82, respectively.

In one aspect, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises a light chain variable region comprising a L-CDR1, L-CDR2 and L-CDR3 combination listed above, and a heavy chain variable region comprising a H-CDR1, H-CDR2 and H-CDR3 combination listed above.

In specific embodiments, it is contemplated that chimeric antibodies with switched CDR regions (i.e., for example switching one or two CDRs of one of the mouse antibodies or humanized antibody derived therefrom with the analogous CDR from another mouse antibody or humanized antibody derived therefrom) between these exemplary immunoglobulins may yield useful antibodies.

In certain embodiments, the humanized anti-IL-23p19 antibody is an antibody fragment. Various antibody fragments have been generally discussed above and there are

techniques that have been developed for the production of antibody fragments. Fragments can be derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., 1992, Journal of Biochemical and Biophysical Methods 24:107-117; and Brennan et al., 1985, Science 229:81). Alternatively, the fragments can be produced directly in recombinant host cells. For example, Fab'-SH fragments can be directly recovered from E. coli and chemically coupled to form $F(ab')_2$ fragments (see, e.g., Carter et al., 1992, Bio/Technology 10:163-167). By another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. Accordingly, in one aspect, the present invention provides antibody fragments comprising the CDRs described herein, in particular one of the combinations of L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2 and H-CDR3 described herein. In a further aspect, the present invention provides antibody fragments comprising the variable regions described herein, for example one of the combinations of light chain variable regions and heavy chain variable regions described herein.

Certain embodiments include an $F(ab')_2$ fragment of a humanized anti-IL-23p19 antibody comprise a light chain sequence of any of SEQ ID NO: 174 or 180 in combination with a heavy chain sequence of SEQ ID NO: 176 or 178. Such embodiments can include an intact antibody comprising such an $F(ab')_2$.

In some embodiments, the antibody or antibody fragment includes a constant region that mediates effector function. The constant region can provide antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and/or complement-dependent cytotoxicity (CDC) responses against an IL-23 expressing target cell. The effector domain(s) can be, for example, an Fc region of an Ig molecule.

The effector domain of an antibody can be from any suitable vertebrate animal species and isotypes. The isotypes from different animal species differ in the abilities to mediate effector functions. For example, the ability of human immunoglobulin to mediate CDC and ADCC/ADCP is generally in the order of $IgM \approx IgG_1 \approx IgG_3 > IgG_2 > IgG_4$ and $IgG_1 \approx IgG_3 > IgG_2/IgM/IgG_4$, respectively. Murine immunoglobulins mediate CDC and ADCC/ADCP generally in the order of murine $IgM \approx IgG_3 >> IgG_{2b} > IgG_{2a} >> IgG_1$ and

IgG_{2b}>IgG_{2a}>IgG_1>>IgG_3, respectively. In another example, murine IgG_{2a} mediates ADCC while both murine IgG_{2a} and IgM mediate CDC.

Antibody Modifications

The humanized anti-IL-23p19 antibodies and agents can include modifications of the humanized anti-IL-23p19 antibody or antigen-binding fragment thereof. For example, it may be desirable to modify the antibody with respect to effector function, so as to enhance the effectiveness of the antibody in treating cancer. One such modification is the introduction of cysteine residue(s) into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and/or antibody-dependent cellular cytotoxicity (ADCC). See, for example, Caron et al., 1992, J. Exp Med. 176:1191-1195; and Shopes, 1992, J. Immunol. 148:2918-2922. Homodimeric antibodies having enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al., 1993, Cancer Research 53: 2560-2565. Alternatively, an antibody can be engineered to contain dual Fc regions, enhancing complement lysis and ADCC capabilities of the antibody. See Stevenson et al., 1989, Anti-Cancer Drug Design 3: 219-230.

Antibodies with improved ability to support ADCC have been generated by modifying the glycosylation pattern of their Fc region. This is possible since antibody glycosylation at the asparagine residue, N297, in the C_{H2} domain is involved in the interaction between IgG and Fcγ receptors prerequisite to ADCC. Host cell lines have been engineered to express antibodies with altered glycosylation, such as increased bisecting N-acetylglucosamine or reduced fucose. Fucose reduction provides greater enhancement to ADCC activity than does increasing the presence of bisecting N-acetylglucosamine. Moreover, enhancement of ADCC by low fucose antibodies is independent of the FcγRIIIa V/F polymorphism.

Modifying the amino acid sequence of the Fc region of antibodies is an alternative to glycosylation engineering to enhance ADCC. The binding site on human IgG_1 for Fcγ receptors has been determined by extensive mutational analysis. This led to the

generation of humanized IgG_1 antibodies with Fc mutations that increase the binding affinity for FcγRIIIa and enhance ADCC in vitro. Additionally, Fc variants have been obtained with many different permutations of binding properties, e.g., improved binding to specific FcγR receptors with unchanged or diminished binding to other FcγR receptors.

Another aspect includes immunoconjugates comprising the humanized antibody or fragments thereof conjugated to a cytotoxic agent such as a chemotherapeutic agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used to form useful immunoconjugates include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), Momordica charantia inhibitor, curcin, crotin, Sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, the tricothecenes, and the like. A variety of radionuclides are available for the production of radioconjugated humanized anti-IL-23p19 antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the humanized anti-IL-23p19 antibody and cytotoxic or chemotherapeutic agent can be made by known methods, using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., 1987, Science 238:1098. Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent

for conjugation of radionucleotide to the antibody. Conjugates also can be formed with a cleavable linker.

The humanized anti-IL-23p19 antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., 1985, Proc. Natl. Acad. Sci. USA 82:3688; Hwang et al., 1980, Proc. Natl. Acad. Sci. USA 77:4030; and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes having enhanced circulation time are disclosed, for example, in U.S. Pat. No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of an antibody disclosed herein can be conjugated to the liposomes as described in Martin et al., 1982, J. Biol. Chem. 257:286-288 via a disulfide interchange reaction. A chemotherapeutic agent (such as doxorubicin) is optionally contained within the liposome. See, e.g., Gabizon et al., 1989, J. National Cancer Inst. 81(19):1484.

The antibodies described and disclosed herein can also be used in ADEPT (Antibody-Directed Enzyme Prodrug Therapy) procedures by conjugating the antibody to a prodrug-activating enzyme that converts a prodrug (e.g., a peptidyl chemotherapeutic agent), to an active anti-cancer drug. See, for example, WO 81/01145, WO 88/07378, and U.S. Pat. No. 4,975,278. The enzyme component of the immunoconjugate useful for ADEPT is an enzyme capable of acting on a prodrug in such a way so as to covert it into its more active, cytotoxic form. Specific enzymes that are useful in ADEPT include, but are not limited to, alkaline phosphatase for converting phosphate-containing prodrugs into free drugs; arylsulfatase for converting sulfate-containing prodrugs into free drugs; cytosine deaminase for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases, and cathepsins (such as cathepsins B and L), for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, for converting prodrugs containing D-amino acid substituents; carbohydrate-cleaving enzymes such as

β-galactosidase and neuraminidase for converting glycosylated prodrugs into free drugs; β-lactamase for converting drugs derivatized with β-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies having enzymatic activity ("abzymes") can be used to convert the prodrugs into free active drugs (see, for example, Massey, 1987, Nature 328: 457-458). Antibody-abzyme conjugates can be prepared by known methods for delivery of the abzyme to a tumor cell population, for example, by covalently binding the enzyme to the humanized anti-IL-23p19antibody/heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody disclosed herein linked to at least a functionally active portion of an enzyme as described above can be constructed using recombinant DNA techniques (see, e.g., Neuberger et al., 1984, Nature 312:604-608).

In certain embodiments, it may be desirable to use a humanized anti-IL-23p19 antibody fragment, rather than an intact antibody, to increase tissue penetration, for example. It may be desirable to modify the antibody fragment in order to increase its serum half life. This can be achieved, for example, by incorporation of a salvage receptor binding epitope into the antibody fragment. In one method, the appropriate region of the antibody fragment can be altered (e.g., mutated), or the epitope can be incorporated into a peptide tag that is then fused to the antibody fragment at either end or in the middle, for example, by DNA or peptide synthesis. See, e.g., WO 96/32478.

In other embodiments, covalent modifications of the humanized anti-IL-23p19 antibody are also included. Covalent modifications include modification of cysteinyl residues, histidyl residues, lysinyl and amino-terminal residues, arginyl residues, tyrosyl residues, carboxyl side groups (aspartyl or glutamyl), glutaminyl and asparaginyl residues, or seryl, or threonyl residues. Another type of covalent modification involves chemically or enzymatically coupling glycosides to the antibody. Such modifications may be made by chemical synthesis or by enzymatic or chemical cleavage of the antibody, if applicable. Other types of covalent modifications of the antibody can be introduced into the

molecule by reacting targeted amino acid residues of the antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the amino- or carboxy-terminal residues.

Removal of any carbohydrate moieties present on the antibody can be accomplished chemically or enzymatically. Chemical deglycosylation is described by Hakimuddin et al., 1987, Arch. Biochem. Biophys. 259:52 and by Edge et al., 1981, Anal. Biochem., 118:131. Enzymatic cleavage of carbohydrate moieties on antibodies can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., 1987, Meth. Enzymol 138:350.

Another type of useful covalent modification comprises linking the antibody to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in one or more of U.S. Pat. No. 4,640,835, U.S. Pat. No. 4,496,689, U.S. Pat. No. 4,301,144, U.S. Pat. No. 4,670,417, U.S. Pat. No. 4,791,192 and U.S. Pat. No. 4,179,337.

Humanization and Amino Acid Sequence Variants

Amino acid sequence variants of the anti-IL-23p19 antibody can be prepared by introducing appropriate nucleotide changes into the anti-IL-23p19 antibody DNA, or by peptide synthesis. Such variants include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-IL-23p19 antibodies of the examples herein. Any combination of deletions, insertions, and substitutions is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the humanized or variant anti-IL-23p19 antibody, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions of the anti-IL-23p19 antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis," as described by Cunningham and Wells (Science, 244:1081-1085 (1989)). Here, a residue or group of target residues are identified (e.g., charged residues

such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (typically alanine) to affect the interaction of the amino acids with IL-23p19 antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation per se need not be predetermined. For example, to analyze the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the expressed anti-IL-23p19 antibody variants are screened for the desired activity.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an anti-IL-23p19 antibody fused to an epitope tag. Other insertional variants of the anti-IL-23p19 antibody molecule include a fusion to the N- or C-terminus of the anti-IL-23p19 antibody of an enzyme or a polypeptide which increases the serum half-life of the antibody.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the anti-IL-23p19 antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 5 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions", or as further described below in reference to amino acid classes, may be introduced and the products screened.

TABLE 8:

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)		val; leu; ile **val**
Arg (R)		lys; gln; asn **lys**

Asn (N)	**gln**	gln; his; asp, lys; arg
Asp (D)		glu; asn **glu**
Cys (C)		ser; ala **ser**
Gln (Q)		asn; glu **asn**
Glu (E)		asp; gln **asp**
Gly (G)		ala **ala**
His (H)	**arg**	arg; asn; gln; lys;
Ile (I) phe; norleucine	**leu**	leu; val; met; ala;
Leu (L) met; ala; phe	**ile**	ile; norleucine; val;
Lys (K)		arg; gln; asn **arg**
Met (M)		leu; phe; ile **leu**
Phe (F)	**tyr**	tyr; leu; val; ile; ala;
Pro (P)		ala **ala**
Ser (S)		thr **thr**
Thr (T)		ser **ser**
Trp (W)		tyr; phe **tyr**
Tyr (Y)	**phe**	phe;trp; thr; ser
Val (V) ala; norleucine;	**leu**	leu; ile; met; phe

In protein chemistry, it is generally accepted that the biological properties of the antibody can be accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gin, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the humanized or variant anti-IL-23p19 antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule, prevent aberrant crosslinking, or provide for established points of conjugation to a cytotoxic or cytostatic compound. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

A type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants is affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the

gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity). In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or in addition, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and human IL-23p19. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Another type of amino acid variant of the antibody alters the original glycosylation pattern of the antibody. By "altering" is meant deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more glycosylation sites that are not present in the antibody.

In some embodiments, it may be desirable to modify the antibodies of the invention to add glycosylations sites. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. 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. Thus, in order to glycosylate a given protein, e.g., an antibody, the amino acid sequence of the protein is engineered to contain one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

Nucleic acid molecules encoding amino acid sequence variants of the anti-IL-23p19 antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-IL-23p19 antibody.

Polynucleotides, Vectors, Host Cells, and Recombinant Methods

Other embodiments encompass isolated polynucleotides that comprise a sequence encoding a humanized anti-IL-23p19 antibody, vectors, and host cells comprising the polynucleotides, and recombinant techniques for production of the humanized antibody. The isolated polynucleotides can encode any desired form of the anti-IL-23p19 antibody including, for example, full length monoclonal antibodies, Fab, Fab', $F(ab')_2$, and Fv fragments, diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments.

Some embodiments include isolated polynucleotides comprising sequences that encode the light chain variable region of an antibody or antibody fragment having the amino acid sequence of any of SEQ ID NO: SEQ ID NO:84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO:83, 85, 87, 89, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116 and 118. Some embodiments include isolated polynucleotides comprising sequences that encode the heavy chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID NO:121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO: 120, 122, 124, 126, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 or 155.

Some embodiments include isolated polynucleotides comprising sequences that encode the light chain variable region of an antibody or antibody fragment having the amino acid sequence of any of SEQ ID NO:158, 160, 162 or 164. Exemplary polynucleotide

sequences encoding such amino acid sequences are SEQ ID NO:157, 159, 161 or 163. Some embodiments include isolated polynucleotides comprising sequences that encode the heavy chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID NO: 166, 168, 170 or 172. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO: 165, 167, 169 or 171.

Some embodiments include isolated polynucleotides comprising sequences that encode the light chain of an antibody having the amino acid sequence of any of SEQ ID NO:174 or 180. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO:173 or 179. Some embodiments include isolated polynucleotides comprising sequences that encode the heavy chain of an antibody having the amino acid sequence of SEQ ID NO:176 or 178. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO:175 or 177.

In one aspect, the isolated polynucleotide sequence(s) encodes an antibody or antibody fragment having a light chain and a heavy chain variable region comprising the amino acid sequences of SEQ ID NO:174 and SEQ ID NO:176, respectively; SEQ ID NO:174 and SEQ ID NO:178, respectively; SEQ ID NO:180 and SEQ ID NO:176, respectively; SEQ ID NO:180 and SEQ ID NO:178, respectively. Exemplary polynucleotide sequences encoding such amino acid sequences are SEQ ID NO: 173 and 175, respectively, SEQ ID NO: 173 and 177, respectively, SEQ ID NO: 179 and 175, respectively, SEQ ID NO: 179 and 177, respectively.

The polynucleotide(s) that comprise a sequence encoding a humanized anti-IL-23p19 antibody or a fragment or chain thereof can be fused to one or more regulatory or control sequence, as known in the art, and can be contained in suitable expression vectors or host cell as known in the art. Each of the polynucleotide molecules encoding the heavy or light chain variable domains can be independently fused to a polynucleotide sequence encoding a constant domain, such as a human constant domain, enabling the production of intact antibodies. Alternatively, polynucleotides, or portions thereof, can be fused together, providing a template for production of a single chain antibody.

For recombinant production, a polynucleotide encoding the antibody is inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Many suitable vectors for expressing the recombinant antibody are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence.

The humanized anti-IL-23p19 antibodies can also be produced as fusion polypeptides, in which the antibody is fused with a heterologous polypeptide, such as a signal sequence or other polypeptide having a specific cleavage site at the amino terminus of the mature protein or polypeptide. The heterologous signal sequence selected is typically one that is recognized and processed (i.e., cleaved by a signal peptidase) by the host cell. For prokaryotic host cells that do not recognize and process the humanized anti-IL-23p19 antibody signal sequence, the signal sequence can be substituted by a prokaryotic signal sequence. The signal sequence can be, for example, alkaline phosphatase, penicillinase, lipoprotein, heat-stable enterotoxin II leaders, and the like. For yeast secretion, the native signal sequence can be substituted, for example, with a leader sequence obtained from yeast invertase alpha-factor (including Saccharomyces and Kluyveromyces α-factor leaders), acid phosphatase, C. albicans glucoamylase, or the signal described in WO90/13646. In mammalian cells, mammalian signal sequences as well as viral secretory leaders, for example, the herpes simplex gD signal, can be used. The DNA for such precursor region is ligated in reading frame to DNA encoding the humanized anti-IL-23p19 antibody.

Expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Generally, in cloning vectors this sequence is one that enables the vector to replicate independently of the host chromosomal DNA, and includes origins of replication or autonomously replicating sequences. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2-υ. plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV, and BPV) are useful for cloning vectors in mammalian cells.

Generally, the origin of replication component is not needed for mammalian expression vectors (the SV40 origin may typically be used only because it contains the early promoter).

Expression and cloning vectors may contain a gene that encodes a selectable marker to facilitate identification of expression. Typical selectable marker genes encode proteins that confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, or alternatively, are complement auxotrophic deficiencies, or in other alternatives supply specific nutrients that are not present in complex media, e.g., the gene encoding D-alanine racemase for Bacilli.

One example of a selection scheme utilizes a drug to arrest growth of a host cell. Those cells that are successfully transformed with a heterologous gene produce a protein conferring drug resistance and thus survive the selection regimen. Examples of such dominant selection use the drugs neomycin, mycophenolic acid, and hygromycin. Common selectable markers for mammalian cells are those that enable the identification of cells competent to take up a nucleic acid encoding a humanized anti-IL-23p19 antibody, such as DHFR (dihydrofolate reductase), thymidine kinase, metallothionein-I and -II (such as primate metallothionein genes), adenosine deaminase, ornithine decarboxylase, and the like. Cells transformed with the DHFR selection gene are first identified by culturing all of the transformants in a culture medium that contains methotrexate (Mtx), a competitive antagonist of DHFR. An appropriate host cell when wild-type DHFR is employed is the Chinese hamster ovary (CHO) cell line deficient in DHFR activity (e.g., DG44).

Alternatively, host cells (particularly wild-type hosts that contain endogenous DHFR) transformed or co-transformed with DNA sequences encoding anti-IL-23p19 antibody, wild-type DHFR protein, and another selectable marker such as aminoglycoside 3'-phosphotransferase (APH), can be selected by cell growth in medium containing a selection agent for the selectable marker such as an aminoglycosidic antibiotic, e.g., kanamycin, neomycin, or G418. See, e.g., U.S. Pat. No. 4,965,199.

Where the recombinant production is performed in a yeast cell as a host cell, the TRP1 gene present in the yeast plasmid YRp7 (Stinchcomb et al., 1979, Nature 282: 39) can

be used as a selectable marker. The TRP1 gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 (Jones, 1977, Genetics 85:12). The presence of the trp1 lesion in the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan. Similarly, Leu2p-deficient yeast strains such as ATCC 20,622 and 38,626 are complemented by known plasmids bearing the LEU2 gene.

In addition, vectors derived from the 1.6 μm circular plasmid pKD1 can be used for transformation of Kluyveromyces yeasts. Alternatively, an expression system for large-scale production of recombinant calf chymosin was reported for K. lactis (Van den Berg, 1990, Bio/Technology 8:135). Stable multi-copy expression vectors for secretion of mature recombinant human serum albumin by industrial strains of Kluyveromyces have also been disclosed (Fleer et al., 1991, Bio/Technology 9:968-975).

Expression and cloning vectors usually contain a promoter that is recognized by the host organism and is operably linked to the nucleic acid molecule encoding an anti-IL-23p19 antibody or polypeptide chain thereof. Promoters suitable for use with prokaryotic hosts include phoA promoter, β-lactamase and lactose promoter systems, alkaline phosphatase, tryptophan (trp) promoter system, and hybrid promoters such as the tac promoter. Other known bacterial promoters are also suitable. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the humanized anti-IL-23p19 antibody.

Many eukaryotic promoter sequences are known. Virtually all eukaryotic genes have an AT-rich region located approximately 25 to 30 bases upstream from the site where transcription is initiated. Another sequence found 70 to 80 bases upstream from the start of transcription of many genes is a CNCAAT region where N may be any nucleotide. At the 3' end of most eukaryotic genes is an AATAAA sequence that may be the signal for addition of the poly A tail to the 3' end of the coding sequence. All of these sequences are suitably inserted into eukaryotic expression vectors.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase or other glycolytic enzymes, such as enolase,

glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Inducible promoters have the additional advantage of transcription controlled by growth conditions. These include yeast promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, derivative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657. Yeast enhancers also are advantageously used with yeast promoters.

Humanized anti-IL-23p19 antibody transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, or from heat-shock promoters, provided such promoters are compatible with the host cell systems.

The early and late promoters of the SV40 virus are conveniently obtained as an SV40 restriction fragment that also contains the SV40 viral origin of replication. The immediate early promoter of the human cytomegalovirus is conveniently obtained as a HindIII E restriction fragment. A system for expressing DNA in mammalian hosts using the bovine papilloma virus as a vector is disclosed in U.S. Pat. No. 4,419,446. A modification of this system is described in U.S. Pat. No. 4,601,978. See also Reyes et al., 1982, Nature 297:598-601, disclosing expression of human p-interferon cDNA in mouse cells under the control of a thymidine kinase promoter from herpes simplex virus. Alternatively, the Rous sarcoma virus long terminal repeat can be used as the promoter.

Another useful element that can be used in a recombinant expression vector is an enhancer sequence, which is used to increase the transcription of a DNA encoding a humanized anti-IL-23p19 antibody by higher eukaryotes. Many enhancer sequences are

now known from mammalian genes (e.g., globin, elastase, albumin, α-fetoprotein, and insulin). Typically, however, an enhancer from a eukaryotic cell virus is used. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. See also Yaniv, 1982, Nature 297:17-18 for a description of enhancing elements for activation of eukaryotic promoters. The enhancer may be spliced into the vector at a position 5' or 3' to the humanized anti-IL-23p19 antibody-encoding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) can also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-IL-23p19 antibody. One useful transcription termination component is the bovine growth hormone polyadenylation region. See WO94/11026 and the expression vector disclosed therein. In some embodiments, humanized anti-IL-23p19 antibodies can be expressed using the CHEF system. (See, e.g., U.S. Pat. No. 5,888,809; the disclosure of which is incorporated by reference herein.)

Suitable host cells for cloning or expressing the DNA in the vectors herein are the prokaryote, yeast, or higher eukaryote cells described above. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as Escherichia, e.g., E. coli, Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e.g., Salmonella typhimurium, Serratia, e.g., Serratia marcescans, and Shigella, as well as Bacilli such as B. subtilis and B. licheniformis (e.g., B. licheniformis 41 P disclosed in DD 266,710 published Apr. 12, 1989), Pseudomonas such as P. aeruginosa, and Streptomyces. One preferred E. coli cloning host is E. coli 294 (ATCC 31,446), although other strains such as E. coli B, E. coli X1776 (ATCC

31,537), and E. coli W3110 (ATCC 27,325) are suitable. These examples are illustrative rather than limiting.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for humanized anti-IL-23p19antibody-encoding vectors. Saccharomyces cerevisiae, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as Schizosaccharomyces pombe; Kluyveromyces hosts such as, e.g., K. lactis, K. fragilis (ATCC 12,424), K. bulgaricus (ATCC 16,045), K. wickeramii (ATCC 24,178), K. waltii (ATCC 56,500), K. drosophilarum (ATCC 36,906), K. thermotolerans, and K. marxianus; yarrowia (EP 402,226); Pichia pastors (EP 183,070); Candida; Trichoderma reesia (EP 244,234); Neurospora crassa; Schwanniomyces such as Schwanniomyces occidentalis; and filamentous fungi such as, e.g., Neurospora, Penicillium, Tolypocladium, and Aspergillus hosts such as A. nidulans and A. niger.

Suitable host cells for the expression of glycosylated humanized anti-IL-23p19 antibody are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells, including, e.g., numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as Spodoptera frugiperda (caterpillar), Aedes aegypti (mosquito), Aedes albopictus (mosquito), Drosophila melanogaster (fruitfly), and Bombyx mori (silk worm). A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of Autographa californica NPV and the Bm-5 strain of Bombyx mori NPV, and such viruses may be used, particularly for transfection of Spodoptera frugiperda cells.

Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco can also be utilized as hosts.

In another aspect, expression of humanized anti-IL-23p19 is carried out in vertebrate cells. The propagation of vertebrate cells in culture (tissue culture) has become routine procedure and techniques are widely available. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651), human embryonic kidney line (293 or 293 cells subcloned for growth in suspension

culture, (Graham et al., 1977, J. Gen Virol. 36: 59), baby hamster kidney cells (BHK, ATCC CCL 10), Chinese hamster ovary cells/-DHFR1 (CHO, Urlaub et al., 1980, Proc. Natl. Acad. Sci. USA 77: 4216; e.g., DG44), mouse sertoli cells (TM4, Mather, 1980, Biol. Reprod. 23:243-251), monkey kidney cells (CV1 ATCC CCL 70), African green monkey kidney cells (VERO-76, ATCC CRL-1587), human cervical carcinoma cells (HELA, ATCC CCL 2), canine kidney cells (MDCK, ATCC CCL 34), buffalo rat liver cells (BRL 3A, ATCC CRL 1442), human lung cells (W138, ATCC CCL 75), human liver cells (Hep G2, HB 8065), mouse mammary tumor (MMT 060562, ATCC CCL51), TR1 cells (Mather et al., 1982, Annals N.Y. Acad. Sci. 383: 44-68), MRC 5 cells, FS4 cells, and human hepatoma line (Hep G2).

Host cells are transformed with the above-described expression or cloning vectors for humanized anti-IL-23p19 antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

The host cells used to produce a humanized anti-IL-23p19 antibody described herein may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma-Aldrich Co., St. Louis, Mo.), Minimal Essential Medium ((MEM), (Sigma-Aldrich Co.), RPMI-1640 (Sigma-Aldrich Co.), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma-Aldrich Co.) are suitable for culturing the host cells. In addition, any of the media described in one or more of Ham et al., 1979, Meth. Enz. 58: 44, Barnes et al., 1980, Anal. Biochem. 102: 255, U.S. Pat. No. 4,767,704, U.S. Pat. No. 4,657,866, U.S. Pat. No. 4,927,762, U.S. Pat. No. 4,560,655, U.S. Pat. No. 5,122,469, WO 90/103430, and WO 87/00195 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as gentamicin), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Other supplements may also be included at appropriate concentrations that would be known to those skilled

in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, the cells may be disrupted to release protein as a first step. Particulate debris, either host cells or lysed fragments, can be removed, for example, by centrifugation or ultrafiltration. Carter et al., 1992, Bio/Technology 10:163-167 describes a procedure for isolating antibodies that are secreted to the periplasmic space of E. coli. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 minutes. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants. A variety of methods can be used to isolate the antibody from the host cell.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being a typical purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human gamma1, gamma2, or gamma4 heavy chains (see, e.g., Lindmark et al., 1983 J. Immunol. Meth. 62:1-13). Protein G is recommended for all mouse isotypes and for human gamma3 (see, e.g., Guss et al., 1986 EMBO J. 5:1567-1575). A matrix to which an affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_{H3} domain, the

Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, reverse phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, typically performed at low salt concentrations (e.g., from about 0-0.25M salt).

Also included are nucleic acids that hybridize under low, moderate, and high stringency conditions, as defined herein, to all or a portion (e.g., the portion encoding the variable region) of the nucleotide sequence represented by isolated polynucleotide sequence(s) that encode an antibody or antibody fragment of the present invention.The hybridizing portion of the hybridizing nucleic acid is typically at least 15 (e.g., 20, 25, 30 or 50) nucleotides in length. The hybridizing portion of the hybridizing nucleic acid is at least 80%, e.g., at least 90%, at least 95%, or at least 98%, identical to the sequence of a portion or all of a nucleic acid encoding an anti-IL-23p19 polypeptide (e.g., a heavy chain or light chain variable region), or its complement. Hybridizing nucleic acids of the type described herein can be used, for example, as a cloning probe, a primer, e.g., a PCR primer, or a diagnostic probe.

Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the amino acid sequence of any one of SEQ ID NO: 84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119, and that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the polynucleotide sequences of SEQ ID NO:83, 85, 87, 89, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116 or 118.

Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the amino acid sequence of any one of SEQ ID NO: 158, 160, 162 or 164, and that is at least 80%, at least 90%, at least 95%, at least

98%, or at least 99% identical to the polynucleotide sequences of SEQ ID NO:157, 159, 161 or 163.

Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the amino acid sequence of any one of SEQ ID NO: 121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156, and that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the polynucleotide sequences of SEQ ID NO: 120, 122, 124, 126, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 or 155.

Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the amino acid sequence of any one of SEQ ID NO: 166, 168, 170 or 172, and that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the polynucleotide sequences of SEQ ID NO: 165, 167, 169 or 171.

Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the light chain variable region amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NO: 84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119. Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the light chain variable region amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NO:158, 160, 162 or 164. Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the heavy chain variable region amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of any one of SEQ ID NO:121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156. Some embodiments include isolated polynucleotides including sequences that encode an antibody or antibody fragment having the heavy chain variable region amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 98%, or at least 99%

identical to the amino acid sequence of any of one SEQ ID NO:166, 168, 170 or 172. As used herein, the terms "identical" or "percent identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence. To determine the percent identity, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=# of identical positions/total # of positions (e.g., overlapping positions)x100). In some embodiments, the two sequences that are compared are the same length after gaps are introduced within the sequences, as appropriate (e.g., excluding additional sequence extending beyond the sequences being compared). For example, when variable region sequences are compared, the leader and/or constant domain sequences are not considered. For sequence comparisons between two sequences, a "corresponding" CDR refers to a CDR in the same location in both sequences (e.g., CDR-H1 of each sequence).

The determination of percent identity or percent similarity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al., 1990, J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12, to obtain nucleotide sequences homologous to a nucleic acid encoding a protein of interest. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3, to obtain amino acid sequences

homologous to protein of interest. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997, Nucleic Acids Res. 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, 1994, Comput. Appl. Biosci. 10:3-5; and FASTA described in Pearson and Lipman, 1988, Proc. Natl. Acad. Sci. USA 85:2444-8. Within FASTA, ktup is a control option that sets the sensitivity and speed of the search. If ktup=2, similar regions in the two sequences being compared are found by looking at pairs of aligned residues; if ktup=1, single aligned amino acids are examined. ktup can be set to 2 or 1 for protein sequences, or from 1 to 6 for DNA sequences. The default if ktup is not specified is 2 for proteins and 6 for DNA. Alternatively, protein sequence alignment may be carried out using the CLUSTAL W algorithm, as described by Higgins et al., 1996, Methods Enzymol. 266:383-402.

Non-Therapeutic Uses

The antibodies described herein are useful as affinity purification agents. In this process, the antibodies are immobilized on a solid phase such a Protein A resin, using methods well known in the art. The immobilized antibody is contacted with a sample containing the IL-23p19 protein (or fragment thereof) to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the IL-2319 protein, which is bound to the immobilized antibody. Finally,

the support is washed with another suitable solvent that will release the IL-23p19 protein from the antibody.

Anti-IL-23p19 antibodies, for example humanized anti-IL-23p19 antibodies, are also useful in diagnostic assays to detect and/or quantify IL-23 protein, for example, detecting IL-23 expression in specific cells, tissues, or serum. The anti-IL-23p19 antibodies can be used diagnostically to, for example, monitor the development or progression of a disease as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment and/or prevention regimen. Detection can be facilitated by coupling the anti-IL-23p19 antibody. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.

The anti-IL-23p19 antibodies can be used in methods for diagnosing an IL-23-associated disorder (e.g., a disorder characterized by abnormal expression of IL-23) or to determine if a subject has an increased risk of developing an IL-23-associated disorder. Such methods include contacting a biological sample from a subject with an IL-23p19 antibody and detecting binding of the antibody to IL-23p19. By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source of cells potentially expressing IL-23. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art.

In some embodiments, the method can further comprise comparing the level of IL-23 in a patient sample to a control sample (e.g., a subject that does not have an IL-23-associated disorder) to determine if the patient has an IL-23-associated disorder or is at risk of developing an IL-23-associated disorder.

It will be advantageous in some embodiments, for example, for diagnostic purposes to label the antibody with a detectable moiety. Numerous detectable labels are available, including radioisotopes, fluorescent labels, enzyme substrate labels and the like. The label may be indirectly conjugated with the antibody using various known techniques.

For example, the antibody can be conjugated with biotin and any of the three broad categories of labels mentioned above can be conjugated with avidin, or vice versa. Biotin binds selectively to avidin and thus, the label can be conjugated with the antibody in this indirect manner. Alternatively, to achieve indirect conjugation of the label with the antibody, the antibody can be conjugated with a small hapten (such as digoxin) and one of the different types of labels mentioned above is conjugated with an anti-hapten antibody (e.g., anti-digoxin antibody). Thus, indirect conjugation of the label with the antibody can be achieved.

Exemplary radioisotopes labels include ^{35}S, ^{14}C, ^{125}I, ^{3}H, and ^{131}I. The antibody can be labeled with the radioisotope, using the techniques described in, for example, Current Protocols in Immunology, Volumes 1 and 2, 1991, Coligen et al., Ed. Wiley-Interscience, New York, N.Y., Pubs. Radioactivity can be measured, for example, by scintillation counting.

Exemplary fluorescent labels include labels derived from rare earth chelates (europium chelates) or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, Lissamine, phycoerythrin, and Texas Red are available. The fluorescent labels can be conjugated to the antibody via known techniques, such as those disclosed in Current Protocols in Immunology, for example. Fluorescence can be quantified using a fluorimeter.

There are various well-characterized enzyme-substrate labels known in the art (see, e.g., U.S. Pat. No. 4,275,149 for a review). The enzyme generally catalyzes a chemical alteration of the chromogenic substrate that can be measured using various techniques. For example, alteration may be a color change in a substrate that can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence are described above. The chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light that can be measured, using a chemiluminometer, for example, or donates energy to a fluorescent acceptor.

Examples of enzymatic labels include luciferases such as firefly luciferase and bacterial luciferase (U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (such as glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocydic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described, for example, in O'Sullivan et al., 1981, Methods for the Preparation of Enzyme-Antibody Conjugates for use in Enzyme Immunoassay, in Methods in Enzym. (J. Langone & H. Van Vunakis, eds.), Academic press, N.Y., 73: 147-166.

Examples of enzyme-substrate combinations include, for example: Horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor such as orthophenylene diamine (OPD) or 3,3',5,5'-tetramethyl benzidine hydrochloride (TMB); alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and β-D-galactosidase (β-D-Gal) with a chromogenic substrate such as p-nitrophenyl-β-D-galactosidase or fluorogenic substrate 4-methylumbelliferyl-β-D-galactosidase.

Numerous other enzyme-substrate combinations are available to those skilled in the art. For a general review of these, see U.S. Pat. No. 4,275,149 and U.S. Pat. No. 4,318,980.

In another embodiment, the humanized anti-IL-23p19 antibody is used unlabeled and detected with a labeled antibody that binds the humanized anti-IL-23p19 antibody.

The antibodies described herein may be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. See, e.g., Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc. 1987).

The anti-IL-23p19 antibody or antigen binding fragment thereof can be used to inhibit the binding of IL-23 to the IL-23 receptor. Such methods comprise administering an anti-IL-23p19 antibody or antigen binding fragment thereof to a cell (e.g., a mammalian cell) or cellular environment, whereby signaling mediated by the IL-23 receptor is inhibited. These methods can be performed *in vitro* or *in vivo*. By "cellular environment"

is intended the tissue, medium, or extracellular matrix surrounding a cell. The anti-IL-23p19 antibody or antigen binding fragment thereof is administered to the cellular environment of a cell in such a manner that the antibody or fragment is capable of binding to IL-23 molecules outside of and surrounding the cell, therefore, preventing the binding of IL-23 to its receptor.

Diagnostic Kits

An anti-IL-23p19 antibody can be used in a diagnostic kit, i.e., a packaged combination of reagents in predetermined amounts with instructions for performing the diagnostic assay. Where the antibody is labeled with an enzyme, the kit may include substrates and cofactors required by the enzyme such as a substrate precursor that provides the detectable chromophore or fluorophore. In addition, other additives may be included such as stabilizers, buffers (for example a block buffer or lysis buffer), and the like. The relative amounts of the various reagents may be varied widely to provide for concentrations in solution of the reagents that substantially optimize the sensitivity of the assay. The reagents may be provided as dry powders, usually lyophilized, including excipients that on dissolution will provide a reagent solution having the appropriate concentration.

Therapeutic Uses

In another embodiment, a humanized anti-IL-23p19 antibody disclosed herein is useful in the treatment of various disorders associated with the expression of IL-23p19 as described herein. Methods for treating an IL-23 associated disorder comprise administering a therapeutically effective amount of a humanized anti-IL-23p19 antibody to a subject in need thereof.

The humanized anti-IL-23p19 antibody or agent is administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration (including perfusing or otherwise contacting the graft with the antibody before transplantation). The

humanized anti-IL-23p19 antibody or agent can be administered, for example, as an infusion or as a bolus. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In addition, the humanized anti-IL-23p19 antibody is suitably administered by pulse infusion, particularly with declining doses of the antibody. In one aspect, the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic.

For the prevention or treatment of disease, the appropriate dosage of antibody will depend on a variety of factors such as the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

Depending on the type and severity of the disease, about 1 µg/kg to 20 mg/kg (e.g., 0.1-15 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays. An exemplary dosing regimen is that disclosed in WO 94/04188.

The term "suppression" is used herein in the same context as "amelioration" and "alleviation" to mean a lessening of one or more characteristics of the disease.

The antibody composition will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the antibody to

be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat the disorder associated with IL-23 expression.

The antibody need not be, but is optionally, formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of humanized anti-IL-23p19 antibody present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as used hereinbefore or about from 1 to 99% of the heretofore employed dosages.

IL-23-Associated Disorders

The anti-IL-23p19 antibodies or agents are useful for treating or preventing an immunological disorder characterized by abnormal expression of IL-23, e.g., by inappropriate activation of immune cells (e.g., lymphocytes or dendritic cells). Such abnormal expression of IL-23 can be due to, for example, increased IL-23 protein levels. The anti-IL-23p19 antibodies or antigen binding fragments thereof also find use in the treatment or prevention of respiratory disorders, metabolic disorders, for example diabetes mellitus, and certain cancers. Treatment or prevention of the immunological disorder, respiratory disorder, metabolic disorder or cancer, according to the methods described herein, is achieved by administering to a subject in need of such treatment or prevention an effective amount of the anti-IL-23p19 antibody or agent, whereby the antibody decreases the activity of IL-23 associated with the disease state.

Immunological diseases that are characterized by inappropriate activation of immune cells and that can be treated or prevented by the methods described herein can be classified, for example, by the type(s) of hypersensitivity reaction(s) that underlie the disorder. These reactions are typically classified into four types: anaphylactic reactions, cytotoxic (cytolytic) reactions, immune complex reactions, or cell-mediated immunity (CMI) reactions (also referred to as delayed-type hypersensitivity (DTH) reactions). (See, e.g., Fundamental Immunology (William E. Paul ed., Raven Press, N.Y., 3rd ed. 1993).) Immunological diseases include inflammatory diseases and autoimmune diseases.

Specific examples of such immunological diseases include the following: rheumatoid arthritis, autoimmune demyelinative diseases (e.g., multiple sclerosis, allergic encephalomyelitis), endocrine opthalmopathy, uveoretinitis, systemic lupus erythematosus, myasthenia gravis, Grave's disease, glomerulonephritis, autoimmune hepatological disorder, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), anaphylaxis, allergic reaction, Sjogren's syndrome, type I diabetes mellitus, primary biliary cirrhosis, Wegener's granulomatosis, fibromyalgia, polymyositis, dermatomyositis, inflammatory myositis, multiple endocrine failure, Schmidt's syndrome, autoimmune uveitis, Addison's disease, adrenalitis, thyroiditis, Hashimoto's thyroiditis, autoimmune thyroid disease, pernicious anemia, gastric atrophy, chronic hepatitis, lupoid hepatitis, atherosclerosis, subacute cutaneous lupus erythematosus, hypoparathyroidism, Dressler's syndrome, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, pemphigus vulgaris, pemphigus, dermatitis herpetiformis, alopecia arcata, pemphigoid, scleroderma, progressive systemic sclerosis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyl), and telangiectasia), male and female autoimmune infertility, ankylosing spondolytis, ulcerative colitis, mixed connective tissue disease, polyarteritis nedosa, systemic necrotizing vasculitis, atopic dermatitis, atopic rhinitis, Goodpasture's syndrome, Chagas' disease, sarcoidosis, rheumatic fever, asthma, recurrent abortion, anti-phospholipid syndrome, farmer's lung, erythema multiforme, post cardiotomy syndrome, Cushing's syndrome, autoimmune chronic active hepatitis, bird-fancier's lung, toxic epidermal necrolysis, Alport's syndrome, alveolitis, allergic alveolitis, fibrosing alveolitis, interstitial lung disease, erythema nodosum, pyoderma gangrenosum, transfusion reaction, Takayasu's arteritis, polymyalgia rheumatica, temporal arteritis, schistosomiasis, giant cell arteritis, ascariasis, aspergillosis, Sampter's syndrome, eczema, lymphomatoid granulomatosis, Behcet's disease, Caplan's syndrome, Kawasaki's disease, dengue, encephalomyelitis, endocarditis, endomyocardial fibrosis, endophthalmitis, erythema elevatum et diutinum, psoriasis, psoriatic arthritis, erythroblastosis fetalis, eosinophilic faciitis, Shulman's syndrome, Felty's syndrome, filariasis, cyclitis, chronic cyclitis, heterochronic cyclitis, Fuch's cyclitis, IgA nephropathy, Henoch-Schonlein purpura, graft versus host disease, transplantation rejection,

cardiomyopathy, Eaton-Lambert syndrome, relapsing polychondritis, cryoglobulinemia, Waldenstrom's macroglobulemia, Evan's syndrome, acute respiratory distress syndrome, pulmonary inflammation, osteoporosis, delayed type hypersensitivity and autoimmune gonadal failure.

In some embodiments, the immunological disorder is a T cell-mediated immunological disorder and accordingly, the anti-IL-23p19 antibodies and agents as described herein are also useful for treating or preventing T cell-mediated immunological disorders.

In one aspect, the anti-IL-23p19 antibodies or agents are useful for treating or preventing a respiratory disorder in which IL-23 is abnormally expressed. Treatment or prevention of the respiratory disorder, according to the methods described herein, is achieved by administering to a subject in need of such treatment or prevention an effective amount of the anti-IL-23p19 antibody or agent, whereby the antibody decreases the activity of IL-23 associated with the disease state.These include, but are not limited to: respiratory complaints, obstructive pulmonary diseases of various origins, pulmonary emphysema of various origins, restrictive pulmonary diseases, interstitial pulmonary diseases, interstitial lung disease, cystic fibrosis, bronchitis of various origins, bronchiectasis, ARDS (adult respiratory distress syndrome) and all forms of pulmonary oedema; obstructive pulmonary diseases selected from among COPD (chronic obstructive pulmonary disease), asthma, bronchial asthma, paediatric asthma, severe asthma, acute asthma attacks and chronic bronchitis; pulmonary emphysema which has its origins in COPD (chronic obstructive pulmonary disease) or α1-proteinase inhibitor deficiency; restrictive pulmonary diseases selected from among allergic alveolitis, restrictive pulmonary diseases triggered by work-related noxious substances, such as asbestosis or silicosis, and restriction caused by lung tumours, such as lymphangiosis carcinomatosa, bronchoalveolar carcinoma and lymphomas; pneumonia caused by infections, such as for example infection by viruses, bacteria, fungi, protozoa, helminths or other pathogens, pneumonitis caused by various factors, such as for example aspiration and left heart insufficiency, radiation-induced pneumonitis or fibrosis, collagenoses, such as for example lupus erythematosus, systemic scleroderma or sarcoidosis, granulomatoses, such as for example Boeck's disease, idiopathic interstitial

pneumonia or idiopathic pulmonary fibrosis (IPF); mucoviscidosis, bronchitis caused by bacterial or viral infection, allergic bronchitis and toxic bronchitis; bronchiectasis; pulmonary oedema, for example, toxic pulmonary oedema after aspiration or inhalation of toxic substances and foreign substances; rhinitis, arthritis and related arthropathies, psoriasis, myeloid leukemia, multiple sclerosis, Alzheimer's disease, glomerulonephritis, and chronic atopic dermatitis.

In another aspect, the anti-IL-23p19 antibodies and agents as described herein are also useful for treating cancers, in which IL-23 is abnormally expressed.

IL-23-expressing cancers that can be treated by the methods described herein include, for example, leukemia, such as acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (e.g., myeloblastic, promyelocytic, myelomonocytic, monocytic, or erythroleukemia), chronic leukemia, chronic myelocytic (granulocytic) leukemia, or chronic lymphocytic leukemia; Polycythemia vera; Lymphoma (e.g., Hodgkin's disease or Non-Hodgkin's disease); multiple myeloma, Waldenstrom's macroglobulinemia; heavy chain disease; solid tumors such sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, osteosarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, colorectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, uterine cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, retinoblastoma, nasopharyngeal carcinoma, or esophageal carcinoma).

Pharmaceutical Compositions and Administration Thereof

A composition comprising an IL-23p19 binding agent (e.g., an anti-IL-23p19 antibody) can be administered to a subject having or at risk of having an immunological disorder, respiratory disorder or a cancer. The invention further provides for the use of a IL-23p19 binding agent (e.g., an anti-IL-23p19 antibody) in the manufacture of a medicament for prevention or treatment of a cancer , respiratory disorder or immunological disorder. The term "subject" as used herein means any mammalian patient to which an IL-23p19binding agent can be administered, including, e.g., humans and non-human mammals, such as primates, rodents, and dogs. Subjects specifically intended for treatment using the methods described herein include humans. The antibodies or agents can be administered either alone or in combination with other compositions in the prevention or treatment of the immunological disorder, respiratory disorder or cancer. Such compositions which can be administered in combination with the antibodies or agents include methotrexate (MTX) and immunomodulators, e.g. antibodies or small molecules.

Examples of antibodies for use in such pharmaceutical compositions are those that comprise a humanized antibody or antibody fragment having the light chain variable region amino acid sequence of any of SEQ ID NO: 84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119. Examples of antibodies for use in such pharmaceutical compositions are also those that comprise a humanized antibody or antibody fragment having the heavy chain variable region amino acid sequence of any of SEQ ID NO: 121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156.

Further examples of antibodies for use in such pharmaceutical compositions are also those that comprise a humanized antibody or antibody fragment having the light chain variable region amino acid sequence of any of SEQ ID NO:158, 160, 162 or 164. Preferred antibodies for use in such pharmaceutical compositions are also those that comprise a humanized antibody or antibody fragment having the heavy chain variable region amino acid sequence of any of SEQ ID NO:166, 168, 170 or 172.

Further examples of antibodies for use in such pharmaceutical compositions are also those that comprise a humanized antibody or antibody fragment having the light chain variable region and heavy chain variable region of any of SEQ ID NO: 160 and 166, SEQ ID NO: 160 and 168, SEQ ID NO: 158 and 166 or SEQ ID NO: 158 and 168.

Further examples of antibodies for use in such pharmaceutical compositions are also those that comprise a humanized antibody having the light chain region amino acid sequence of any of SEQ ID NO:174 or 180. Preferred antibodies for use in such pharmaceutical compositions are also those that comprise humanized antibody having the heavy chain variable region amino acid sequence of any of SEQ ID NO:176 or 178.

Further examples of antibodies for use in such pharmaceutical compositions are also those that comprise Antibody A, Antibody B, Antibody C or Antibody D.

Various delivery systems are known and can be used to administer the IL-23p19 binding agent. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The IL-23p19 binding agent can be administered, for example by infusion, bolus or injection, and can be administered together with other biologically active agents such as chemotherapeutic agents. Administration can be systemic or local. In preferred embodiments, the administration is by subcutaneous injection. Formulations for such injections may be prepared in for example prefilled syringes that may be administered once every other week.

In specific embodiments, the IL-23p19 binding agent composition is administered by injection, by means of a catheter, by means of a suppository, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including a membrane, such as a sialastic membrane, or a fiber. Typically, when administering the composition, materials to which the anti-IL-23p19 antibody or agent does not absorb are used.

In other embodiments, the anti-IL-23p19 antibody or agent is delivered in a controlled release system. In one embodiment, a pump may be used (see, e.g., Langer, 1990, Science 249:1527-1533; Sefton, 1989, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al., 1980, Surgery 88:507; Saudek et al., 1989, N. Engl. J. Med. 321:574). In another

embodiment, polymeric materials can be used. (See, e.g., Medical Applications of Controlled Release (Langer and Wise eds., CRC Press, Boca Raton, Fla., 1974); Controlled Drug Bioavailability, Drug Product Design and Performance (Smolen and Ball eds., Wiley, New York, 1984); Ranger and Peppas, 1983, Macromol. Sci. Rev. Macromol. Chem. 23:61. See also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 71:105.) Other controlled release systems are discussed, for example, in Langer, supra.

An IL-23p19 binding agent (e.g., an anti-IL-23p19 antibody) can be administered as pharmaceutical compositions comprising a therapeutically effective amount of the binding agent and one or more pharmaceutically compatible ingredients.

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

Further, the pharmaceutical composition can be provided as a pharmaceutical kit comprising (a) a container containing a IL-23p19 binding agent (e.g., an anti-IL-23p19 antibody) in lyophilized form and (b) a second container containing a pharmaceutically acceptable diluent (e.g., sterile water) for injection. The pharmaceutically acceptable diluent can be used for reconstitution or dilution of the lyophilized anti-IL-23p19 antibody or agent. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of

pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The amount of the IL-23p19 binding agent (e.g., anti-IL-23p19 antibody) that is effective in the treatment or prevention of an immunological disorder or cancer can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the stage of immunological disorder or cancer, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Generally, the dosage of an anti-IL-23p19 antibody or IL-23p19 binding agent administered to a patient with an immunological disorder or IL-23p19-expressing cancer is typically about 0.1 mg/kg to about 100 mg/kg of the subject's body weight. The dosage administered to a subject is about 0.1 mg/kg to about 50 mg/kg, about 1 mg/kg to about 30 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, or about 1 mg/kg to about 10 mg/kg of the subject's body weight.

Exemplary doses include, but are not limited to, from 1 ng/kg to 100 mg/kg. In some embodiments, a dose is about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg or about 16 mg/kg. The dose can be administered, for example, daily, once per week (weekly), twice per week, thrice per week, four times per week, five times per week, six times per week, biweekly or monthly, every two months, or every three months. In specific embodiments, the dose is about 0.5 mg/kg/week, about 1 mg/kg/week, about 2 mg/kg/week, about 3 mg/kg/week, about 4 mg/kg/week, about 5 mg/kg/week, about 6 mg/kg/week, about 7 mg/kg/week, about 8 mg/kg/week, about 9 mg/kg/week, about 10 mg/kg/week, about 11 mg/kg/week, about 12 mg/kg/week, about 13 mg/kg/week, about 14 mg/kg/week, about 15 mg/kg/week or about 16 mg/kg/week. In some embodiments, the dose ranges from about 1 mg/kg/week to about 15 mg/kg/week.

In some embodiments, the pharmaceutical compositions comprising the IL-23p19 binding agent can further comprise a therapeutic agent, either conjugated or unconjugated to the binding agent. The anti-IL-23p19 antibody or IL-23p19 binding agent can be co-administered in combination with one or more therapeutic agents for the treatment or prevention of immunological disorders or cancers.

Such combination therapy administration can have an additive or synergistic effect on disease parameters (e.g., severity of a symptom, the number of symptoms, or frequency of relapse).

With respect to therapeutic regimens for combinatorial administration, in a specific embodiment, an anti-IL-23p19 antibody or IL-23p19 binding agent is administered concurrently with a therapeutic agent. In another specific embodiment, the therapeutic agent is administered prior or subsequent to administration of the anti-IL-23p19 antibody or IL-23p19 binding agent, by at least an hour and up to several months, for example at least an hour, five hours, 12 hours, a day, a week, a month, or three months, prior or subsequent to administration of the anti-IL-23p19 antibody or IL-23p19 binding agent.

Articles of Manufacture

In another aspect, an article of manufacture containing materials useful for the treatment of the disorders described above is included. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for treating the condition and may have a sterile access port. For example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle. The active agent in the composition is the humanized anti-IL-23p19 antibody. The label on or associated with the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, and dextrose solution. It may further include other materials desirable

from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

The invention is further described in the following examples, which are not intended to limit the scope of the invention.

5

Examples

Example 1: Production of Humanized Anti-IL-23p19 Antibodies

Mouse lead antibody 6B8 was converted to a chimeric antibody consisting of the mouse variable domain of 6B8 and a human constant IgG1KO domain. Mouse antibody 6B8 is shown in Tables 1 and 2 herein above. The IgG1KO (knock out) has two replacement mutations (Leu234Ala and Leu235Ala) that eliminate ADCC and CDC activity by reducing effector functions such as FcγR and complement binding. The variable domains of the mouse and chimeric antibodies are identical. Chimeric antibodies are generated to confirm the function of the antibody and to ensure the correct sequence has been obtained. The variable region of the antibody is then humanized through a design and screening process. A library was made where human and mouse residues were varied in such a way that in any given position there could be either a human or mouse residue. Such a library was made for those amino acids that were different between human germline and mouse antibody. Only the clones that retain the function of the parent mouse antibody were selected. Representative humanized variable regions for antibody 6B8 are shown in Tables 5 and 6.

In this manner, Antibody A, Antibody B, Antibody C and Antibody D were humanized antibodies derived from mouse antibody 6B8 (cloned into a human IgG1-KO (KO=knock-out)/kappa backbone. Antibodies A, B, C and D are shown in Table 7.

Example 2: Binding of antibodies to recombinant IL-23 protein

A) Kinetics and affinity of mouse anti-IL-23p19 antibodies binding to recombinant human IL-23 are shown below (Table 9). Kinetics and binding affinities were measured using the Fortebio Octet (Fortebio, Menlo Park, CA) using material generated from hybridoma following single column purification. Since the Octet is not a fluidics based technology, this method does not provide precise determination of off-rate. In some cases, only a estimate of affinity can be obtained.

Table 9

Antibody	ka(1/Ms)	kd(1/s)	KD(pM)
18C4	3.84E+05	2.14E-06	5.57
18E 5	3.29E+05	2.61E-06	7.93
18D3	3.19E+05	2.16E-06	6.78
20 E8	4.21E+05	2.69E-04	638
22 E2	3.46E+05	3.53E-04	1024
24A5	2.02E+05	4.57E-06	22.6
15C11	4.11E+05	1.07E-05	26
43F5	1.72E+05	5.96E-06	34.6
27G8	1.57E+05	4.26E-06	27.2
31H9	2.99E+05	3.45E-06	11.5
2D1		< 1e-6	< 1
9D12		< 1e-6	< 1
6B8		< 1e-6	< 1
73H10	5.29E+04	5.24E-06	99.2
74H3	3.06E+04	2.09E-06	68.3
35H8			
26F7	4.76E+05	1.34E-05	28.1
34G3	9.18E+05	3.10E-05	32.8
34D9	3.44E+03	1.87E-06	544

B) Affinities were measured for humanized antibodies derived from mouse antibody 6B8. Kinetic binding data, measured using the ProteON XPR36 (Biorad, Hercules, CA) and globally fit to a 1:1 binding model, demonstrated the interactions with recombinant IL-23 either with or without a 21 amino acid linker covalently joining the p19 and p40 subunits to be of high affinity, in the range of 1 pM ~ 100 pM (Table 10). Antibody 6H12 (disclosed in WO 2007/027714), antibody QF20 (disclosed in WO 2007/024846) and antibody C1273 (disclosed in WO 2007/005955) were also tested.

Table 10

Antibody	Human IL-23 with linker			Human IL-23 no linker		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
Mouse 6B8				5.57E+05	1.38E-05	24.5
Antibody A	6.27E+05	< 1e-6	< 1	5.51E+05	< 1e-6	< 1
Antibody B	3.56E+05	< 1e-6	< 1	5.17E+05	< 1e-6	< 1
Antibody C	3.74E+05	1.19E-05	31.8	4.54E+05	1.65E-05	36.3
Antibody D	3.82E+05	4.07E-05	107	3.66E+05	4.93E-05	135
C-1273				3.60E+05	5.75E-06	15.8
6H12				4.99E+05	1.07E-04	214
QF20				2.03E+05	5.89E-06	2.91

C) Affinity and kinetic data for the anti-IL-23p19 antibodies binding to cynomologous IL-23 were measured on the ProteON XPR36, and globally fit to a 1:1 binding model (Table 11). Antibody 6H12 (disclosed in WO 2007/027714), antibody QF20 (disclosed in WO 2007/024846) and antibody C1273 (disclosed in WO 2007/005955) were also tested.

Table 11

Antibody	K_D (pM)	k_a (1/Ms)	k_d (1/s)
Antibody A	< 1	2.95E+06	< 1e-6
Antibody B	< 1	2.99E+06	< 1e-6
Antibody C	2.9	3.23E+06	9.36E-06
Antibody D	15.9	2.07E+06	3.29E-05
C-1273	>5,000	n/a	n/a
6H12	157	9.91E+05	1.56E-04
QF20	1.2	3.90E+06	4.78E-06

D) Molecular Selectivity over human IL-12

The anti-IL-23p19 antibodies were also injected over a human IL-12 surface at a concentration of 100 nM. The binding signal for these antibodies measured using the Fortebio Octet is zero, which indicates that these antibodies selectively bind to human IL-23. The binding of the anti-IL-23p19 antibodies to IL-23 was also analyzed in the presence of 50% human serum and no significant effect of serum on binding on-rate was observed demonstrating high specificity.

Example 3: Competition binding assay of human IL-23 binding to human IL-23R/Fc

Human IL-23R-Fc was captured on the biosensor surface and 10 nM of human IL-23 was injected. The sensorgram indicates the specific binding between IL-23 and the IL-23 receptor (Figure 2, top trace). Antibodies were then co-injected with 10 nM human IL-23 to assess whether antibody binding to the IL-23 could inhibit the interaction between IL-23 and the IL-23 receptor. In this example, if the antibody binds to human IL-23 and is able to inhbit the interaction then reduced or no binding will be observed (Figure 2, bottom trace). In the example shown an equivalent molar concentration of Antibody A was co-injected with 10 nM recombinant human IL-23.

Example 4: Functional Cell Assays, Inhibition of IL-17 production from IL-23 stimulated mouse splenocytes

One functional cell assay for anti-IL-23p19 antibodies measures their ability to inhibit IL-23 stimulated IL-17 production from mononuclear cells isolated from mouse spleens. Human recombinant IL-23 protein is capable of stimulating IL-17 release from mouse splenocytes. In addition, a natural source of human IL-23 found in the supernatant of activated human monocytic THP-1 cells can be used to stimulate IL-17 production from mouse mononuclear cells.

Human recombinant IL-23 or natural human IL-23 from activated THP-1 cells was preincubated with titrated anti-IL-23p19 antibodies. The IL-23/antibody combinations were then added to freshly isolated murine splenocytes. Recombinant IL-23 alone was used as a positive control. After two days in culture, cell supernatants were collected and assayed for IL-17 by ELISA (R&D Systems, Minneapolis, MN). Representative IC_{50}

values for anti-IL-23p19 antibodies are shown below. The tested antibodies are mouse antibodies derived from hybridomas (rows 1-19, see tables 1 and 2), chimeric antibodies (rows 20-23), and Antibodies A to D. Antibody 6H12 (disclosed in WO 2007/027714), antibody QF20 (disclosed in WO 2007/024846) and antibody C1273 (disclosed in WO 2007/005955) were also tested.

Table 12

Antibody	**IC_{50} Values (pM), recombinant human IL-23**	**IC_{50} Values (pM), natural human IL-23**
18C4	471	100, 413
18E5	not determined	9, 9, 13
18D3	234	not determined
20E8	not determined	438, 561
22E2	61, 130	117, 35
24A5	22, 37	85, 31
15C11	126	232
43F5	250, 8000	8000
27G8	235	5000
31H9	960	2000
2D1	not determined	2336, 1911, 1597
9D12	59	281, 138
6B8	13	8, 2
73H10	1411	not determined
74H3	1352	not determined
36H8	not determined	not determined
26F7	27	2, 8
34G3	336	27, 25
34D9	510	456
Chimeric 18E5	31	8, 36, 10, 9

Chimeric 22E2	100	9, 178
Chimeric 24A5	404	95, 102
Chimeric 6B8	26, 37, 57	5, 2, 6, 3
Antibody A	5, 5, 5, 15	1, 1
Antibody B	13, 30, 54, 42	9, 8
Antibody C	53, 71, 162, 89	16, 32
Antibody D	236, 225, 614, 458	133, 125
6H12	1600, 806, 1300	957, 4400, 1013, 439
QF20	not determined	7, 12
C1273	not determined	93, 44

Example 5: Functional specificity testing against IL-12 in a human activated T cell assay

Anti-IL-23p19 antibodies were tested for functional inhibition of IL-12 in a human activated T cell assay. Human recombinant IL-12 (1 ng/ml) was preincubated with 5 µg/ml anti-IL-23p19 antibodies. The IL-12/antibody combinations were then added to human PHA-derived T cell blasts. Recombinant IL-12 alone was used as a positive control. An anti-IL-12p70 antibody (Bender MedSystems, Vienna, Austria) was used as a control inhibitory antibody. After two days in culture, cell supernatants were collected and assayed for IFN-γ by ELISA (R&D Systems). Samples were tested in triplicate and the average pg/ml of IFN-γ was determined. Results (with standard deviations) are shown in the table below.

Table 13

Antibody	**Cytokine Stimulation**	**Average pg/ml IFN-γ +/- Standard Deviation**
no antibody	None	87 +/- 7
no antibody	1 ng/ml IL-12	532 +/- 51
chimeric 18E5	1 ng/ml IL-12	511 +/- 3

chimeric 6B8	1 ng/ml IL-12	523 +/- 60
Antibody A	1 ng/ml IL-12	497 +/- 30
Antibody B	1 ng/ml IL-12	537 +/- 2
Antibody C	1 ng/ml IL-12	495 +/- 25
Antibody D	1 ng/ml IL-12	539 +/- 38
anti-IL-12p70 antibody	1 ng/ml IL-12	119 +/- 12

Example 6: Inhibition of IL-23 induced STAT3 phosphorylation in the human cell line DB

The human cell line DB (ATCC, Manassas, VA) responds to IL-23 stimulation through an endogenous IL-23Rcomplex (IL-23R and IL-12Rβ1) and phosphorylates STAT3 in an IL-23 dose dependent manner. An assay was developed for testing anti-IL-23p19 antibody inhibition of IL-23 induced STAT3 phosphorylation. DB cells were plated at 1x10e6 cells/well in a 96 well plate. Antibodies to be tested were serially diluted and pre-incubated with recombinant human IL-23 (10 ng/ml) for 1 hour at room temperature. The antibody/IL-23 mixture was then added to the cells for 30 minutes at 37°C. Cells were harvested by centrifugation at 4°C for 10 minutes and then lysed in ice cold buffer (Cell Signaling Technology, Beverly, MA). A portion of the lysate was run in a phospho-STAT3 ELISA (Invitrogen). Antibody IC_{50} values were calculated as percent inhibition of STAT3 phosphorylation compared to control wells without antibody. Representative IC_{50} values are shown in the table below.

Table 14

Antibody	**IC_{50} (pM)**
Antibody A	25, 15, 38, 23, 13, 18
Antibody B	73, 84
Antibody C	132, 80
Antibody D	158

QF20	26, 26, 27
C-1273	163, 438

Example 7: In vivo model of IL-23 induced cytokine production in the mouse ear

An in vivo model in the mouse was used. Recombinant human IL-23 is injected into the skin of the mouse ear for 4 consecutive days resulting in epidermal thickening and up-regulation of IL-17 and IL-22 protein. Anti-IL-23p19 antibodies were evaluated in this model. A single intraperitoneal injection of 1mg/kg or 5 mg/kg antibody was administered 1 hour prior to the initial IL-23 injection into the skin. Recombinant human IL-23 (with linker) was injected once daily for 3 additional days and tissue was collected for cytokine assessment. Inhibition of cytokine production was demonstrated for the antibodies. The results of three experiments are shown in the table below (exp. 1: rows 1-7, exp. 2: rows 8-10, exp. 3: rows 11-14).

Table 15

	Ear Tissue IL-17 pg/ml Mean +/- SEM	Ear Tissue IL-17 Percent Inhibition	Ear Tissue IL-22 pg/ml Mean +/- SEM	Ear Tissue IL-22 Percent Inhibition
0.1% BSA + Citrate Buffer i.p. (Unstimulated Control)	3 +/- 1	NA	1 +/- 0	NA
0.3ug IL-23 + Citrate Buffer i.p. (Vehicle Control)	25 +/- 3	NA	274 +/- 30	NA
0.3ug IL-23 + 1mg/kg Antibody 6B8	7 +/- 2	81	57 +/- 19	80
0.3ug IL-23 + 1mg/kg Antibody A	2 +/- 1	101	17 +/- 3	94
0.3ug IL-23 + 1mg/kg Antibody B	5 +/- 1	93	30 +/- 2	89
0.3ug IL-23 + 1mg/kg Antibody C	11 +/- 1	66	108 +/- 12	61

0.3ug IL-23 + 1mg/kg Antibody D	10 +/- 1	67	151 +/- 12	45
0.1% BSA + Vehicle (Unstimulated Control)	14 +/- 1	NA	1 +/- 1	NA
0.3ug IL-23 + Vehicle	31 +/- 4	NA	129 +/- 29	NA
0.3ug IL-23 + 5mg/kg 24A5	14 +/- 1	102	10 +/- 5	93
0.1% BSA + mIgG (Unstimulated Control)	17 +/- 1	NA	4 +/- 1	NA
0.3ug IL-23 + mIgG (Vehicle Control)	30 +/- 2	NA	208 +/- 40	NA
0.3ug IL-23 + 5mg/kg 24A5	16 +/- 0	109	28 +/- 5	88
0.3ug IL-23 + 5mg/kg 18E5	21 +/- 2	70	53 +/- 41	80

Example 8: Pharmacokinetic Studies in Cynomolgus Monkey

Humanized anti-IL-23p19 antibodies were administered by ten minute intravenous infusion at a dose of 1.0 mg/kg to three cynomolgus monkeys. Serum samples were collected over a 6 week time course and free antibody concentrations were measured using a specific ELISA. The serum concentration-time profiles for the antibodies and the corresponding pharmacokinetic parameters are summarized in the Table 16 below.

Table 16

Antibody	**CL (ml/d/kg)**	**Vol (ml/kg)**	**AUC (nM•h/ml)**	**$T_{1/2}$ (days)**	**MRT (days)**
Antibody A	5.2	88	32262	12.1	17.2
Antibody B	6.0	87	27030	10.1	14.8
Antibody C	4.7	91	34642	14.1	19.6
Antibody D	3.4	67	47633	12.6	19.8

Example 9: Expression in NSO cells and biophysical data

Transfection of NS0 cells and generation of stable pools:

NS0 cells were grown in the presence of 1% FBS before transfection. 40x10e6 cells were collected and resuspended in 0.8ml in media containing 2% FBS with 20ug of linearized DNA (heavy chain and light chain expression vectors) and then cells were incubated on ice for approximately 15 min before electroporation of the cells at 750V/25uF (Bio-Rad Gene Pulser Xcell). Cells were recovered with 2% FBS for approximately 48 hours at 37°C and 5% CO2 then plated in 96 well plates at 2x10e5 cells/ml containing G418 and mycophenolic acid for 14-21 days until formation of colonies.

Supernatant from 96 well plates with colonies were screened by ELISA. ELISA plates were coated with 1ug/ml of goat anti-kappa (Southern Biotech, Birmingham, AL) in PBS and diluted supernatant were incubated and then detected with goat anti-human IgG Fc-HRP (from Jackson ImmunoResearch Laboratories, West Grove, PA). The positive colonies were pooled for scale up. Titers for antibody production were determined by ForteBio using protein A tips according to manufacture protocol. The titers for Antibody A and Antibody D were between 250-350 mg/L, with more than 80% recovery from protein purification, and more than 94% monomer after IEX purification. Proteins were resuspended in a final buffer containing 20mM Sodium Citrate and 115mM NaCl, pH 6.0 and are stable at 4 °C for at least 4 months and with solubility up to 100 mg/ml in this buffer.

Table 17

	Protein A Column			**IEX Column**	
	Titer (mg/L)	Yield (mg/L)	Recovery	Yield (mg/L)	Recovery
Antibody A	345	275	80%	221	80%
Antibody D	248	225	90%	175	78%

Table 18

	Quality		Stability				Solubility
	AUC fresh (%M)	SEC fresh (%M)	AUC 1month (%M)	SEC 1month (%M)	AUC 4months (%M)	SEC 4months (%M)	AUC at 100 mg/ml (%M)
Antibody A	98	99	97	99	96	99	99
Antibody D	94	100	98	100	99	99	97

AUC: Analytical Ultracentrifugation as measured by the sedimentation velocity method at concentrations of 0.5 -1 mg/ml; SEC: Size exclusion chromatography; %M: percent monomer.

Example 10: Epitope mapping

Hydrogen/Deuterium Exchange Mass Spectrometry (HXMS) was employed to map the epitope of Antibody A binding to human IL-23p19. This method determined the susceptibility of the amide backbone hydrogens of IL-23p19 to exchange with D_2O. The experiment was conducted with IL-23 alone and IL-23 with added Antibody A. Regions of the IL-23p19 sequence showing significant protection from exchange due to binding of Antibody A were thus identified. Resolution of the method is determined by the peptides produced by digestion with pepsin or Protease XVIII. These IL-23p19 derived peptides were identified by additional control experiments with unexchanged samples employing standard accurate mass and HPLC MS/MS technologies.

Recombinant human IL-23 was used. For the protein + antibody sample, 50ul of IL-23 (0.8mg/ml) was incubated with 10ul of Antibody A (12.7mg/ml) for 15 minutes at room temperature. The final molar ratio Antibody A/IL-23 was 1.2:1.

For the exchange 5ul of IL-23 protein was added to 50ul deuterated buffer (50mM PBS in D_2O) and incubated for 100 seconds at room temperature. 50ul of 2M Urea/0.5M TCEP was added and incubated for 60 seconds at room temperature. 5ul pepsin or

Protease XVIII (4mg/ml in 0.1% formic acid) was added and the sample was immediately cooled to 4 °C.

After 5 minutes 50ul of sample was injected onto a Shimadzu HPLC system (SCL10A controller and two LC10AD pumps) under the following conditions:

Mobile Phase A = 99/1/0.1 (water/acetonitrile/formic acid).

Mobile Phase B = 95/5/0.1 (acetonitrile/water/formic acid).

Flow rate = 100ul/min.

Column = Phenomenex Jupiter C5, 5u, 50x1.0mm.

Mobile phase lines, column, injector loop are in ice baths.

Gradient = Time 0 (3%B), Time 2.2 (3%B), Time 10.1 (90%B), Time 12.0 (90%B), Time 12.1 (3%B).

Mass Spectrometry was carried out as follows:

Mass Spec = Thermo Orbitrap Velos (0900865).

Methods:

A. Fragmentation (to ID peptides): 12 minute acquisition time (3 minute start delay), full-scan FTMS at 30,000 resolution, seven ion trap data dependant scans (CID).

B. MS Runs: 12 minute acquisition time (3 minute start delay), full-scan FTMS at 60,000 resolution.

Pepsin and Protease XVIII peptides were identified using fragmentation data and the program Proteome Discoverer (Thermoscientific, Waltham, MA). Identified peptides were visually compared (protein alone vs. protein with antibody present) using Xcalibur software (Thermoscientific). No significant shifts in exchange were observed for IL-23 alone vs. IL-23 with Antibody A outside of the IL-23p19 region. For the p19 portion of the protein, data was analyzed using the program PepMap (Thermoscientific). This program calculates the average mass for exchanged peptides. PepMap results were checked and those peptides that did not yield verified results were calculated with the aid of Microsoft Excel.

The regions of the IL-23 sequence showing significant protection from exchange due to binding of Antibody A were identified as amino acid residues 108 to 126 of SEQ ID NO:181 and amino acid residues 137 to 151 of SEQ ID NO:181.

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Claims:

What is Claimed is:

1) An anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises:
   a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and
   b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 63, 66, 67 or 68 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

2) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:
   a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and
   b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:63 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

3) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:
   a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and
   b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:66 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

4) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:
   a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and
   b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:67 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

5) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:
   a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:19 *(CDR1-L)*; the amino acid sequence of SEQ ID NO:20 *(CDR2-L)*; and the amino acid sequence of SEQ ID NO:21 *(CDR3-L)*; and
   b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:68 *(CDR1-H)*; the amino acid sequence of SEQ ID NO:64 *(CDR2-H)*; and the amino acid sequence of SEQ ID NO:65 *(CDR3-H)*.

6) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of any one of SEQ ID NO:158, 160, 162 or 164; and a heavy chain variable region comprising the amino acid sequence any one of SEQ ID NO:166, 168, 170 or 172.

7) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 6, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

8) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 6, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

9) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 6, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

10) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 6, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

11) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 6, wherein the antibody or antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO:166 or 168 linked to a human IgG1 heavy chain constant region; and the amino acid sequence of SEQ ID NO:158 or 160 linked to a human kappa light chain constant region.

12) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a) a humanized light chain variable domain comprising the CDRs of SEQ ID NO:158 or 160 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain light chain amino acid sequence of SEQ ID NO:158 or 160; and

b) a humanized heavy chain variable domain comprising the CDRs of SEQ ID NO:166 or 168 and framework regions having an amino acid sequence at least 90% identical to the amino acid sequence of the framework regions of the variable domain heavy chain amino acid sequence of SEQ ID NO:166 or 168.

13) The anti-IL-23p19 antibody according to any one of claims 1 to 12, wherein said antibody is a monoclonal antibody.

14) The anti-IL-23p19 antibody according to claim 1, wherein the antibody is humanized monoclonal anti-IL-23p19 antibody comprising a light chain variable region comprising the amino acid sequence selected from the group consisting of any one of SEQ ID NO:158, 160, 162 and 164 and a heavy chain variable region comprising the amino acid sequence selected from the group consisting of any one of SEQ ID NO:166, 168, 170 and 172.

15) The humanized monoclonal anti-IL-23p19 antibody according to claim 14, wherein said antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

16) The humanized monoclonal anti-IL-23p19 antibody according to claim 14, wherein said antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:160 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

17) The humanized monoclonal anti-IL-23p19 antibody according to claim 14, wherein said antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:166.

18) The humanized monoclonal anti-IL-23p19 antibody according to claim 14, wherein said antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:158 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:168.

19) The anti-IL-23p19 antibody according to claim 1, wherein the antibody is a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 or 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176 or 178.

20) The humanized monoclonal anti-IL-23p19 antibody according to claim 19, wherein said antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176.

21) The humanized monoclonal anti-IL-23p19 antibody according to claim 19, wherein said antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:178.

22) The humanized monoclonal anti-IL-23p19 antibody according to claim 19, wherein said antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176.

23) The humanized monoclonal anti-IL-23p19 antibody according to claim 19, wherein said antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 178.

24) An anti-IL-23p19 antibody or antigen-binding fragment thereof that binds to human IL-23p19 at an epitope consisting of amino acid residues 108 to 126 and amino acid residues 137 to 151 of SEQ ID NO: 181.

25) An anti-IL-23p19 antibody or antigen-binding fragment thereof that competitively binds to human IL-23p19 with:

a) a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176; or

b) a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:174 and a heavy chain comprising the amino acid sequence of SEQ ID NO:178; or

c) a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO:180 and a heavy chain comprising the amino acid sequence of SEQ ID NO:176; or

d) a humanized monoclonal anti-IL-23p19 antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO: 180 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 178.

26) The anti-IL-23p19 antibody according to any one of claims 24 or 25, wherein said antibody is a monoclonal antibody.

27) An antibody or antigen-binding fragment according to any one of claims 1 to 26 for use in medicine.

28) The antibody or antigen-binding fragment according to claim 27, wherein the use is the treatment of an inflammatory disease, of an autoimmune disease, of a respiratory disease, of a metabolic disorder or of cancer.

29) The antibody or antigen-binding fragment according to claim 27, wherein the use is for the treatment of psoriasis, inflammatory bowel disease, psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, or ankylosing spondylitis.

30) A pharmaceutical composition comprising an antibody or antigen-binding fragment according to any one of claims 1 to 26 and a pharmaceutically acceptable carrier.

31) A method for treating a subject having an IL-23-associated disorder comprising administering to the subject an antibody or antigen-binding fragment according to any one of claims 1 to 26, or a pharmaceutical composition according to claim 30, which antibody or antigen-binding fragment binds to human IL-23.

32) A method for treating an inflammatory disease, an autoimmune disease, a respiratory disease, a metabolic disorder or cancer comprising administering to a subject in need thereof an effective amount of an antibody or antigen-binding fragment according to any one of claims 1 to 26, or a pharmaceutical composition according to claim 30.

33) The method according to claim 32, wherein the disease is psoriasis, inflammatory bowel disease, psoriatic arthritis, multiple sclerosis, rheumatoid arthritis, or ankylosing spondylitis.

34) A method for inhibiting the binding of IL-23 to the IL-23 receptor on a mammalian cell, comprising administering to the cell an antibody or antigen-binding fragment according to any one of claims 1 to 26, whereby signaling mediated by the IL-23 receptor is inhibited.

35) An anti-IL-23p19 antibody or antigen-binding fragment thereof comprising a light chain variable region comprising:

a) a light chain CDR1 (L-CDR1) sequence of SEQ ID NO:1, 4, 6, 7, 8, 11, 15, 18, 19, 22, 27 or 30;

b) a light chain CDR2 (L-CDR2) sequence of SEQ ID NO:2, 5, 9, 12, 16, 20, 23, 25, 28 or 31; and

c) a light chain CDR3 (L-CDR3) sequence of SEQ ID NO:3, 10, 13, 14, 17, 21, 24, 26, 29, or 32;

and a heavy chain variable region comprising:

d) a heavy chain CDR1 (H-CDR1) sequence of SEQ ID NO:33, 36, 38, 40, 43, 45, 48, 51, 54, 57, 60, 63, 66, 67, 68, 69, 77 or 80;

e) a heavy chain CDR2 (H-CDR2) sequence of SEQ ID NO:34, 39, 41, 46, 49, 52, 55, 58, 61, 64, 70, 72, 73, 75, 78 or 81; and

f) a heavy chain CDR3 (H-CDR3) sequence of SEQ ID NO:35, 37, 42, 44, 47, 50, 53, 56, 59, 62, 65, 71, 74, 76, 79 or 82.

36) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 35, wherein the antibody or antigen-binding fragment thereof comprises:

a) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 33, 34, and 35, respectively; or

b) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:4, 5, 3, 36, 34 and 37, respectively; or

c) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:1, 2, 3, 38, 39 and 35, respectively; or

d) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:6, 2, 3, 40, 41 and 42, respectively; or

e) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 3, 43, 41 and 44, respectively; or

f) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 46 and 47, respectively; or

g) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 48, 49 and 50, respectively; or

h) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:11, 12, 13, 51, 52 and 53, respectively; or

i) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:7, 2, 14, 54, 55 and 56, respectively; or

j) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:15, 16, 17, 57, 58 and 59, respectively; or

k) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:18, 16, 17, 60, 61 and 62, respectively; or

l) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:19, 20, 21, 63, 66, 67 or 68, 64 and 65, respectively; or

m) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 23, 24, 69, 70 and 71, respectively; or

n) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:22, 25, 26, 55, 72 and 71, respectively; or

o) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 45, 73 and 74, respectively; or

p) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:27, 28, 29, 45, 75 and 76, respectively; or

q) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:8, 9, 10, 77, 78 and 79, respectively; or

r) a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3 sequence of SEQ ID NO:30, 31, 32, 80, 81 and 82, respectively.

37) The anti-IL-23p19 antibody or antigen-binding fragment thereof according to claim 36, wherein the antibody or antigen-binding fragment thereof comprises:

a) a light chain variable region comprising the amino acid sequence of SEQ ID NO:84 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:121; or

b) a light chain variable region comprising the amino acid sequence of SEQ ID NO:86 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:123; or

c) a light chain variable region comprising the amino acid sequence of SEQ ID NO:88 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:125; or

d) a light chain variable region comprising the amino acid sequence of SEQ ID NO:90 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:127; or

e) a light chain variable region comprising the amino acid sequence of SEQ ID NO:91 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:128; or

f) a light chain variable region comprising the amino acid sequence of SEQ ID NO:93 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:130; or

g) a light chain variable region comprising the amino acid sequence of SEQ ID NO:95 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:132; or

h) a light chain variable region comprising the amino acid sequence of SEQ ID NO:97 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:134; or

i) a light chain variable region comprising the amino acid sequence of SEQ ID NO:99 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:136; or

j) a light chain variable region comprising the amino acid sequence of SEQ ID NO:101 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:138; or

k) a light chain variable region comprising the amino acid sequence of SEQ ID NO:103 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:140; or

l) a light chain variable region comprising the amino acid sequence of SEQ ID NO:105 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:142; or

m) a light chain variable region comprising the amino acid sequence of SEQ ID NO:107 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:144; or

n) a light chain variable region comprising the amino acid sequence of SEQ ID NO:109 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:146; or

o) a light chain variable region comprising the amino acid sequence of SEQ ID NO:111 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:148; or

p) a light chain variable region comprising the amino acid sequence of SEQ ID NO:113 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:150; or

q) a light chain variable region comprising the amino acid sequence of SEQ ID NO:115 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:152; or

r) a light chain variable region comprising the amino acid sequence of SEQ ID NO:117 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:154; or

s) a light chain variable region comprising the amino acid sequence of SEQ ID NO:119 and a heavy chain variable region comprising the amino acid sequence SEQ ID NO:156.

38) An isolated polynucleotide comprising a sequence encoding a light chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID NO:84, 86, 88, 90, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117 or 119, or encoding a heavy chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID

NO:121, 123, 125, 127, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156.

39) An isolated polynucleotide comprising a sequence encoding a light chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID NO:158, 160, 162 or 164, or encoding a heavy chain variable region of an antibody or antibody fragment having the amino acid sequence of SEQ ID NO: 166, 168, 170 or 172.

40) The isolated polynucleotide according to claim 39, wherein said polynucleotide comprises a sequence encoding a light chain of an antibody having the amino acid sequence of SEQ ID NO:174 or 180, or encoding a heavy chain of an antibody having the amino acid sequence of SEQ ID NO:176 or 178.

SEQUENCE LISTING

<110> Barrett, Rachel Rebecca
Canada, Keith
Catron, Katrina Mary
Copenhaver, Robert
Frego, Lee Edward
Raymond, Ernest Lee
Singh, Sanjaya
Zhu, Xiangyang

<120> Anti-IL-23 Antibodies

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65   70   75   80
Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Thr Asn
                85   90   95
Glu Asp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg
            100   105   110

<210> 85
<211> 321
<212> DNA
<213> Mouse

<400> 85
gacattgtga tgacccagtc tcacaaattc ttgtccacat cagtgggaga cagggtcacc 60
atcacttgca aggccagtcg ggatgtggct attgctgtag cctggtatca acagaaacca 120
gggcaatctc ctaaactact tcttttctgg gcatccaccc gacacactgg ggtccctgat 180
cgcttcacag gcagtggatc tcggacagat ttcactctca ccattagcaa tgtgcagtct 240
gaagacttgg cagattattt ctgtcaccaa tatagcagct atccattcac gttcggctcg 300
gggacaaagt tggaaataaa g   321

<210> 86
<211> 107
<212> PRT
<213> Mouse

<400> 86
Asp Ile Val Met Thr Gln Ser His Lys Phe Leu Ser Thr Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Leu
        35   40   45
Phe Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80
Glu Asp Leu Ala Asp Tyr Phe Cys His Gln Tyr Ser Ser Tyr Pro Phe
85 90 95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 87
<211> 333
<212> DNA
<213> Mouse

<400> 87
gacattgcgc tgacccaatc tccagcttct ttggctgtgt ctctggggca gagggccacc 60
atatcctgca gagccagtga aactattaat ttttatggca ctagttttat gcactggtac 120
cagcagaaac caggacagtc acccaaactc ctcatctatc gtgcatccaa cctagaatct 180
gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattaat 240
cctgtggagg ctgatgatgt tgcaacctat tactgtcagc aaactaatga ggatccgtac 300
acgttcggag gggggactaa gttggaaata aaa 333

<210> 88
<211> 111
<212> PRT
<213> Mouse

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

<210> 89
<211> 336
<212> DNA
<213> Mouse

<400> 89
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60
atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120
tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180
tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240
aacagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg 300
tacacgttcg gaggggggac ccagctggaa ataaaa 336

<210> 90
<211> 112
<212> PRT
<213> Mouse

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

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

<210> 91
<211> 107
<212> PRT
<213> Mouse

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

<210> 92
<211> 321
<212> DNA
<213> Mouse

<400> 92
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ctttcctgca gggccagtca gagtattagc gactacttat actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaattt gcttcccaat ccatctctgg gatcccctcc 180
aggttcactg gcagtggatc agggtcagat ttcactctca gtatcgacag tgtggaacct 240
gatgatgttg gagtcttttt ctgtcaaaat ggtcacagct ttccgttcac gttcggaggg 300
gggaccaagc tggaaataaa a 321

<210> 93
<211> 107
<212> PRT
<213> Mouse

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

<210> 94

<211> 321
<212> DNA
<213> Mouse

<400> 94
gacattgtga tgactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtctct 60
ctttcctgca gggccagcca gagtattagc gagtacttac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaatat gcttcccaat ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggtcagat ttcactctca gtatcaacag tgtggaacct 240
gaagatgttg gagtgtatta ctgtcaaaat ggtcacagct ttccattcac gttcggctcg 300
gggacaaagt tggaaataaa a 321

<210> 95
<211> 107
<212> PRT
<213> Mouse

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

<210> 96
<211> 321
<212> DNA
<213> Mouse

<400> 96
gacattgtga tgactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtctct 60
ctttcctgca gggccagcca gagtattagc gactacttat actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaattt gcttcccaat ccatctctgg gatcccctcc 180
aggttcactg gcagtggatc agggtcagat ttcactctca gtatcgacag tgtggaacct 240
gatgatgttg gagtcttttt ctgtcaaaat ggtcacagct ttccgttcac gttcggaggg 300
gggaccaagc tggaaataaa a 321

<210> 97
<211> 107
<212> PRT
<213> Mouse

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

<210> 98
<211> 321
<212> DNA
<213> Mouse

<400> 98
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ctttcctgca gggccagcca gagtattagc gagtatttac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaatat gcttcccaat ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggtcagat ttcactctca gtatcaacag tgtggaacct 240
gaagatgttg gagtttatta ctgtcaaaat ggtcacagct ttccattcac gttcggctcg 300
gggacaaagt tggaaataaa a 321

<210> 99
<211> 107
<212> PRT
<213> Mouse

<400> 99
Asp Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
 1   5   10   15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
            20   25   30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35   40   45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro
65   70   75   80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Ser Phe Pro Phe
                85   90   95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 100
<211> 321
<212> DNA
<213> Mouse

<400> 100
gacattgtga tgactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtctct 60
ctctcctgca gggccagcca gagtattagc gtctacttac actggtatca acaaaaatca 120
cctgagtctc caaggcttct catcaaatat gcttcccaat ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggtcagat ttcactctca gtatcaacag tgtggaacct 240
gaagatgttg gagtttatta ctgtcaaaat ggtcacagct ttccattcac gttcggctcg 300
gggacaaagt tggaaataaa a 321

<210> 101
<211> 107
<212> PRT
<213> Mouse

<400> 101
Asp Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
 1   5   10   15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Val Tyr
            20   25   30
Leu His Trp Tyr Gln Gln Lys Ser Pro Glu Ser Pro Arg Leu Leu Ile
        35   40   45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro
65   70   75   80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Ser Phe Pro Phe
                85   90   95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 102
<211> 321
<212> DNA
<213> Mouse

<400> 102
gacattgtga tgactcagtc tccagccacc ctgtctgtga ctccaggaaa tagagtctct 60
ctttcctgca gggccagcca gagtattagc gactacttac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaatat gcttcccaat ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggtcaaat ttcactctca gtatcaacag tgtggaacct 240
gaagatgttg gagtgtatta ttgtcaaaat ggtcacagct ttccattcac gttcggctcg 300
gggacaaagt tggaaataaa a 321

<210> 103
<211> 107
<212> PRT
<213> Mouse

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

<210> 104
<211> 333
<212> DNA
<213> Mouse

<400> 104
gacattgtgc tgacacagtc tcctgcttcc ttagctgttt ctctggggca gagggccacc 60
atctcatgca gggccagcaa aagtgtcaga ttctctgact atttttatat gcactggtac 120
caacagaaac caggacagcc acccaaactc ctcatctacc ttgcatccaa cctagaatct 180
ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240
cctgtggagg aggaggatgc tgcaacctat tactgtcaga acagtaggga gcttccgtac 300
acgttcggag gggggaccaa gctggagata aaa 333

<210> 105
<211> 111
<212> PRT
<213> Mouse

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

85 90 95
Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 106
<211> 333
<212> DNA
<213> Mouse

<400> 106
gacattgtgt tgacacagtc tcctgcttcc ttagctgtat ctctggggca gagggccacc 60
atctcatgca gggccagcaa aagtgtcagt acatctggct atagttatat acactggtac 120
caacagaaac cgggacagcc acccaaattc ctcatctatc ttgcatccaa cctagattct 180
ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240
cctgtggagg aggaggatgc tgcaacctat tactgtcagc acagtaggga gcttccgtac 300
acgttcggag gggggaccaa gctggaaata aaa 333

<210> 107
<211> 111
<212> PRT
<213> Mouse

<400> 107
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30
Gly Tyr Ser Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45
Lys Phe Leu Ile Tyr Leu Ala Ser Asn Leu Asp Ser Gly Val Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80
Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95
Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 108
<211> 321
<212> DNA
<213> Mouse

<400> 108
gacattgtga tgactcagtc tccagccacc ctgtctgtga ctccaggaga tagagtctct 60
ctttcctgca gggccagcca gagtattagc gactacttac actggtatca acaaaaatca 120
catgagtctc caaggcttct catcaaatat gcttcccaat ccatctctgg gatcccctcc 180
aggttcagtg gcagtggatc agggtcagat ttcactctca gtatcaacag tgtggaacct 240
gaagatgttg gagtgtatta ctgtcaaaat ggtcacagct ttccgtacac gttcggaggg 300
gggaccaagc tggaaataaa a 321

<210> 109
<211> 107
<212> PRT
<213> Mouse

<400> 109
Asp Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15
Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro

65 70 75 80
Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 110
<211> 336
<212> DNA
<213> Mouse

<400> 110
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60
atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120
tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180
tctggggtcc ccgacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240
agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg 300
tacacgttcg gaggggggac caagctggaa ataaat 336

<210> 111
<211> 112
<212> PRT
<213> Mouse

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

<210> 112
<211> 318
<212> DNA
<213> Mouse

<400> 112
gacattatga tgacccagtc tcacaaattc atgtccacat cagtaggaga cagggtcagc 60
atcacctgca aggccagtca ggatgtgggt aatgctgtgg tctggtatca acaaaaacca 120
gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacattgg agtccctgat 180
cgcttcacag gcagtggatc tgggacagat ttcactctca ccattaccaa tgtgcagtct 240
gaagacttgg cagattattt ctgtcagcaa tatagcagct atctcacgtt cggtgctggg 300
accaagctgg agctgaaa 318

<210> 113
<211> 106
<212> PRT
<213> Mouse

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

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    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65                  70                  75                  80
Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser Ser Tyr Leu Thr
                85                  90                  95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
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<210> 114
<211> 336
<212> DNA
<213> Mouse

<400> 114
gatgttgtga tgacccaatc tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60
atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tctacattgg 120
tacctgctga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180
tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240
agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg 300
tacacgttcg gaggggggac caagctggaa ataaaa 336

<210> 115
<211> 112
<212> PRT
<213> Mouse

<400> 115
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Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
 1               5                  10                  15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30
Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Leu Lys Pro Gly Gln Ser
        35                  40                  45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95
Thr His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
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<210> 116
<211> 321
<212> DNA
<213> Mouse

<400> 116
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atcacatgtc gagcaagtga gaatattgac agttatttag catggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctttgct gcacgaaact tagcagatgg tgtgccatca 180
aggttcagtg gcagtggatc aggcacacag tattctctca agatcaacag aatgcagtct 240
gaagatgttg cgagatacta ctgtcaacat tattatagta ctccattcac gttcggctcg 300
gggacaaagt tggaaataga a 321

<210> 117
<211> 107
<212> PRT
<213> Mouse

<400> 117
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Asp Ile Gln Met Thr Gln Ser Pro Val Phe Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
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```
        35                  40                  45
Phe Ala Ala Arg Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Arg Met Gln Ser
65                  70                  75                  80
Glu Asp Val Ala Arg Tyr Tyr Cys Gln His Tyr Tyr Ser Thr Pro Phe
                85                  90                  95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Glu
            100                 105
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<210> 118
<211> 321
<212> DNA
<213> Mouse

<400> 118
gacatccaga tgactcagtc gccagcttcc ctgtctgcat ctgtgggaga aactgtcatc 60
ttcacatgtc gagcaagtga gaatattgac agttatttag catggtatca gcagaaacag 120
ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca 180
aggttcagtg gcagtggatc aggcacacag tattctctca agatcaacag cctgcagtct 240
gaagatgttg cgagatatta ctgtctacat tattatagta ctccattcac gttcggctcg 300
gggacagagt tggaaataaa a   321

<210> 119
<211> 107
<212> PRT
<213> Mouse

<400> 119
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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Glu Thr Val Ile Phe Thr Cys Arg Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
        35                  40                  45
Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Val Ala Arg Tyr Tyr Cys Leu His Tyr Tyr Ser Thr Pro Phe
                85                  90                  95
Thr Phe Gly Ser Gly Thr Glu Leu Glu Ile Lys
            100                 105
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<210> 120
<211> 357
<212> DNA
<213> Mouse

<400> 120
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acatgcactg tctctgggtt ctcattaacc acctatgcta taagctgggt tcgccagtca 120
ccaggaaagg gtctggagtg gcttggagtc atatggactg gtggaggcac aaaatataat 180
tcagctctca aatccagact gagcatcagc aaagacaact ccaagagtca agttttctta 240
aaaatgaaca gtctgcaaac tgatgacaca gccaggtact actgtgccag aaaggactat 300
aattacgggg gtgctatgga ctactggggt caaggaacct cagtcaccgt ctcctca   357

<210> 121
<211> 119
<212> PRT
<213> Mouse

<400> 121
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Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
 1               5                  10                  15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
```

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

<210> 122
<211> 360
<212> DNA
<213> Mouse

<400> 122
caggttcagc tgcaacagtc tgacgctgag ttggtgaaac ctggcacttc agtgaagaca 60
tcctgcaaaa tttctggcaa caccttcact gaccaaacta ttcactggat gaagcagagg 120
cctgaacagg gcctggaatg gattggatat atttatccta gagatgatag tcctaagtac 180
aatgagaact tcaagggcaa ggccacattg actgcagaca aatcctccag cacagcctac 240
atgcagctca acagtctgac atctgaggac tctgcagtct atttctgtgc aatcccagac 300
aggtcaggct acgcctggtt tatttactgg ggccaaggga ctctggtcac tgtctcttca 360

<210> 123
<211> 120
<212> PRT
<213> Mouse

<400> 123
```
Gln Val Gln Leu Gln Gln Ser Asp Ala Glu Leu Val Lys Pro Gly Thr
 1               5                  10                  15
Ser Val Lys Thr Ser Cys Lys Ile Ser Gly Asn Thr Phe Thr Asp Gln
            20                  25                  30
Thr Ile His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Ile Tyr Pro Arg Asp Asp Ser Pro Lys Tyr Asn Glu Asn Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
Ala Ile Pro Asp Arg Ser Gly Tyr Ala Trp Phe Ile Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 124
<211> 357
<212> DNA
<213> Mouse

<400> 124
caggtgcagc tgaaggagtc aggacctgtc ctggtggcgc cctcacagag cctgtccatc 60
acatgcactg tctctgggtt ctcattaaac aactttgcta taagttgggt tcgtcagcca 120
ccaggaaagg gtctggagtg gcttggagca atatggactg gtggaggcac aaattataat 180
tcagctctca aatccagact gagcatcagc aaagacaact ccaagagtca agttttctta 240
aaaatgaaca gtctgcaaac tgatgacaca gccaggtatt attgtgtcag aaaggactat 300
agttacgggg gtgctatgga ctactggggt caaggaacct cagtcaccgt ctcctca 357

<210> 125
<211> 119

<212> PRT
<213> Mouse

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

<210> 126
<211> 354
<212> DNA
<213> Mouse

<400> 126
gaggtccagc tgcaacagtc tggacctgtg ctggtgaagc ctggggcttc agtgaagatg 60
tcctgtaagg cttctggata cacattcact gactactata tgaactgggt gaagcagagc 120
catggaaaga gccttgagtg gattggagtt attattcctt acaacggtgg tactagctac 180
aaccagaagt tcaagggcaa ggccacattg actgttgaca agtcctccag cacagcctac 240
atggagctca acagcctgac atctgaggac tctgcagtct attactgtgc acgagatggt 300
caccgctggt acttcgatgt ctggggcaca gggaccacgg tcaccgtctc ctca 354

<210> 127
<211> 118
<212> PRT
<213> Mouse

<400> 127
Glu Val Gln Leu Gln Gln Ser Gly Pro Val Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Val Ile Ile Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly His Arg Trp Tyr Phe Asp Val Trp Gly Thr Gly Thr
100 105 110
Thr Val Thr Val Ser Ser
115

<210> 128
<211> 115
<212> PRT
<213> Mouse

<400> 128
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Cys Cys

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


<210> 129
<211> 345
<212> DNA
<213> Mouse

<400> 129
gaggtccagc tgcagcagtc tggacctgag ctggtcaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact cgctatctta ttcactgggt gaaacagaag 120
cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaaatac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtac ctctaactgg 300
gacctcgact actggggcca aggcaccact ctcacagtct cctca                  345

<210> 130
<211> 115
<212> PRT
<213> Mouse

<400> 130
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30
Leu Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Thr Ser Asn Trp Asp Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
            100                 105                 110
Val Ser Ser
        115


<210> 131
<211> 345
<212> DNA
<213> Mouse

<400> 131
gaggtccagc tgcagcagtc tggacctgaa gtggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cctctggata cacattcact agttctgtta tacactgggt gaagcagaag 120
gctgggcagg gccttgagtg gattggatat atcaatccct ataatgatgg tactaagtac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca gatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtac aagacggttg 300
gacgaggctt actggggcca agggactctg gtcactgtct ctgca                  345

<210> 132
<211> 115
<212> PRT
```

<213> Mouse

<400> 132
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
            20   25   30
Val Ile His Trp Val Lys Gln Lys Ala Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Arg Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Thr Arg Arg Leu Asp Glu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ala
        115

<210> 133
<211> 345
<212> DNA
<213> Mouse

<400> 133
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggctgc agtgaagatg 60
tcctgcaagg cttctggata cacattcact cgctatctta ttcactgggt gaagcagaag 120
cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaaatat 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtac ctctaattgg 300
gacctcgact actggggcca aggcaccact ctcacagtct cctca   345

<210> 134
<211> 115
<212> PRT
<213> Mouse

<400> 134
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ala Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20   25   30
Leu Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Thr Ser Asn Trp Asp Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
            100   105   110
Val Ser Ser
        115

<210> 135
<211> 345
<212> DNA
<213> Mouse

<400> 135
gaggtccagc tgcagcagtc tggacctgaa ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cctctggata cacattcact agttctgtta tgcactgggt gaagcagaag 120
gctgggcagg gccttgagtg gattggatat atcaatccct ataatgatgg tactcagtac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca aattttccag cacagcctac 240

atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtac aagacggttg 300
gacgaggctt actggggcca agggactctg gtcactgtct ctgca 345

<210> 136
<211> 115
<212> PRT
<213> Mouse

<400> 136
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
            20   25   30
Val Met His Trp Val Lys Gln Lys Ala Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Gln Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Phe Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Thr Arg Arg Leu Asp Glu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ala
        115

<210> 137
<211> 345
<212> DNA
<213> Mouse

<400> 137
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact agctctatta ttcactgggt gaagcagagg 120
cctgggcagg gccttgagtg gattggatat attaatcctt acgatgatgt tactaagtac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagacggtgg 300
gacgagtctt actggggcca agggactctg gtcactgtct ctgca 345

<210> 138
<211> 115
<212> PRT
<213> Mouse

<400> 138
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
            20   25   30
Ile Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asp Asp Val Thr Lys Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Arg Trp Asp Glu Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ala
        115

<210> 139
<211> 345
<212> DNA
<213> Mouse

<400> 139
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cactttcact acctctatta tgcactgggt gaaacagaag 120
cctgggcagg gccttgagtg gattggatat attaatcctt acgatgatgt tactaagtac 180
aatgaaaagt tcaaaggcaa ggccacattg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcagtct attactgtgt aagacggtgg 300
gacgaggctt actggggcca agggactctg gtcactgtct ctgca 345

<210> 140
<211> 115
<212> PRT
<213> Mouse

<400> 140
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Ser
            20   25   30
Ile Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asp Asp Val Thr Lys Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Val Arg Arg Trp Asp Glu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ala
        115

<210> 141
<211> 357
<212> DNA
<213> Mouse

<400> 141
gaggtccagc tgcaacaatc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60
tcctgtaagg cttctggata cacgtttact gactactaca tgaactgggt gaggcagagc 120
catggagaga gccttgagtg gattggagat tttaatcata acaatgatgt tattacttac 180
aacccgaagt tcaagggcaa ggtcacattg actgtagaga agtcttccac cacagcctac 240
atggagctcc gcagcctgtc atctgaggac tctgcagtct attactgtgc aaggggggcta 300
cgaggctact atgctatgga ctactggggt caaggaacct cagtcaccgt ctcctca 357

<210> 142
<211> 119
<212> PRT
<213> Mouse

<400> 142
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Tyr Met Asn Trp Val Arg Gln Ser His Gly Glu Ser Leu Glu Trp Ile
        35   40   45
Gly Asp Phe Asn His Asn Asn Asp Val Ile Thr Tyr Asn Pro Lys Phe
    50   55   60
Lys Gly Lys Val Thr Leu Thr Val Glu Lys Ser Ser Thr Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Ser Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Gly Leu Arg Gly Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Ser Val Thr Val Ser Ser
        115

<210> 143
<211> 354
<212> DNA
<213> Mouse

<400> 143
caggttcagc tgcaacagtc tgacgctgag ttggtgaaac ctggagcttc agtgaagata 60
tcctgcaagg tttctggcta caccttcact gaccatacta ttcactggat gaagcagagg 120
cctgaacagg gcctggaatg gattggatat atttatccta gagatggtta tcctaagttc 180
aatgagaagt tcaagggcaa ggccacattg actgcagaca aatcctccag cacagcctac 240
atgcagctca acagcctgac atctgaggac tctgcagtct atttctgtgc aagacggccc 300
ccttactatg ctatggacta ctggggtcaa ggaacctcag tcgccgtctc ctca 354

<210> 144
<211> 118
<212> PRT
<213> Mouse

<400> 144
Gln Val Gln Leu Gln Gln Ser Asp Ala Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp His
            20   25   30
Thr Ile His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Tyr Pro Arg Asp Gly Tyr Pro Lys Phe Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Arg Arg Pro Pro Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100   105   110
Ser Val Ala Val Ser Ser
        115

<210> 145
<211> 345
<212> DNA
<213> Mouse

<400> 145
gaggtccaac tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact aggtatctta tgcactgggt gaagcagaag 120
cctgggcagg gccttgagtg gattggttat attaatcctt acaatgatgg tactaattac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgttc ccttaactgg 300
gactatgctt actggggcca agggactctg gtcactgtct ctgca 345

<210> 146
<211> 115
<212> PRT
<213> Mouse

<400> 146
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20   25   30
Leu Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Asn Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80

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

<210> 147
<211> 360
<212> DNA
<213> Mouse

<400> 147
gagttccagc tgcagcagtc tggacctgag ctggtgaagc ctggcgcttc agtgaagata 60
tcctgcaagg cttctggtta ctcattcact gactacaaca tgaactgggt gaagcagagc 120
aaaggaaaga gccttgagtg gattggagta attattccta actatggttt tactagctac 180
aatcagaact tcaagggcaa ggccactttg actgtagacc agtcttccag cacagcccac 240
atgcagctca acagtgtgac atctgaggac tctgcagtct attactgtgt aagagatggg 300
ggaatactcc tctggtatct cgatgtctgg ggcacaggga ccacggtcac cgtctcctca 360

<210> 148
<211> 120
<212> PRT
<213> Mouse

<400> 148
Glu Phe Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
20 25 30
Asn Met Asn Trp Val Lys Gln Ser Lys Gly Lys Ser Leu Glu Trp Ile
35 40 45
Gly Val Ile Ile Pro Asn Tyr Gly Phe Thr Ser Tyr Asn Gln Asn Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Val Asp Gln Ser Ser Ser Thr Ala His
65 70 75 80
Met Gln Leu Asn Ser Val Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Val Arg Asp Gly Gly Ile Leu Leu Trp Tyr Leu Asp Val Trp Gly Thr
100 105 110
Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 149
<211> 366
<212> DNA
<213> Mouse

<400> 149
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60
ccctgcaagg cttctggata cacattcact gactacaaca tggactgggt gaagaagagc 120
catggaaaga gccttgagtg gattggagat atcaatcctc acaatggtgg tactatctac 180
aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccag cacagcccac 240
atggagctcc gcagcctgac atctgaggac actgcagtct attactgtgc aagaaattac 300
tacggtagta gttacggctg gtacttcgat gtctggggca cagggaccac ggtcaccgtc 360
tcgtca 366

<210> 150
<211> 122
<212> PRT
<213> Mouse

<400> 150
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

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

<210> 151
<211> 360
<212> DNA
<213> Mouse

<400> 151
gaggtccagc tgcagcagtc tggacctgag ctggtgaagc ctggggcttc agtgaagatt 60
tcctgcaggg cttctggtta ctcattcact ggctactaca tgaactgggt gaagcaaagt 120
cctgaaaaga gccttgagtg gattggagag attattccta ccactggtgg tacttcctac 180
aaccagaagt tcaaggccaa ggccacattg actgtagaca aatcctccag cacagcctac 240
atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagagagagc 300
ggtgggttct actggtactt cgatgtctgg ggcacaggga ccacggtcac cgtctcctca 360

<210> 152
<211> 120
<212> PRT
<213> Mouse

<400> 152
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Ile Ser Cys Arg Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30
Tyr Met Asn Trp Val Lys Gln Ser Pro Glu Lys Ser Leu Glu Trp Ile
35 40 45
Gly Glu Ile Ile Pro Thr Thr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Ala Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ser Gly Gly Phe Tyr Trp Tyr Phe Asp Val Trp Gly Thr
100 105 110
Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 153
<211> 345
<212> DNA
<213> Mouse

<400> 153
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact aggtatgtta tgcactgggt gaagcagaag 120
cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgt tactaagtac 180
aatgagaagt tcaaaggcaa ggccacactg acttcagaca gatcctccag cacagcctac 240
atgaaactca gcagcctgac ctctgaggac tctgcggtct attattgtgc aagaaactgg 300
gacgttcctt actggggcca agggactctg atcactgtct ctgca 345

<210> 154

<211> 115
<212> PRT
<213> Mouse

<400> 154
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20   25   30
Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Arg Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Lys Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asn Trp Asp Val Pro Tyr Trp Gly Gln Gly Thr Leu Ile Thr
            100   105   110
Val Ser Ala
        115

<210> 155
<211> 345
<212> DNA
<213> Mouse

<400> 155
gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60
tcctgcaagg cttctggata cacattcact aggtatctta tgcactgggt gaagcagaag 120
cctggacagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaagtac 180
aatgagaggt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240
atggagctca gcagcctgac ctctgaggac tctgcggtct attactgtgc aagaaactgg 300
gacgtacctt actggggcca agggactctg gtcactgtct ctgca   345

<210> 156
<211> 115
<212> PRT
<213> Mouse

<400> 156
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20   25   30
Leu Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Arg Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asn Trp Asp Val Pro Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110
Val Ser Ala
        115

<210> 157
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 157
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gctgttctgg gccagcaccc gccacaccgg cgtgccagac 180
cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacctgg ccgactacta ctgccaccag tacagcagct acccattcac cttcggccag 300
ggcaccaagc tggagatcaa g 321

<210> 158
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 158
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Leu
        35   40   45
Phe Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Leu Ala Asp Tyr Tyr Cys His Gln Tyr Ser Ser Tyr Pro Phe
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 159
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 159
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gatctactgg gccagcaccc gccacaccgg cgtgccaagc 180
cgcttcagcg gcagcggcag ccgcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacgtgg ccgactactt ctgccaccag tacagcagct acccattcac cttcggcagc 300
ggcaccaagc tggagatcaa g 321

<210> 160
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 160
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
        35   40   45
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

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

<210> 161
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 161
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gatctactgg gccagcaccc gccacaccgg cgtgccaagc 180
cgcttcagcg gcagcggcag ccgcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacgtgg ccgactactt ctgccaccag tacagcagct acccattcac cttcggcagc 300
ggcaccaagc tggagatcaa g 321

<210> 162
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 162
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Leu
35 40 45
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys His Gln Tyr Ser Ser Tyr Pro Phe
85 90 95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 163
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 163
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gctgttctgg gccagcaccc gccacaccgg cgtgccagac 180
cgcttcagcg gcagcggcag ccgcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacctgg ccgactacta ctgccaccag tacagcagct acccattcac cttcggcagc 300
ggcaccaagc tggagatcaa g 321

<210> 164
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 164
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Leu
        35   40   45
Phe Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Leu Ala Asp Tyr Tyr Cys His Gln Tyr Ser Ser Tyr Pro Phe
                85   90   95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 165
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 165
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaaggtg 60
agctgcaagg ccagcggcta caccttcacc gaccagacca tccactggat gcgccaggcc 120
ccaggccagg gcctggagtg gatcggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaact tcaagggcaa ggtcaccatc accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc catcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360

<210> 166
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 166
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 Tyr Thr Phe Thr Asp Gln
            20   25   30
Thr Ile His Trp Met Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Tyr Pro Arg Asp Asp Ser Pro Lys Tyr Asn Glu Asn Phe
    50   55   60
Lys Gly Lys Val Thr Ile Thr Ala Asp Lys 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 Ile Pro Asp Arg Ser Gly Tyr Ala Trp Phe Ile Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 167
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 167
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaaggtg 60
agctgcaagg ccagcggctt caccttcacc gaccagacca tccactgggt gcgccaggcc 120
ccaggccagg gcctggagtg gatgggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaact tcaagggcaa ggtcaccctg accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc catcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360

<210> 168
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 168
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 Phe Thr Phe Thr Asp Gln
            20   25   30
Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Tyr Ile Tyr Pro Arg Asp Asp Ser Pro Lys Tyr Asn Glu Asn Phe
    50   55   60
Lys Gly Lys Val Thr Leu Thr Ala Asp Lys 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 Ile Pro Asp Arg Ser Gly Tyr Ala Trp Phe Ile Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 169
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 169
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaagacc 60
agctgcaagg ccagcggcgg caccttcacc gaccagacca tccactgggt gcgccagcgc 120
ccaggccagg gcctggagtg gatgggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaact tcaagggccg cgtcaccatc accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc catcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360

<210> 170
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 170
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1   5   10   15

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

<210> 171
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 171
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaaggtg 60
agctgcaagg ccagcggcgg caccttcacc gaccagacca tccactgggt gcgccaggcc 120
ccaggccagg gcctggagtg gatgggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaatt tcaagggccg cgtcaccctg accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt acttctgcgc ccgcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360

<210> 172
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 172
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 Thr Asp Gln
20 25 30
Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Tyr Ile Tyr Pro Arg Asp Asp Ser Pro Lys Tyr Asn Glu Asn Phe
50 55 60
Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95
Ala Arg Pro Asp Arg Ser Gly Tyr Ala Trp Phe Ile Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 173
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 173
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gatctactgg gccagcaccc gccacaccgg cgtgccaagc 180
cgcttcagcg gcagcggcag ccgcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacgtgg ccgactactt ctgccaccag tacagcagct acccattcac cttcggcagc 300
ggcaccaagc tggagatcaa gcgtactgtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 174
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 174
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
        35   40   45
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Val Ala Asp Tyr Phe Cys His Gln Tyr Ser Ser Tyr Pro Phe
                85   90   95
Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115   120   125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130   135   140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145   150   155   160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165   170   175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180   185   190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195   200   205
Phe Asn Arg Gly Glu Cys
    210

<210> 175
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 175
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaaggtg 60
agctgcaagg ccagcggcta caccttcacc gaccagacca tccactggat gcgccaggcc 120
ccaggccagg gcctggagtg gatcggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaact tcaagggcaa ggtcaccatc accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc catcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 600
tacatctgca acgtgaatca caagcccagc aacaccaagg tcgacaagag agttgagccc 660
aaatcttgtg acaaaactca cacatgccca ccgtgcccag caccagaagc tgctggggga 720
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 780
gaggtcacat gcgtcgtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 840
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 900
agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 960
gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 1020
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 1080
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 1140
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1200
ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1260
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320
cagaagagcc tctccctgtc tccgggt 1347

<210> 176
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 176

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	Tyr	Thr	Phe	Thr	Asp	Gln
			20					25					30		
Thr	Ile	His	Trp	Met	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Tyr	Ile	Tyr	Pro	Arg	Asp	Asp	Ser	Pro	Lys	Tyr	Asn	Glu	Asn	Phe
	50					55					60				
Lys	Gly	Lys	Val	Thr	Ile	Thr	Ala	Asp	Lys	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	Ile	Pro	Asp	Arg	Ser	Gly	Tyr	Ala	Trp	Phe	Ile	Tyr	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
		115					120					125			
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
	130					135					140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
		195					200					205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp
	210					215					220				
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly
225					230					235					240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			260					265					270		
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
	290					295					300				
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
305					310					315					320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
				325					330					335	

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445
Gly
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<210> 177
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 177

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caggtgcagc tggtgcagag cggcgccgag gtgaagaagc caggcagcag cgtgaaggtg 60
agctgcaagg ccagcggctt caccttcacc gaccagacca tccactgggt gcgccaggcc 120
ccaggccagg gcctggagtg gatgggctac atctacccac gcgacgacag cccaaagtac 180
aacgagaact tcaagggcaa ggtcaccctg accgccgaca agagcaccag caccgcctac 240
atggagctga gcagcctgcg cagcgaggac accgccgtgt actactgcgc catcccagac 300
cgcagcggct acgcctggtt catctactgg ggccagggca ccctggtgac cgtgagcagc 360
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 600
tacatctgca acgtgaatca caagcccagc aacaccaagg tcgacaagag agttgagccc 660
aaatcttgtg acaaaactca cacatgccca ccgtgcccag caccagaagc tgctggggga 720
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 780
gaggtcacat gcgtcgtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 840
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 900
agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 960
gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 1020
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgccccatc ccgggaggag 1080
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 1140
gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1200
ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1260
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320
cagaagagcc tctccctgtc tccgggt                                    1347
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<210> 178
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 178

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

Lys Gly Lys Val Thr Leu Thr Ala Asp Lys 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 Ile Pro Asp Arg Ser Gly Tyr Ala Trp Phe Ile Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445
Gly

<210> 179
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 179
gacatccaga tgacccagag cccaagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
atcacctgca aggccagccg cgacgtggcc atcgccgtgg cctggtacca gcagaagcca 120
ggcaaggtgc caaagctgct gctgttctgg gccagcaccc gccacaccgg cgtgccagac 180
cgcttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagcca 240
gaggacctgg ccgactacta ctgccaccag tacagcagct acccattcac cttcggccag 300
ggcaccaagc tggagatcaa gcgtactgtg gctgcaccat ctgtcttcat cttcccgcca 360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 180
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized sequence.

<400> 180
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Val Ala Ile Ala
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Leu
35 40 45
Phe Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Leu Ala Asp Tyr Tyr Cys His Gln Tyr Ser Ser Tyr Pro Phe
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 181
<211> 189
<212> PRT
<213> Homo sapiens

<400> 181
Met Leu Gly Ser Arg Ala Val Met Leu Leu Leu Leu Pro Trp Thr
1 5 10 15
Ala Gln Gly Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln
20 25 30
Cys Gln Gln Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His
35 40 45
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
100 105 110
Pro Ser Leu Leu Pro Asp Ser Pro Val Gly Gln Leu His Ala Ser Leu
115 120 125
Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
130 135 140

```
Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu
145                 150                 155                 160
Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala
                165                 170                 175
Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro
            180                 185
```