ANTI-IL-6 MONOCLONAL ANTIBODIES AND USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to the field of monoclonal antibodies and their use in the treatment of diseases and disorders. More specifically, the invention relates to monoclonal antibodies that specifically bind to the cytokine IL-6, and to uses of the antibodies for the treatment of diseases and disorders associated with IL-6 activity or expression.

Related Art

[0002] Interleukin-6 (IL-6) is a 22 to 27 kDa secreted glycoprotein which exhibits growth stimulatory and proimflammatory activities. IL-6 is also known as interferon-β2 (IFN-β2), IL-1 inducible 26-kDa protein, hepatocyte-stimulating factor, cytotoxic T-cell differentiation factor, and B-cell stimulatory factor. (Trikha *et al.*, *Clin. Cancer Res.* *9*:4653-4665 (2003)). IL-6 is secreted by various cell types. IL-6 exerts its activities through binding to a high-affinity receptor complex consisting of two membrane glycoproteins: an 80 kDa component receptor that binds IL-6 with low affinity (IL-6R) and a signal-transducing component of 130 kDa (gp130) that does not bind IL-6 by itself, but is required for high-affinity binding of IL-6 by the complex. (*See* FIG. 11; BioCarta). IL-6R can be cleaved by a transmembrane metalloproteinase to yield the soluble IL-6R.

[0003] IL-6 blood levels are elevated in numerous infectious, inflammatory, and autoimmune diseases and in cancer in association with increased synthesis of other cytokines stimulated by infection, trauma, and immunological challenge. (Trikha *et al.*, *Clin. Cancer Res.* *9*:4653-4665 (2003)).

[0004] IL-6 has been implicated in various diseases and disorders such as multiple myeloma (Rossi *et al.*, *Bone Marrow Transplantation* *36*:771-779 (2005)), lymphomas (Emilie *et al.*, *Blood* *84*:2472-2479 (1994)), neurological disorders such as neurodegeneration, astrocytosis and cerebral angiogenesis (Campbell *et al.*, *Proc. Natl. Acad. Sci.* *90*:10061-10065 (1993)), autoimmune disorders (such as, *e.g.*, rheumatoid arthritis), inflammatory diseases, Alzheimer's disease, myocardial infarction, Paget's

disease, osteoporosis, solid tumors, prostatic and bladder cancers (Trikha *et al.*, *Clin. Cancer Res. 9*:4653-4665 (2003)), septic shock, transplant, acute infections of the central nervous system, cardiac myxoma (Wijdenes *et al.*, *Mol. Immunol. 28*:1183-1192 (1991)), tumor-induced cachexia (Cahlin *et al.*, *Cancer Res. 60*:5488-5489 (2000)), cancer-associated depression, and cerebral edema secondary to brain tumors (Musselman *et al.*, *Am. J. Psychiatry 158*:1252-1257 (2001)).

[0005] In addition, anti-IL-6 antibodies have been shown to be effective in treating several diseases and disorders. For example, anti-IL-6 monoclonal antibodies have been shown to block the proliferation of myeloma cells both *in vivo* and *in vitro*. (Rossi *et al.*, *Bone Marrow Transplantation 36*:771-779 (2005)). Administration of anti-IL-6 antibodies to chronic rheumatoid arthritis patients was found to alleviate the symptoms of the disease (Wendling *et al.*, *J. Rheumatol. 20*:259-262 (1993)). Anti-IL-6 antibodies have also been shown to be effective in treating AIDS-associated lymphoma (Emilie *et al.*, *Blood 84*:2472-2479 (1994)), and metastatic renal cell carcinoma (Blay *et al.*, *Int. J. Cancer 72*:424-430 (1997). Clinical results involving the administration of anti-IL-6 antibodies to treat various other diseases and disorders are summarized in Trikha *et al.*, *Clin. Cancer Res. 9*:4653-4665 (2003).

[0006] Anti-IL-6 antibodies are known in the art. For example, reshaped human (*i.e.*, humanized) anti-IL6 monoclonal antibodies derived from a mouse monoclonal antibody (SK2) are set forth in U.S. Patent Nos. 5,618,700 and 5,856,135. Other anti-IL-6 antibodies include an antibody known as CLB-6/8 (Brakenhoff *et al.*, *J. Immunol. 145*:561-568 (1990)) and a chimeric form thereof, known as cCLB8 (Van Zaanen *et al.*, *J. Clin. Invest. 98*:1441-1448 (1996). A murine anti-IL-6 monoclonal antibody (mAb) designated B-E8 has been clinically used to treat various IL-6-associated diseases and disorders. (*See, e.g.*, Bataille *et al.*, *Blood 86*:685-691 (1995), Rossi *et al.*, *Bone Marrow Transplantation 36*:771-779 (2005), Haddad *et al.*, *Blood 15*:1590-1597 (2001), and Emilie *et al.*, *Blood 84*:2472-2479 (1994)).

[0007] The use of murine antibodies, including murine anti-IL-6 antibodies, is compromised by problems such as variable selectivity for the target antigen, short serum half-lives, and the development of human anti-murine antibodies (HAMA). These issues are reduced to some extent by the development of chimeric antibodies (in which rodent constant regions are replaced by their human counterparts) or humanized/CDR-

grafted/reshaped antibodies (in which only the CDRs are of non-human origin). (*See generally*, Vaughan *et al.*, *Nat. Biotech. 16*:535-539 (1998)). Nonetheless, a number of practical limitations are associated with humanized antibodies, such as (1) the limited number of options for routes for efficient construction of humanized mAbs, (2) the need for detailed knowledge of antibody structure or modeling, (3) unpredictable immunogenicity due to a compromise between affinity retention and introduced foreign amino acids, and (4) limitations in the antibody repertoire to the animal in which the progenitor mAb originated. (Vaughan *et al.*, *Nat. Biotechnol. 16*:535-539 (1998)). These limitations may be addressed by the use of human monoclonal antibodies. (Lonberg, *Nat. Biotechnol. 23*:1117-1125 (2005)).

[0008] There is therefore a need in the art for additional anti-IL-6 monoclonal antibodies for clinical applications, including human anti-IL-6 mAbs. The present invention addresses this existing need in the art.

SUMMARY OF THE INVENTION

[0009] The present invention provides novel monoclonal antibodies that bind specifically to IL-6. The antibodies of the invention comprise a variable heavy chain (VH) region selected from any of the VH regions disclosed herein as well as amino acid variants thereof, and/or a variable light chain (VL) region selected from any of the VL regions disclosed herein as well as amino acid variants thereof.

[0010] In one exemplary embodiment of the invention, multiple VH and VL regions were obtained from a library of human VH and VL genes. Antibody heavy chains containing human VH regions obtained from the library were paired with light chains from a known murine anti-IL-6 mAb (*i.e.*, B-E8). Likewise, antibody light chains containing human VL regions obtained from the library were paired with heavy chains from a known murine anti-IL-6 mAb (*i.e.*, B-E8). The resulting antibodies were screened for their ability to bind specifically to an IL-6 antigen. From this process, eighteen human VLs (represented by SEQ ID NOs:1 to 18) and seven human VHs (represented by SEQ ID NOs:19 to 25) were identified.

[0011] All of the identified VLs were cross paired with all of the identified VHs. The resulting antibodies were tested for binding affinity to IL-6 by ELISA and for the ability

to block IL-6-induced cell proliferation. From this process, 33 human VH/VL pairings were identified that exhibited substantial binding affinity and blocking activity.

[0012] Amino acid substitutions were introduced into certain human VHs and VLs identified by the above-described process. The variant VHs and VLs were paired with human VLs and VHs, respectively, and the resulting antibodies were again tested for IL-6 binding affinity and blocking activity. From these experiments, several antibodies were identified with binding and blocking activities comparable to that of the original murine B-E8 antibody (or a chimera thereof). The present invention therefore also includes antibodies comprising any combination of the variant VHs and VLs obtained by the process outlined above and described in detail in the Examples below.

[0013] The invention also includes nucleic acid molecules that encode any of the VH and/or VL regions disclosed herein, and vectors and host cells comprising the nucleic acid molecules.

[0014] In some embodiments, the novel monoclonal antibodies of the present invention demonstrate species specificity, binding to or aiding in the detection of human IL-6. In some embodiments, the novel monoclonal antibodies of the present invention bind to or aid in the detection of human and monkey IL-6 but not murine or rat IL-6.

[0015] In some embodiments, the novel monoclonal antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) myeloma cells or human U266 myleoma cells.

[0016] In some embodiments, the novel monoclonal antibodies of the present invention bind to IL-6 but not to other IL-6 superfamily members.

[0017] In some embodiments, the novel monoclonal antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor.

[0018] The invention also includes methods of producing an antibody of the present invention, the method comprising: (i) culturing a host cell expressing one or more nucleic acid sequences encoding an antibody of the present invention, and (ii) recovering the antibody from the culture medium.

[0019] The invention also includes pharmaceutical compositions comprising an antibody of the present invention. It is contemplated that the pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, an adjuvant, or a combination thereof.

[0020] The invention also includes methods of preventing or treating diseases and/or disorders associated with IL-6 activity or expression, wherein the methods comprise administering an antibody of the present invention to a patient in need thereof. In one embodiment, the methods comprise administering a therapeutically or prophylactically effective amount of a pharmaceutical composition comprising an antibody of the present invention and a pharmaceutically acceptable carrier to a patient in need thereof. In some embodiments, the disease or disorder includes any disease or disorder mediated by, associated with, or caused by the action of IL-6. In some embodiments, the disease or disorder to be treated is selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenille arthritis, and fibrotic conditions.

[0021] The invention also includes use of an antibody of the present invention for the manufacture of a medicament for the treatment of a disease or disorder mediated by, associated with, or caused by the action of IL-6. In a particular embodiment, the invention is also directed to use of an anitbody of the present invention for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenille arthritis, and fibrotic conditions.

[0022] The invention also includes an antibody of the present invention for use in the treatment of a disease or disorder mediated by, associated with, or caused by the action of IL-6. In a particular embodiment, the invention is also directed to use of an antibody of the present invention for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenille arthritis, and fibrotic conditions.

BRIEF DESCRIPTION OF THE FIGURES

[0023] FIG. 1 shows an alignment of exemplary human VH regions, represented by SEQ ID NOs:19-25, that can be included within the antibodies of the invention.

[0024] FIG. 2 shows the results of an IL-6 binding inhibition assay in which biotinylated human recombinant IL-6 was incubated with various anti-IL-6 antibodies, followed by the addition of IL-6 receptor-bearing U266 cells. Flow cytometry analysis was used to quantitate the percent inhibition of IL-6 binding at various anti-IL-6 antibody concentrations.

[0025] FIG. 3 depicts the general process used for affinity selection of mAbs from libraries generated by site-directed mutagenesis.

[0026] FIG. 4 shows the results of an IL-6 binding inhibition assay in which human recombinant IL-6 was incubated with various anti-IL-6 antibodies, followed by the addition of IL-6 receptor-bearing U266 cells. A purified mouse IL-6 antibody and an APC-conjugated polyclonal goat-anti-mouse secondary antibody were then added. Flow cytometry analysis was used to quantitate the IL-6 blocking activity at various anti-IL-6 antibody concentrations.

[0027] FIGs. 5A and 5B show the results of binding specificity experiments in which a control mAb 88 (chimeric B-E8) (FIG. 5A), or a candidate, affinity-improved human mAb 1339 (FIG. 5B) were tested by ELISA for binding to a panel of IL-6 superfamily members.

[0028] FIGs. 6A and 7A show the results of experiments in which IL-6-specific mAbs were tested for their ability to inhibit the interaction between IL-6 and the IL-6 receptor expressed on U266 cells, as analyzed by flow cytometry. Each column represents a mean of three experiments +/- standard deviation.

[0029] In FIG. 6A, the concentration of mAb was 0.5 μg/ml. For each mAb, the four columns from left to right indicate the percent inhibition of IL-6 binding to IL-6 receptor at IL-6 concentrations of 100.0, 50.0, 25.0, and 12.5 ng/ml, respectively.

[0030] In FIG. 7A, the concentration of IL-6 was 500 ng/ml. For each mAb in FIG. 7A, the eight columns from left to right indicate the percent inhibition of IL-6 binding to IL-6 receptor at mAb concentrations of 5000, 2500, 1250, 625.0, 156.3, 78.1, and 39.1 ng/ml, respectively.

[0031] FIGs. 6B and 7B show the results of single, representative experiments at 100 ng/ml IL-6 which illustrate the inhibitory effect of various anti-IL-6 mAbs on the interaction between IL-6 and the IL-6 receptor expressed on U266 cells, as analyzed by flow cytometry. The dark solid lines represent 100 ng/ml IL-6 alone in the absence of

mAb; the light solid lines represent 100 ng/ml IL-6 in the presence of mAb; and the dashed lines represent mAb alone in the absence of IL-6. In FIG. 6B, the concentration of mAb, if present, was 0.5 μg/ml mAb. In FIG. 7B, the concentration of mAb, if present, was 0.3 μg/ml mAb.

[0032] FIG. 8 is a summary chart showing the results of three separate IL-6 binding inhibition assays.

[0033] FIG. 9 is a map of the mAb 1339 double gene vector (expressing a heavy chain containing the H1579 heavy chain variable region and a light chain contaning the L298 light chain variable region).

[0034] FIG. 10 shows the mAb yields obtained with various CHO-based cell line isolates expressing the mAb 1339 double gene vector.

[0035] FIG. 11 is a schematic representation of IL-6 signaling pathways (*available at* BioCarta).

[0036] FIG. 12 shows the results of experiments in which IL-6-specific mAbs were tested for their ability to inhibit the IL-6-dependent proliferation of the murine B9 (ECACC) myeloma cell line. IgG1 Kappa and mB-Z1 are human and mouse IgG1 isotype control antibodies, respectively. For each mAb, the seven columns from left to right indicate the percent inhibition of IL-6 (10 pg/ml)-induced B9 cell proliferation at mAb concentrations of 100, 10, 1, 0.1, 0.01, 0.001, and 0.0001 ng/ml, respectively. Each column represents a mean of three experiments +/- standard deviation.

[0037] FIG. 13 shows the results of experiments in which IL-6-specific mAbs were tested for their ability to inhibit the IL-6-dependent proliferation of the human U266 myeloma cell line. For each mAb, the six columns from left to right indicate the percent inhibition of IL-6 (500 pg/ml)-induced U266 cell proliferation at mAb concentrations of 1000, 333, 111, 37, 12, and 4 ng/ml, respectively. Each column represents a mean of three experiments +/- standard deviation.

[0038] FIGs. 14 and 15 show the results of experiments in which IL-6-specific mAbs were tested for their ability to detect murine IL-6 (FIG. 14) or rat IL-6 (FIG. 15) by ELISA. Biotinylated polyclonal antibody (pAb) controls were anti-human IL-6, anti-mouse IL-6, anti-rat IL-6, and anti-human IL-2. For sample "0," no antibody was added. For each sample, the four columns from left to right indicate the optical density associated with binding to 100 ng/ml murine or rat IL-6 at antibody concentrations of

100, 50, 25, and 12.5 ng/ml, respectively. Each column represents a mean of two experiments +/- standard deviation.

[0039] FIG. 16 shows the results of experiments in which IL-6-specific mAbs were tested for their ability to detect natural intracytoplasmic IL-6 in human monocytes from peripheral blood mononuclear cells (PBMNC) activated for 24 hours with LPS. The thicker lines represent mAb detection of IL-6 from LPS-stimulated monocytes while the thinner lines represent absence of added antibody.

[0040] FIG. 17 and 18 show the results of experiments in which IL-6-specific mAbs were tested for their ability to detect IL-6 from plasma. A "Serum only" sample to which no mAb was added served as a reference. Reduction in the optical density signal in the IL-6-specific antibody samples in comparison to the "Serum only" sample indicates interaction of serum IL-6 with the antibodies. Antibodies were tested at 5 μg/ml.

[0041] In FIG. 17, the four columns from left to right indicate the optical density associated with detection of human IL-6 in human serum at serum dilultions of 1, 1/2, 1/4, and 1/8. Each column represents a mean of two experiments +/- standard deviation.

[0042] In FIG. 18, the four columns from left to right indicate the optical density associated with detection of monkey IL-6 in rhesus monkey serum at serum dilultions of 1/10, 1/20, 1/40, 1/80, 1/160, 1/320, and 1/640.

DETAILED DESCRIPTION OF THE INVENTION

[0043] Unless otherwise defined, all technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art for the art to which this invention belongs.

ANTIBODIES

[0044] The present invention provides monoclonal antibodies that specifically bind to IL-6.

[0045] As used herein, the term "antibody" includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is

comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chains of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains. The variable regions of kappa light chains are referred to herein as VK. The expression VL, as used herein, is intended to include both the variable regions from kappa-type light light chains (VK) and from lambda-type light chains. The light chain constant region is comprised of one domain, CL. The VH and VL regions include regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4.

[0046] Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. The present invention includes antibodies of any of the aforementioned classes or subclasses (isotypes).

[0047] The term "antibody" as used herein is also intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof; each containing at least one CDR. Functional fragments include antigen binding fragments that bind to an IL-6 antigen. For example, antibody fragments capable of binding to IL-6 or a portion thereof, including, but not limited to Fab (*e.g.*, by papain digestion), facb (*e.g.*, by plasmin digestion), pFc' (*e.g.*, by pepsin or plasmin digestion), Fd (*e.g.*, by pepsin digestion, partial reduction and reaggregation), Fv or scFv (*e.g.*, by molecular biology techniques) fragments, are encompassed by the present invention. Antibody fragments are also intended to include, *e.g.*, domain deleted

antibodies, diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments.

[0048] The term "monoclonal antibody," as used herein, refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are substantially identical except for possible naturally occurring mutations or minor post-translational variations that may be present. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies of the present invention are preferably made by recombinant DNA methods or are obtained by screening methods as described elsewhere herein.

[0049] The term "monoclonal antibodies," as used herein, includes "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species (*e.g.*, mouse or rat) or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (Morrison *et al.*, *Proc. Natl. Acad. Sci. USA 81*:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.*, Old World Monkey, such as baboon, rhesus or cynomolgus monkey) and human constant region sequences (U.S. Pat. No. 5,693,780).

[0050] Thus, the present invention includes, for example, chimeric monoclonal antibodies comprising a chimeric heavy chain and/or a chimeric light chain. The chimeric heavy chain may comprise any of the heavy chain variable (VH) regions described herein or mutants or variants thereof fused to a heavy chain constant region of a non-human antibody. The chimeric light chain may comprise any of the light chain variable (VL)

regions described herein or mutants or variants thereof fused to a light chain constant region of a non-human antibody.

[0051] The term "human antibody," as used herein, includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat, *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. The human antibody can have at least one position replaced with an amino acid residue, *e.g.*, an activity enhancing amino acid residue which is not encoded by the human germline immunoglobulin sequence. In the context of the present invention, the human antibody can have up to twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence. In other embodiments, up to ten, up to five, up to three or up to two positions are replaced. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0052] The phrase "recombinant human antibody" includes human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal that is transgenic for human immunoglobulin genes, or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences (*See* Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). According to the present invention, recombinant human antibodies include human germline immunoglobulin sequence that have been subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in*

vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*. In certain embodiments, however, such recombinant antibodies are the result of selective mutagenesis approach or backmutation or both.

[0053] The antibodies of the present invention may be isolated antibodies. An "isolated antibody," as used herein, includes an antibody that is substantially free of other antibodies having different antigenic specificities. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0054] The antibodies of the present invention preferably bind specifically to an IL-6 antigen. As used herein, "an IL-6 antigen" is intended to include, *e.g.*, the complete IL-6 protein or a fragment of the IL-6 protein. The term "IL-6 antigen" is intended to encompass naturally occurring IL-6 (*e.g.*, IL-6 purified from a cell that expresses IL-6 under normal conditions) as well as recombinant IL-6 and variants and mutants thereof. Preferably, the IL-6 antigen is capable of binding to the IL-6 receptor.

[0055] An antibody of the present invention binds specifically to an IL-6 antigen if, *e.g.*, the antibody binds to an IL-6 antigen and will not show any significant binding to non-IL-6 molecules. In certain embodiments, an antibody binds specifically to an IL-6 antigen if it binds to an IL-6 antigen with an affinity that is at least 1000 fold, at least 500 fold, at least 200 fold, at least 100 fold, at least 90 fold, at least 80 fold, at least 70 fold, at least 60 fold, at least 50 fold, at least 40 fold, at least 30 fold, at least 20 fold, at least 10 fold or at least 2 fold greater than the affinity with which it binds to an antigen other than an IL-6 antigen.

[0056] Whether an antibody of the invention binds specifically to an IL-6 antigen can be determined, *e.g.*, by a binding assay such as an ELISA, employing a panel of antigens including an IL-6 antigen as well as at least one other non-IL-6 antigen. An exemplary method for assessing specificity is set forth in Example 5, below. Here, a human anti-IL-6 antibody of the invention (mAb 1339) was tested by ELISA for binding to unrelated antigens such as human insulin, human serum albumin, human hemoglobin, and bovine serum albumin. Since no binding to the non-IL-6 antigens was observed, mAb 1339 was deemed to bind specifically to IL-6.

[0057] In certain embodiments, an antibody of the present invention binds specifically to IL-6 but not to other IL-6 superfamily members. In certain embodiments, an antibody of the invention binds specifically to an IL-6 antigen if it binds to an IL-6 antigen with an affinity that is at least 1000 fold, at least 500 fold, at least 200 fold, at least 100 fold, at least 90 fold, at least 80 fold, at least 70 fold, at least 60 fold, at least 50 fold, at least 40 fold, at least 30 fold, at least 20 fold, at least 10 fold or at least 2 fold greater than the affinity with which it binds to an IL-6 superfamily member such as, *e.g.*, CNFT, oncostatin M, IL-11 or NNT-1. For example, mAb 1339 was shown by ELISA to bind to IL-6 and showed insignificant levels of binding to CNFT, oncostatin M, IL-11 or NNT-1. (See Example 5 and FIG. 5B). This or a similar assay can be used to assess whether any antibody specifically binds to an IL-6 antigen.

[0058] In other embodiments, an antibody of the invention binds specifically to an IL-6 antigen when the dissociation constant (K_d) is about 10^{-8} M. The antibody, in certain embodiments, is said to bind specifically to an IL-6 antigen with "high affinity" when the K_d is about $5x10^{-9}$ M, and with "very high affinity" when the K_d is about $5x10^{-10}$ M.

[0059] Whether an antibody binds specifically to an IL-6 antigen in the context of the present invention can also be determined by functional assay. For example, an assay can be conducted in which cells expressing IL-6 receptor are incubated with IL-6 in the presence of a test antibody. In a parallel assay, cells expressing another receptor are incubated with the ligand for the receptor in the presence of the test antibody. If the antibody shows an inhibitory effect in the first assay (which includes IL-6 and cells expressing the IL-6 receptor) but does not show an inhibitory effect in the second assay (which includes a different ligand and cells expressing the receptor for that ligand), then it can be concluded that the antibody binds specifically to an IL-6 antigen. Assays for determining whether an antibody inhibits the biological effects of IL-6 binding to an IL-6 receptor on cells are discussed elsewhere herein. For instance, Example 5 shows the ability of human anti-IL-6 antibodies of the invention to inhibit IL-6-induced human myeloma cell proliferation.

[0060] In some embodiments, the antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) or human U266 myleoma cells. In some embodiments, the antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) human U266 myeloma cells at a level

of 100% (*i.e.*, complete) inhibition. In some embodiments, the antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) or human U266 myeloma cells at a level of 90% or greater inhibition. In some embodiments, the antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) or human U266 myeloma cells at a level of 80% or greater inhibition. In some embodiments, the antibodies of the present invention inhibit IL-6-induced proliferation of cells such as murine B9 (ECACC) or human U266 myeloma cells at a level of 70% or greater, 60% or greater, 50% or greater, 40% or greater, 30% or greater, 20% or greater, 10% or greater, or 5% or greater, or 1% or greater inhibition.

[0061] In some embodiments, the antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor. In some embodiments, the antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor at a level of 100% (*i.e.*, complete) inhibition. In some embodiments, the antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor at a level of 90% or greater inhibition. In some embodiments, the antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor at a level of 80% or greater inhibition. In some embodiments, the antibodies of the present invention bind specifically to IL-6, inhibiting the binding of IL-6 to its receptor at a level of 70% or greater, 60% or greater, 50% or greater, 40% or greater, 30% or greater, 20% or greater, 10% or greater, 5% or greater, or 1% or greater inhibition.

[0062] In some embodiments, the antibodies of the present invention demonstrate species specificity, binding to or aiding in the detection of human IL-6. In some embodiments, the novel monoclonal antibodies of the present invention bind to or aid in the detection of human or monkey IL-6 but not murine or rat IL-6.

[0063] The human antibodies of the invention can be obtained by a variety of methods. For example, human monoclonal antibodies that bind to IL-6 can be selected, for example, by screening one or more human VL and VH cDNA libraries with IL-6 or a portion thereof, such as by phage display techniques. (McCafferty *et al.*, *Nature 348*:552-554 (1990)). Human antibodies of the invention can also be obtained from transgenic animals such as, *e.g.*, transgenic mice. (Jakobovits, *Curr. Opin. Biotechnol. 6*:561-566

(1995)). The present invention includes human anti-IL-6 antibodies that are obtained by any method known in the art for making human antibodies.

[0064] Exemplary methods that can be used to generate antibodies of the invention are disclosed, *e.g.*, in U.S. Patent Appl. Publication No. 2005/0196755, the content of which is incorporated by reference in its entirety.

[0065] The present invention thus includes monoclonal antibodies that comprise a human heavy chain variable region (VH), wherein the human VH, when paired with a variable light chain region (VL) of a non-human anti-IL-6 monoclonal antibody (such as, *e.g.*, B-E8), results in an antibody the binds specifically to an IL-6 antigen.

[0066] The present invention also includes monoclonal antibodies that comprise a human light chain variable region (VL), wherein the human VL, when paired with a variable heavy chain region (VH) of a non-human anti-IL-6 monoclonal antibody (such as, *e.g.*, B-E8), results in an antibody that binds specifically to an IL-6 antigen. In certain embodiments, the human VL is of the kappa subtype (*i.e.*, VK).

[0067] The present invention also includes monoclonal antibodies that comprise a human heavy chain variable region (VH) and a human light chain variable region (VL), wherein the human VH, when paired with a variable light chain region (VL) of a non-human anti-IL-6 monoclonal antibody (such as, *e.g.*, B-E8), results in an antibody the binds specifically to an IL-6 antigen, and wherein the human VL, when paired with a variable heavy chain region (VH) of a non-human anti-IL-6 monoclonal antibody (such as, *e.g.*, B-E8), results in an antibody that binds specifically to an IL-6 antigen.

[0068] In certain embodiments, the monoclonal antibodies of the invention comprise a variable heavy chain region (VH) comprising an amino acid sequence selected from the group consisting of H415 (SEQ ID NO:19), H884 (SEQ ID NO:20), H1077 (SEQ ID NO:21), H1078 (SEQ ID NO:22), H1079 (SEQ ID NO:23), H1081 (SEQ ID NO:24), H1089 (SEQ ID NO:25), H1511 (SEQ ID NO:26), H1420 (SEQ ID NO:27), H1432 (SEQ ID NO:28), H1515 (SEQ ID NO:29), H1362 (SEQ ID NO:30), H1437 (SEQ ID NO:31), H1461 (SEQ ID NO:32), H1519 (SEQ ID NO:38), H1520 (SEQ ID NO:39), H1521 (SEQ ID NO:40), H1522 (SEQ ID NO:41), H1553 (SEQ ID NO:42), and H1579 (SEQ ID NO:43), wherein the antibodies bind specifically to an IL-6 antigen.

[0069] In certain embodiments, the monoclonal antibodies of the invention comprise a variable light chain region (VL or VK) comprising an amino acid sequence selected from

the group consisting of L112 (SEQ ID NO:1), L151 (SEQ ID NO:2), L158 (SEQ ID NO:3), L159 (SEQ ID NO:4), L164 (SEQ ID NO:5), L165 (SEQ ID NO:6), L166 (SEQ ID NO:7), L167 (SEQ ID NO:8), L168 (SEQ ID NO:9), L169 (SEQ ID NO:10), L170 (SEQ ID NO:11), L171 (SEQ ID NO:12), L172 (SEQ ID NO:13), L173 (SEQ ID NO:14), L174 (SEQ ID NO:15), L175 (SEQ ID NO:16), L189 (SEQ ID NO:17), L198 (SEQ ID NO:18), L314 (SEQ ID NO:33), L305 (SEQ ID NO:34), L303 (SEQ ID NO:35), L298 (SEQ ID NO:36), and L321 (SEQ ID NO:37), wherein the antibodies bind specifically to an IL-6 antigen.

[0070] It will be understood by a person of ordinary skill in the art that "antibodies comprising a variable heavy chain region (VH)" and "antibodies comprising a variable light chain region (VL or VK)," as described in the context of the present invention, may include one or more additional regions (or "domains") that are normally found in antibody molecules, such as, *e.g.*, one or more constant heavy chain regions (*e.g.*, CH1, CH2 and/or CH3), and/or a constant light chain region (CL).

[0071] The antibodies of the invention may, in certain embodiments, comprise a variable heavy chain region (VH) comprising an amino acid sequence that is at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to any one of SEQ ID NOs:19 to 32 or 38 to 43, wherein the antibodies bind specifically to an IL-6 antigen.

[0072] The antibodies of the invention may, in certain embodiments, comprise a variable light chain region (VL or VK) comprising an amino acid sequence that is at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to any one of SEQ ID NOs:1 to 18 or 33 to 37, wherein the antibodies bind specifically to an IL-6 antigen.

[0073] The term "identical," as used herein, refers to a relationship between the sequences of two or more polypeptide molecules as determined by aligning and

comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (i.e., an "algorithm"). Methods that can be used to calculate the identity of the aligned polypeptides include those described in Computational Molecular Biology, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., 1988, SIAM J. Applied Math. 48: 1073.

[0074] In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity may be the GCG program package, which includes GAP (Devereux et al., 1984, Nucl Acid Res 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wisc.). The computer algorithm GAP is used to align the two polypeptides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see Dayhoff et al., 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, Proc. Natl. Acad. Sci. USA 89: 10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0075] Recommended parameters for determining percent identity for polypeptides using the GAP program are the following:

Algorithm: Needleman et al., 1970, J. Mol. Biol. 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, supra;

Gap Penalty: 12 (but with no penalty for end gaps);

Gap Length Penalty: 4;

Threshold of Similarity: 0.

[0076] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

[0077] Amino acid sequence modification(s) of anti-IL-6 antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the anti-IL-6 antibodies.

[0078] Amino acid sequence variants of the anti-IL-6 antibodies may be prepared by introducing appropriate nucleotide changes into a nucleic acid that encodes the heavy or light chains of the antibody, or by peptide synthesis. Exemplary modifications include those that alter the amino acid sequence of a variable region of the heavy and/or light chain of the antibody. Especially preferred are modifications that alter the amino acid sequence of one or more CDR of a variable region of a heavy and/or light chain of an antibody of the invention.

[0079] Exemplary modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-IL-6 antibodies. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics (*e.g.*, the ability to form part of an antibody that binds specifically to an IL-6 antigen). The amino acid changes also may alter post-translational processes of the anti-IL-6 antibodies, such as changing the number or position of glycosylation sites.

[0080] One exemplary method for introducing amino acid changes into the VH and VL regions of the antibodies of the invention is illustrated in Example 2, below. According to this method, NNK is introduced at specific positions, *e.g.*, within a CDR of a VH or

VL, where N can be A, T, G, or C, and K is T or G. Using NNK, all 20 amino acids and 1 stop codon can be introduced at each position.

[0081] Another useful method for identification of certain residues or regions of the anti-IL-6 antibody variable heavy chain regions and variable light chain regions 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 (most preferably alanine or polyalanine). 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 VH variants and/or VL variants are screened for the desired activity when combined with a variable light chain or variable heavy chain, respectively.

[0082] 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-6 VH or an anti-IL-6 VL with an N-terminal methionyl residue, or an anti-IL-6 VH or an anti-IL-6 VL fused to a cytotoxic polypeptide.

[0083] Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the VH or VL molecule replaced by a different residue. The sites of greatest interest for substitutional mutagenesis of VH and VL regions of anti-IL-6 antibodies of the invention include the hypervariable regions, but FR alterations are also contemplated.

[0084] Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions." If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened.

TABLE 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp; lys; arg	gln
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)	asn, gln, lys, arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Tpr (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

[0085] Substantial modifications in the biological properties of the anti-IL-6 antibodies of the invention may 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, gln, his, lys, arg;

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

(6) aromatic: trp, tyr, phe.

[0086] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0087] Any cysteine residue not involved in maintaining the proper conformation of the anti-IL-6 antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-IL-6 antibody to improve its stability (particularly where the anti-IL-6 antibody is an antibody fragment such as an Fv fragment).

[0088] A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent 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 (*e.g.*, improved affinity for an IL-6 antigen). One exemplary method 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) as herein disclosed. 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 additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and antigen. 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.

[0089] Another type of amino acid variant of the anti-IL-6 antibodies set forth herein alters the original glycosylation pattern of the anti-IL-6 antibodies. Such altering includes deleting one or more carbohydrate moieties found in the anti-IL-6 antibody, and/or adding one or more glycosylation sites that are not present in the anti-IL-6 antibody.

[0090] Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The 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.

[0091] Addition of glycosylation sites to an anti-IL-6 antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). 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 anti-IL-6 antibody (for O-linked glycosylation sites).

[0092] The VH domains included in the antibodies of the invention may, in certain embodiments, comprise an amino sequence that is identical to any one of SEQ ID NOs:19 to 32 or 38 to 43, except for a substitution of 1 to 20 amino acids. For example, the VH may have an amino acid sequence that is identical to SEQ ID NOs:19 to 32 or 38 to 43, except for a substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acids. The substitution(s) can be at any position within the sequence found in SEQ ID NOs:19 to 32 or 38 to 43. In certain embodiments, the substitution(s) is/are within one or more CDR of the VH domain. For example, the substitution(s) can be within CDR1, CDR2 and/or CDR3.

[0093] Likewise, the VL domains included in the antibodies of the invention may, in certain embodiments, comprise an amino sequence that is identical to any one of SEQ ID NOs:1 to 18 or 33 to 37, except for a substitution of 1 to 20 amino acids. For example, the VL may have an amino acid sequence that is identical to SEQ ID NOs:1 to 18 or 33 to 37, except for a substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acids. The substitution(s) can be at any position within the sequence found in SEQ ID NOs:1 to 18 or 33 to 37. In certain embodiments, the substitution(s) is/are within one or more CDR of the VL domain. For example, the substitution(s) can be within CDR1, CDR2 and/or CDR3.

[0094] The anti-IL-6 antibodies of the present invention which comprise a VH region that differs from SEQ ID NOs:19 to 32 or 38 to 43 in one or more amino acid residues and/or

a VL region that differs from SEQ ID NOs:1 to 18 or 33 to 37 in one or more amino acid residues will preferably retain the ability to specifically bind to an IL-6 antigen.

[0095] The present invention includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises any one of the CDR1s set forth in Table 2:

Table 2: Exemplary VH CDR1 sequences

VH CDR1 Sequence	SEQ ID NO:
TSGMCVS	51
TSGVAVG	52
TSGVSVG	53
TSGVGVG	54
TSGVAVN	55

[0096] The invention includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises a variant CDR1 having an amino acid sequence that is identical to any one of SEQ ID NOs:51 to 55, except that one or more (*e.g.*, one, two, three, four, five, six or seven) of the amino acids from SEQ ID NOs:51 to 55 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising a variant CDR1 will specifically bind to an IL-6 antigen.

[0097] The invention also includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises any one of the CDR2s set forth in Table 3:

Table 3: Exemplary VH CDR2 sequences

VH CDR2 Sequence	SEQ ID NO:
LIYWDDDKRYNPSLRS	56
LIFWDDDKHYSPSLKS	57
LVYWDDDRRYNPSLKN	58
LIYWDDDKRYSPSLKN	59
FIFWDDDKYYSPSLES	60
VIYWDDDRRYSPSLSS	61
LIYWDDDKRYSPSLET	97

[0098] The invention includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises a variant CDR2 having an amino acid sequence that is identical to any one of SEQ ID NOs:56 to 61 or 97, except that one or more (*e.g.*, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen or sixteen) of the amino acids from SEQ ID NOs:56 to 61 or 97 is replaced with any other amino acid.

Preferably the anti-IL-6 antibodies comprising a variant CDR2 will specifically bind to an IL-6 antigen.

[0099] The invention also includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises any one of the CDR3s set forth in Table 4:

Table 4: Exemplary VH CDR3 sequences

VH CDR3 Sequence	SEQ ID NO:
SYDDYLYYALDY	62
FYDDYLYYALDY	63
SADDYLYYALDY	64
SGDDYLYYALDY	65
SYDDYLMYALDY	66
SYDDYLYYSLDY	67
SYDDYLYYAFDY	68
SYDDYLYYALDT	69
SADDYLYYSLDY	70
SADDYLYYAFDY	71
SADDYLYYSFDY	72
SADDYLYYSFDT	73
SHDDYLYYALDY	98

[0100] The invention includes anti-IL-6 antibodies comprising a VH domain, wherein the VH comprises a variant CDR3 having an amino acid sequence that is identical to any one of SEQ ID NOs:62 to 73 or 98, except that one or more (*e.g.*, one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve) of the amino acids from SEQ ID NOs:62 to 73 or 98 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising a variant CDR3 will specifically bind to an IL-6 antigen.

[0101] In addition, the present invention includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises any one of the CDR1s set forth in Table 5:

Table 5: Exemplary VL CDR1 sequences

VL CDR1 Sequence	SEQ ID NO:
RASQTIDSSYLA	74
RASQDIDNFLA	75
RASQTISSYLN	76
RASQSISIYLN	77
RASQTISDFLN	78
WASQSINDYLN	79

[0102] The invention includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises a variant CDR1 having an amino acid sequence that is identical to any one of SEQ ID NOs:74 to 79, except that one or more (*e.g.*, one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve) of the amino acids from SEQ ID NOs:74 to 79 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising a variant CDR1 will specifically bind to an IL-6 antigen.

[0103] The invention also includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises any one of the CDR2s set forth in Table 6:

Table 6: Exemplary VL CDR2 sequences

VL CDR2 Sequence	SEQ ID NO:
GASSRAT	80
KVSSLRS	81
AASSLES	82
ATSTLQS	83
ASSNLQS	84
AASNLQI	85

[0104] The invention includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises a variant CDR2 having an amino acid sequence that is identical to any one of SEQ ID NOs:80 to 85, except that one or more (*e.g.*, one, two, three, four, five, six, or seven) of the amino acids from SEQ ID NOs:80 to 85 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising a variant CDR2 will specifically bind to an IL-6 antigen.

[0105] The invention also includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises any one of the CDR3s set forth in Table 7:

Table 7: Exemplary VL CDR3 sequences

VL CDR3 Sequence	SEQ ID NO:
QQYAKSPIT	86
QQTRRFPLT	87
QQANSFPLT	88
QQTYRNLFT	89
QQTYSTLGT	90
QNGHSFPLT	91
QSGHSFPLT	92
QHGHSFPLT	93
QLGHSFPLT	94
QNAHSFPLT	95

VL CDR3 Sequence	SEQ ID NO:
QNGWSFPLT	96

[0106] The invention includes anti-IL-6 antibodies comprising a VL domain, wherein the VL comprises a variant CDR3 having an amino acid sequence that is identical to any one of SEQ ID NOs:86 to 96, except that one or more (*e.g.*, one, two, three, four, five, six, seven, eight, or nine) of the amino acids from SEQ ID NOs:86 to 96 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising a variant CDR3 will specifically bind to an IL-6 antigen.

[0107] As shown in Example 1, the first generation human variable heavy chain regions (VHs) identified by screening a library of human VHs share significant sequence identity with one another. The amino sequence identities among the human VHs are shown in Table 10 and are illustrated in FIG. 1. For example, the CDR1s of the identified human VHs all share the amino acid sequence T-S-G-X_1-X_2-V-X_3 (SEQ ID NO:99). Additionally, the CDR2s of the identified human VHs all share the amino acid sequence X_1-X_2-X_3-W-D-D-D-X_4-X_5-Y-X_6-P-S-L-X_7-X_8 (SEQ ID NO:100).

[0108] Thus, the invention includes monoclonal antibodies comprising a variable heavy chain CDR1 (VH-CDR1) having the amino acid sequence T-S-G-X_1-X_2-V-X_3 (SEQ ID NO:99), wherein X_1, X_2 and X_3 can be any amino acid. For example, X_1, X_2 and/or X_3 can be isoleucine (I), leucine (L), valine (V), phenylalanine (P), methionine (M), cysteine (C), alanine (A), glycine (G), proline (P), threonine (T), serine (S), tyrosine (Y), tryptophan (W), glutamine (Q), asparagine (N), histidine (H), glutamic acid (E), aspartic acid (D), lysine (K), or arginine (R). In one exemplary embodiment, X_1 is methionine (M) or valine (V). In another exemplary embodiment, X_1 is valine (V). In another exemplary embodiment, X_2 is cysteine (C), alanine (A), serine (S) or glycine (G). In another exemplary embodiment, X_3 is serine (S) or glycine (G). Preferably, the antibodies of the invention that comprise a VH-CDR1 having the amino acid sequence T-S-G-X_1-X_2-V-X_3 (SEQ ID NO:99) bind specifically to an IL-6 antigen.

[0109] The invention also includes monoclonal antibodies comprising a variable heavy chain CDR2 (VH-CDR2) having the amino acid sequence X_1-X_2-X_3-W-D-D-D-X_4-X_5-Y-X_6-P-S-L-X_7-X_8 (SEQ ID NO:100), wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7 and X_8 can be any amino acid. For example, X_1, X_2, X_3, X_4, X_5, X_6, X_7 and/or X_8 can be isoleucine (I),

leucine (L), valine (V), phenylalanine (P), methionine (M), cysteine (C), alanine (A), glycine (G), proline (P), threonine (T), serine (S), tyrosine (Y), tryptophan (W), glutamine (Q), asparagine (N), histidine (H), glutamic acid (E), aspartic acid (D), lysine (K), or arginine (R). In one exemplary embodiment, X_1 is leucine (L), phenylalanine (F) or valine (V). In another exemplary embodiment, X_1 is leucine (L). In another exemplary embodiment, X_2 is isoleucine (I) or valine (V). In another exemplary embodiment, X_2 is isoleucine (I). In another exemplary embodiment, X_3 is tyrosine (Y) or phenyalanine (F). In another exemplary embodiment, X_4 is lysine (K) or arginine (R). In another exemplary embodiment, X_5 is arginine (R), tyrosine (Y), or histidine (H). In another exemplary embodiment, X_6 is serine (S) or asparagine (N). In another exemplary embodiment, wherein X_6 is serine (S). In another exemplary embodiment, X_7 is arginine (R), lysine (K), glutamic acid (E) or serine (S). In another exemplary embodiment, X_7 is lysine (K). In another exemplary embodiment, X_8 is serine (S) or asparagine (N). Preferably, the antibodies of the invention that comprise a VH-CDR2 having the amino acid sequence X_1-X_2-X_3-W-D-D-D-X_4-X_5-Y-X_6-P-S-L-X_7-X_8 (SEQ ID NO:100) bind specifically to an IL-6 antigen.

[0110] The invention also includes anti-IL-6 antibodies comprising a VL domain, wherein the VL is identical to any one of SEQ ID NOs:1 to 18 or 33 to 37, except that one or more of the non-CDR (*e.g.*, framework region) amino acids from SEQ ID NOs:1 to 18 or 33 to 37 is replaced with any other amino acid. The invention also includes anti-IL-6 antibodies comprising a VH domain, wherein the VH is identical to any one of SEQ ID NOs:19 to 32 or 38 to 43, except that one or more of the non-CDR (*e.g.*, framework region) amino acids from SEQ ID NOs:19 to 32 or 38 to 43 is replaced with any other amino acid. Preferably the anti-IL-6 antibodies comprising one or more amino acid changes in the framework regions of the VH and/or VK sequences will specifically bind to an IL-6 antigen.

[0111] The invention includes antibodies comprising any combination of:

(1) a variable heavy chain region (VH) set forth herein, or a VH comprising one or more CDRs set forth herein; and

(2) a variable light chain region (VL) set forth herein or a VL comprising one or more CDRs set forth herein.

[0112] For example, the invention includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H415 (SEQ ID NO:19) and L112 (SEQ ID NO:1); H415 (SEQ ID NO:19) and L151 (SEQ ID NO:2); H415 (SEQ ID NO:19) and L158 (SEQ ID NO:3); H415 (SEQ ID NO:19) and L159 (SEQ ID NO:4); H415 (SEQ ID NO:19) and L164 (SEQ ID NO:5); H415 (SEQ ID NO:19) and L165 (SEQ ID NO:6); H415 (SEQ ID NO:19) and L166 (SEQ ID NO:7); H415 (SEQ ID NO:19) and L167 (SEQ ID NO:8); H415 (SEQ ID NO:19) and L168 (SEQ ID NO:9); H415 (SEQ ID NO:19) and L169 (SEQ ID NO:10); H415 (SEQ ID NO:19) and L170 (SEQ ID NO:11); H415 (SEQ ID NO:19) and L171 (SEQ ID NO:12); H415 (SEQ ID NO:19) and L172 (SEQ ID NO:13); H415 (SEQ ID NO:19) and L173 (SEQ ID NO:14); H415 (SEQ ID NO:19) and L174 (SEQ ID NO:15); H415 (SEQ ID NO:19) and L175 (SEQ ID NO:16); H415 (SEQ ID NO:19) and L189 (SEQ ID NO:17); H415 (SEQ ID NO:19) and L198 (SEQ ID NO:18); H415 (SEQ ID NO:19) and L314 (SEQ ID NO:33); H415 (SEQ ID NO:19) and L305 (SEQ ID NO:34); H415 (SEQ ID NO:19) and L303 (SEQ ID NO:35); H415 (SEQ ID NO:19) and L298 (SEQ ID NO:36); or H415 (SEQ ID NO:19) and L321 (SEQ ID NO:37).

[0113] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H884 (SEQ ID NO:20) and L112 (SEQ ID NO:1); H884 (SEQ ID NO:20) and L151 (SEQ ID NO:2); H884 (SEQ ID NO:20) and L158 (SEQ ID NO:3); H884 (SEQ ID NO:20) and L159 (SEQ ID NO:4); H884 (SEQ ID NO:20) and L164 (SEQ ID NO:5); H884 (SEQ ID NO:20) and L165 (SEQ ID NO:6); H884 (SEQ ID NO:20) and L166 (SEQ ID NO:7); H884 (SEQ ID NO:20) and L167 (SEQ ID NO:8); H884 (SEQ ID NO:20) and L168 (SEQ ID NO:9); H884 (SEQ ID NO:20) and L169 (SEQ ID NO:10); H884 (SEQ ID NO:20) and L170 (SEQ ID NO:11); H884 (SEQ ID NO:20) and L171 (SEQ ID NO:12); H884 (SEQ ID NO:20) and L172 (SEQ ID NO:13); H884 (SEQ ID NO:20) and L173 (SEQ ID NO:14); H884 (SEQ ID NO:20) and L174 (SEQ ID NO:15); H884 (SEQ ID NO:20) and L175 (SEQ ID NO:16); H884 (SEQ ID NO:20) and L189 (SEQ ID NO:17); H884 (SEQ ID NO:20) and L198 (SEQ ID NO:18); H884 (SEQ ID NO:20) and L314 (SEQ ID NO:33); H884 (SEQ ID NO:20) and L305 (SEQ ID NO:34); H884 (SEQ ID NO:20) and L303 (SEQ ID NO:35); H884 (SEQ ID NO:20) and L298 (SEQ ID NO:36); or H884 (SEQ ID NO:20) and L321 (SEQ ID NO:37).

[0114] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1077 (SEQ ID NO:21) and L112 (SEQ ID NO:1); H1077 (SEQ ID NO:21) and L151 (SEQ ID NO:2); H1077 (SEQ ID NO:21) and L158 (SEQ ID NO:3); H1077 (SEQ ID NO:21) and L159 (SEQ ID NO:4); H1077 (SEQ ID NO:21) and L164 (SEQ ID NO:5); H1077 (SEQ ID NO:21) and L165 (SEQ ID NO:6); H1077 (SEQ ID NO:21) and L166 (SEQ ID NO:7); H1077 (SEQ ID NO:21) and L167 (SEQ ID NO:8); H1077 (SEQ ID NO:21) and L168 (SEQ ID NO:9); H1077 (SEQ ID NO:21) and L169 (SEQ ID NO:10); H1077 (SEQ ID NO:21) and L170 (SEQ ID NO:11); H1077 (SEQ ID NO:21) and L171 (SEQ ID NO:12); H1077 (SEQ ID NO:21) and L172 (SEQ ID NO:13); H1077 (SEQ ID NO:21) and L173 (SEQ ID NO:14); H1077 (SEQ ID NO:21) and L174 (SEQ ID NO:15); H1077 (SEQ ID NO:21) and L175 (SEQ ID NO:16); H1077 (SEQ ID NO:21) and L189 (SEQ ID NO:17); H1077 (SEQ ID NO:21) and L198 (SEQ ID NO:18); H1077 (SEQ ID NO:21) and L314 (SEQ ID NO:33); H1077 (SEQ ID NO:21) and L305 (SEQ ID NO:34); H1077 (SEQ ID NO:21) and L303 (SEQ ID NO:35); H1077 (SEQ ID NO:21) and L298 (SEQ ID NO:36); or H1077 (SEQ ID NO:21) and L321 (SEQ ID NO:37).

[0115] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1078 (SEQ ID NO:22) and L112 (SEQ ID NO:1); H1078 (SEQ ID NO:22) and L151 (SEQ ID NO:2); H1078 (SEQ ID NO:22) and L158 (SEQ ID NO:3); H1078 (SEQ ID NO:22) and L159 (SEQ ID NO:4); H1078 (SEQ ID NO:22) and L164 (SEQ ID NO:5); H1078 (SEQ ID NO:22) and L165 (SEQ ID NO:6); H1078 (SEQ ID NO:22) and L166 (SEQ ID NO:7); H1078 (SEQ ID NO:22) and L167 (SEQ ID NO:8); H1078 (SEQ ID NO:22) and L168 (SEQ ID NO:9); H1078 (SEQ ID NO:22) and L169 (SEQ ID NO:10); H1078 (SEQ ID NO:22) and L170 (SEQ ID NO:11); H1078 (SEQ ID NO:22) and L171 (SEQ ID NO:12); H1078 (SEQ ID NO:22) and L172 (SEQ ID NO:13); H1078 (SEQ ID NO:22) and L173 (SEQ ID NO:14); H1078 (SEQ ID NO:22) and L174 (SEQ ID NO:15); H1078 (SEQ ID NO:22) and L175 (SEQ ID NO:16); H1078 (SEQ ID NO:22) and L189 (SEQ ID NO:17); H1078 (SEQ ID NO:22) and L198 (SEQ ID NO:18); H1078 (SEQ ID NO:22) and L314 (SEQ ID NO:33); H1078 (SEQ ID NO:22) and L305 (SEQ ID NO:34); H1078 (SEQ ID NO:22) and L303 (SEQ ID NO:35); H1078 (SEQ ID NO:22) and L298 (SEQ ID NO:36); or H1078 (SEQ ID NO:22) and L321 (SEQ ID NO:37).

[0116] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1079 (SEQ ID NO:23) and L112 (SEQ ID NO:1); H1079 (SEQ ID NO:23) and L151 (SEQ ID NO:2); H1079 (SEQ ID NO:23) and L158 (SEQ ID NO:3); H1079 (SEQ ID NO:23) and L159 (SEQ ID NO:4); H1079 (SEQ ID NO:23) and L164 (SEQ ID NO:5); H1079 (SEQ ID NO:23) and L165 (SEQ ID NO:6); H1079 (SEQ ID NO:23) and L166 (SEQ ID NO:7); H1079 (SEQ ID NO:23) and L167 (SEQ ID NO:8); H1079 (SEQ ID NO:23) and L168 (SEQ ID NO:9); H1079 (SEQ ID NO:23) and L169 (SEQ ID NO:10); H1079 (SEQ ID NO:23) and L170 (SEQ ID NO:11); H1079 (SEQ ID NO:23) and L171 (SEQ ID NO:12); H1079 (SEQ ID NO:23) and L172 (SEQ ID NO:13); H1079 (SEQ ID NO:23) and L173 (SEQ ID NO:14); H1079 (SEQ ID NO:23) and L174 (SEQ ID NO:15); H1079 (SEQ ID NO:23) and L175 (SEQ ID NO:16); H1079 (SEQ ID NO:23) and L189 (SEQ ID NO:17); H1079 (SEQ ID NO:23) and L198 (SEQ ID NO:18); H1079 (SEQ ID NO:23) and L314 (SEQ ID NO:33); H1079 (SEQ ID NO:23) and L305 (SEQ ID NO:34); H1079 (SEQ ID NO:23) and L303 (SEQ ID NO:35); H1079 (SEQ ID NO:23) and L298 (SEQ ID NO:36); or H1079 (SEQ ID NO:23) and L321 (SEQ ID NO:37).

[0117] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1081 (SEQ ID NO:24) and L112 (SEQ ID NO:1); H1081 (SEQ ID NO:24) and L151 (SEQ ID NO:2); H1081 (SEQ ID NO:24) and L158 (SEQ ID NO:3); H1081 (SEQ ID NO:24) and L159 (SEQ ID NO:4); H1081 (SEQ ID NO:24) and L164 (SEQ ID NO:5); H1081 (SEQ ID NO:24) and L165 (SEQ ID NO:6); H1081 (SEQ ID NO:24) and L166 (SEQ ID NO:7); H1081 (SEQ ID NO:24) and L167 (SEQ ID NO:8); H1081 (SEQ ID NO:24) and L168 (SEQ ID NO:9); H1081 (SEQ ID NO:24) and L169 (SEQ ID NO:10); H1081 (SEQ ID NO:24) and L170 (SEQ ID NO:11); H1081 (SEQ ID NO:24) and L171 (SEQ ID NO:12); H1081 (SEQ ID NO:24) and L172 (SEQ ID NO:13); H1081 (SEQ ID NO:24) and L173 (SEQ ID NO:14); H1081 (SEQ ID NO:24) and L174 (SEQ ID NO:15); H1081 (SEQ ID NO:24) and L175 (SEQ ID NO:16); H1081 (SEQ ID NO:24) and L189 (SEQ ID NO:17); H1081 (SEQ ID NO:24) and L198 (SEQ ID NO:18); H1081 (SEQ ID NO:24) and L314 (SEQ ID NO:33); H1081 (SEQ ID NO:24) and L305 (SEQ ID NO:34); H1081 (SEQ ID NO:24) and L303 (SEQ ID NO:35); H1081 (SEQ ID NO:24) and L298 (SEQ ID NO:36); or H1081 (SEQ ID NO:24) and L321 (SEQ ID NO:37).

[0118] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1089 (SEQ ID NO:25) and L112 (SEQ ID NO:1); H1089 (SEQ ID NO:25) and L151 (SEQ ID NO:2); H1089 (SEQ ID NO:25) and L158 (SEQ ID NO:3); H1089 (SEQ ID NO:25) and L159 (SEQ ID NO:4); H1089 (SEQ ID NO:25) and L164 (SEQ ID NO:5); H1089 (SEQ ID NO:25) and L165 (SEQ ID NO:6); H1089 (SEQ ID NO:25) and L166 (SEQ ID NO:7); H1089 (SEQ ID NO:25) and L167 (SEQ ID NO:8); H1089 (SEQ ID NO:25) and L168 (SEQ ID NO:9); H1089 (SEQ ID NO:25) and L169 (SEQ ID NO:10); H1089 (SEQ ID NO:25) and L170 (SEQ ID NO:11); H1089 (SEQ ID NO:25) and L171 (SEQ ID NO:12); H1089 (SEQ ID NO:25) and L172 (SEQ ID NO:13); H1089 (SEQ ID NO:25) and L173 (SEQ ID NO:14); H1089 (SEQ ID NO:25) and L174 (SEQ ID NO:15); H1089 (SEQ ID NO:25) and L175 (SEQ ID NO:16); H1089 (SEQ ID NO:25) and L189 (SEQ ID NO:17); H1089 (SEQ ID NO:25) and L198 (SEQ ID NO:18); H1089 (SEQ ID NO:25) and L314 (SEQ ID NO:33); H1089 (SEQ ID NO:25) and L305 (SEQ ID NO:34); H1089 (SEQ ID NO:25) and L303 (SEQ ID NO:35); H1089 (SEQ ID NO:25) and L298 (SEQ ID NO:36); or H1089 (SEQ ID NO:25) and L321 (SEQ ID NO:37).

[0119] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1511 (SEQ ID NO:26) and L112 (SEQ ID NO:1); H1511 (SEQ ID NO:26) and L151 (SEQ ID NO:2); H1511 (SEQ ID NO:26) and L158 (SEQ ID NO:3); H1511 (SEQ ID NO:26) and L159 (SEQ ID NO:4); H1511 (SEQ ID NO:26) and L164 (SEQ ID NO:5); H1511 (SEQ ID NO:26) and L165 (SEQ ID NO:6); H1511 (SEQ ID NO:26) and L166 (SEQ ID NO:7); H1511 (SEQ ID NO:26) and L167 (SEQ ID NO:8); H1511 (SEQ ID NO:26) and L168 (SEQ ID NO:9); H1511 (SEQ ID NO:26) and L169 (SEQ ID NO:10); H1511 (SEQ ID NO:26) and L170 (SEQ ID NO:11); H1511 (SEQ ID NO:26) and L171 (SEQ ID NO:12); H1511 (SEQ ID NO:26) and L172 (SEQ ID NO:13); H1511 (SEQ ID NO:26) and L173 (SEQ ID NO:14); H1511 (SEQ ID NO:26) and L174 (SEQ ID NO:15); H1511 (SEQ ID NO:26) and L175 (SEQ ID NO:16); H1511 (SEQ ID NO:26) and L189 (SEQ ID NO:17); H1511 (SEQ ID NO:26) and L198 (SEQ ID NO:18); H1511 (SEQ ID NO:26) and L314 (SEQ ID NO:33); H1511 (SEQ ID NO:26) and L305 (SEQ ID NO:34); H1511 (SEQ ID NO:26) and L303 (SEQ ID NO:35); H1511 (SEQ ID NO:26) and L298 (SEQ ID NO:36); or H1511 (SEQ ID NO:26) and L321 (SEQ ID NO:37).

[0120] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1420 (SEQ ID NO:27) and L112 (SEQ ID NO:1); H1420 (SEQ ID NO:27) and L151 (SEQ ID NO:2); H1420 (SEQ ID NO:27) and L158 (SEQ ID NO:3); H1420 (SEQ ID NO:27) and L159 (SEQ ID NO:4); H1420 (SEQ ID NO:27) and L164 (SEQ ID NO:5); H1420 (SEQ ID NO:27) and L165 (SEQ ID NO:6); H1420 (SEQ ID NO:27) and L166 (SEQ ID NO:7); H1420 (SEQ ID NO:27) and L167 (SEQ ID NO:8); H1420 (SEQ ID NO:27) and L168 (SEQ ID NO:9); H1420 (SEQ ID NO:27) and L169 (SEQ ID NO:10); H1420 (SEQ ID NO:27) and L170 (SEQ ID NO:11); H1420 (SEQ ID NO:27) and L171 (SEQ ID NO:12); H1420 (SEQ ID NO:27) and L172 (SEQ ID NO:13); H1420 (SEQ ID NO:27) and L173 (SEQ ID NO:14); H1420 (SEQ ID NO:27) and L174 (SEQ ID NO:15); H1420 (SEQ ID NO:27) and L175 (SEQ ID NO:16); H1420 (SEQ ID NO:27) and L189 (SEQ ID NO:17); H1420 (SEQ ID NO:27) and L198 (SEQ ID NO:18); H1420 (SEQ ID NO:27) and L314 (SEQ ID NO:33); H1420 (SEQ ID NO:27) and L305 (SEQ ID NO:34); H1420 (SEQ ID NO:27) and L303 (SEQ ID NO:35); H1420 (SEQ ID NO:27) and L298 (SEQ ID NO:36); or H1420 (SEQ ID NO:27) and L321 (SEQ ID NO:37).

[0121] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1432 (SEQ ID NO:28) and L112 (SEQ ID NO:1); H1432 (SEQ ID NO:28) and L151 (SEQ ID NO:2); H1432 (SEQ ID NO:28) and L158 (SEQ ID NO:3); H1432 (SEQ ID NO:28) and L159 (SEQ ID NO:4); H1432 (SEQ ID NO:28) and L164 (SEQ ID NO:5); H1432 (SEQ ID NO:28) and L165 (SEQ ID NO:6); H1432 (SEQ ID NO:28) and L166 (SEQ ID NO:7); H1432 (SEQ ID NO:28) and L167 (SEQ ID NO:8); H1432 (SEQ ID NO:28) and L168 (SEQ ID NO:9); H1432 (SEQ ID NO:28) and L169 (SEQ ID NO:10); H1432 (SEQ ID NO:28) and L170 (SEQ ID NO:11); H1432 (SEQ ID NO:28) and L171 (SEQ ID NO:12); H1432 (SEQ ID NO:28) and L172 (SEQ ID NO:13); H1432 (SEQ ID NO:28) and L173 (SEQ ID NO:14); H1432 (SEQ ID NO:28) and L174 (SEQ ID NO:15); H1432 (SEQ ID NO:28) and L175 (SEQ ID NO:16); H1432 (SEQ ID NO:28) and L189 (SEQ ID NO:17); H1432 (SEQ ID NO:28) and L198 (SEQ ID NO:18); H1432 (SEQ ID NO:28) and L314 (SEQ ID NO:33); H1432 (SEQ ID NO:28) and L305 (SEQ ID NO:34); H1432 (SEQ ID NO:28) and L303 (SEQ ID NO:35); H1432 (SEQ ID NO:28) and L298 (SEQ ID NO:36); or H1432 (SEQ ID NO:28) and L321 (SEQ ID NO:37).

[0122] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1515 (SEQ ID NO:29) and L112 (SEQ ID NO:1); H1515 (SEQ ID NO:29) and L151 (SEQ ID NO:2); H1515 (SEQ ID NO:29) and L158 (SEQ ID NO:3); H1515 (SEQ ID NO:29) and L159 (SEQ ID NO:4); H1515 (SEQ ID NO:29) and L164 (SEQ ID NO:5); H1515 (SEQ ID NO:29) and L165 (SEQ ID NO:6); H1515 (SEQ ID NO:29) and L166 (SEQ ID NO:7); H1515 (SEQ ID NO:29) and L167 (SEQ ID NO:8); H1515 (SEQ ID NO:29) and L168 (SEQ ID NO:9); H1515 (SEQ ID NO:29) and L169 (SEQ ID NO:10); H1515 (SEQ ID NO:29) and L170 (SEQ ID NO:11); H1515 (SEQ ID NO:29) and L171 (SEQ ID NO:12); H1515 (SEQ ID NO:29) and L172 (SEQ ID NO:13); H1515 (SEQ ID NO:29) and L173 (SEQ ID NO:14); H1515 (SEQ ID NO:29) and L174 (SEQ ID NO:15); H1515 (SEQ ID NO:29) and L175 (SEQ ID NO:16); H1515 (SEQ ID NO:29) and L189 (SEQ ID NO:17); H1515 (SEQ ID NO:29) and L198 (SEQ ID NO:18); H1515 (SEQ ID NO:29) and L314 (SEQ ID NO:33); H1515 (SEQ ID NO:29) and L305 (SEQ ID NO:34); H1515 (SEQ ID NO:29) and L303 (SEQ ID NO:35); H1515 (SEQ ID NO:29) and L298 (SEQ ID NO:36); or H1515 (SEQ ID NO:29) and L321 (SEQ ID NO:37).

[0123] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1362 (SEQ ID NO:30) and L112 (SEQ ID NO:1); H1362 (SEQ ID NO:30) and L151 (SEQ ID NO:2); H1362 (SEQ ID NO:30) and L158 (SEQ ID NO:3); H1362 (SEQ ID NO:30) and L159 (SEQ ID NO:4); H1362 (SEQ ID NO:30) and L164 (SEQ ID NO:5); H1362 (SEQ ID NO:30) and L165 (SEQ ID NO:6); H1362 (SEQ ID NO:30) and L166 (SEQ ID NO:7); H1362 (SEQ ID NO:30) and L167 (SEQ ID NO:8); H1362 (SEQ ID NO:30) and L168 (SEQ ID NO:9); H1362 (SEQ ID NO:30) and L169 (SEQ ID NO:10); H1362 (SEQ ID NO:30) and L170 (SEQ ID NO:11); H1362 (SEQ ID NO:30) and L171 (SEQ ID NO:12); H1362 (SEQ ID NO:30) and L172 (SEQ ID NO:13); H1362 (SEQ ID NO:30) and L173 (SEQ ID NO:14); H1362 (SEQ ID NO:30) and L174 (SEQ ID NO:15); H1362 (SEQ ID NO:30) and L175 (SEQ ID NO:16); H1362 (SEQ ID NO:30) and L189 (SEQ ID NO:17); H1362 (SEQ ID NO:30) and L198 (SEQ ID NO:18); H1362 (SEQ ID NO:30) and L314 (SEQ ID NO:33); H1362 (SEQ ID NO:30) and L305 (SEQ ID NO:34); H1362 (SEQ ID NO:30) and L303 (SEQ ID NO:35); H1362 (SEQ ID NO:30) and L298 (SEQ ID NO:36); or H1362 (SEQ ID NO:30) and L321 (SEQ ID NO:37).

[0124] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1437 (SEQ ID NO:31) and L112 (SEQ ID NO:1); H1437 (SEQ ID NO:31) and L151 (SEQ ID NO:2); H1437 (SEQ ID NO:31) and L158 (SEQ ID NO:3); H1437 (SEQ ID NO:31) and L159 (SEQ ID NO:4); H1437 (SEQ ID NO:31) and L164 (SEQ ID NO:5); H1437 (SEQ ID NO:31) and L165 (SEQ ID NO:6); H1437 (SEQ ID NO:31) and L166 (SEQ ID NO:7); H1437 (SEQ ID NO:31) and L167 (SEQ ID NO:8); H1437 (SEQ ID NO:31) and L168 (SEQ ID NO:9); H1437 (SEQ ID NO:31) and L169 (SEQ ID NO:10); H1437 (SEQ ID NO:31) and L170 (SEQ ID NO:11); H1437 (SEQ ID NO:31) and L171 (SEQ ID NO:12); H1437 (SEQ ID NO:31) and L172 (SEQ ID NO:13); H1437 (SEQ ID NO:31) and L173 (SEQ ID NO:14); H1437 (SEQ ID NO:31) and L174 (SEQ ID NO:15); H1437 (SEQ ID NO:31) and L175 (SEQ ID NO:16); H1437 (SEQ ID NO:31) and L189 (SEQ ID NO:17); H1437 (SEQ ID NO:31) and L198 (SEQ ID NO:18); H1437 (SEQ ID NO:31) and L314 (SEQ ID NO:33); H1437 (SEQ ID NO:31) and L305 (SEQ ID NO:34); H1437 (SEQ ID NO:31) and L303 (SEQ ID NO:35); H1437 (SEQ ID NO:31) and L298 (SEQ ID NO:36); or H1437 (SEQ ID NO:31) and L321 (SEQ ID NO:37).

[0125] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1461 (SEQ ID NO:32) and L112 (SEQ ID NO:1); H1461 (SEQ ID NO:32) and L151 (SEQ ID NO:2); H1461 (SEQ ID NO:32) and L158 (SEQ ID NO:3); H1461 (SEQ ID NO:32) and L159 (SEQ ID NO:4); H1461 (SEQ ID NO:32) and L164 (SEQ ID NO:5); H1461 (SEQ ID NO:32) and L165 (SEQ ID NO:6); H1461 (SEQ ID NO:32) and L166 (SEQ ID NO:7); H1461 (SEQ ID NO:32) and L167 (SEQ ID NO:8); H1461 (SEQ ID NO:32) and L168 (SEQ ID NO:9); H1461 (SEQ ID NO:32) and L169 (SEQ ID NO:10); H1461 (SEQ ID NO:32) and L170 (SEQ ID NO:11); H1461 (SEQ ID NO:32) and L171 (SEQ ID NO:12); H1461 (SEQ ID NO:32) and L172 (SEQ ID NO:13); H1461 (SEQ ID NO:32) and L173 (SEQ ID NO:14); H1461 (SEQ ID NO:32) and L174 (SEQ ID NO:15); H1461 (SEQ ID NO:32) and L175 (SEQ ID NO:16); H1461 (SEQ ID NO:32) and L189 (SEQ ID NO:17); H1461 (SEQ ID NO:32) and L198 (SEQ ID NO:18); H1461 (SEQ ID NO:32) and L314 (SEQ ID NO:33); H1461 (SEQ ID NO:32) and L305 (SEQ ID NO:34); H1461 (SEQ ID NO:32) and L303 (SEQ ID NO:35); H1461 (SEQ ID NO:32) and L298 (SEQ ID NO:36); or H1461 (SEQ ID NO:32) and L321 (SEQ ID NO:37).

[0126] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1519 (SEQ ID NO:38) and L112 (SEQ ID NO:1); H1519 (SEQ ID NO:38) and L151 (SEQ ID NO:2); H1519 (SEQ ID NO:38) and L158 (SEQ ID NO:3); H1519 (SEQ ID NO:38) and L159 (SEQ ID NO:4); H1519 (SEQ ID NO:38) and L164 (SEQ ID NO:5); H1519 (SEQ ID NO:38) and L165 (SEQ ID NO:6); H1519 (SEQ ID NO:38) and L166 (SEQ ID NO:7); H1519 (SEQ ID NO:38) and L167 (SEQ ID NO:8); H1519 (SEQ ID NO:38) and L168 (SEQ ID NO:9); H1519 (SEQ ID NO:38) and L169 (SEQ ID NO:10); H1519 (SEQ ID NO:38) and L170 (SEQ ID NO:11); H1519 (SEQ ID NO:38) and L171 (SEQ ID NO:12); H1519 (SEQ ID NO:38) and L172 (SEQ ID NO:13); H1519 (SEQ ID NO:38) and L173 (SEQ ID NO:14); H1519 (SEQ ID NO:38) and L174 (SEQ ID NO:15); H1519 (SEQ ID NO:38) and L175 (SEQ ID NO:16); H1519 (SEQ ID NO:38) and L189 (SEQ ID NO:17); H1519 (SEQ ID NO:38) and L198 (SEQ ID NO:18); H1519 (SEQ ID NO:38) and L314 (SEQ ID NO:33); H1519 (SEQ ID NO:38) and L305 (SEQ ID NO:34); H1519 (SEQ ID NO:38) and L303 (SEQ ID NO:35); H1519 (SEQ ID NO:38) and L298 (SEQ ID NO:36); or H1519 (SEQ ID NO:38) and L321 (SEQ ID NO:37).

[0127] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1520 (SEQ ID NO:39) and L112 (SEQ ID NO:1); H1520 (SEQ ID NO:39) and L151 (SEQ ID NO:2); H1520 (SEQ ID NO:39) and L158 (SEQ ID NO:3); H1520 (SEQ ID NO:39) and L159 (SEQ ID NO:4); H1520 (SEQ ID NO:39) and L164 (SEQ ID NO:5); H1520 (SEQ ID NO:39) and L165 (SEQ ID NO:6); H1520 (SEQ ID NO:39) and L166 (SEQ ID NO:7); H1520 (SEQ ID NO:39) and L167 (SEQ ID NO:8); H1520 (SEQ ID NO:39) and L168 (SEQ ID NO:9); H1520 (SEQ ID NO:39) and L169 (SEQ ID NO:10); H1520 (SEQ ID NO:39) and L170 (SEQ ID NO:11); H1520 (SEQ ID NO:39) and L171 (SEQ ID NO:12); H1520 (SEQ ID NO:39) and L172 (SEQ ID NO:13); H1520 (SEQ ID NO:39) and L173 (SEQ ID NO:14); H1520 (SEQ ID NO:39) and L174 (SEQ ID NO:15); H1520 (SEQ ID NO:39) and L175 (SEQ ID NO:16); H1520 (SEQ ID NO:39) and L189 (SEQ ID NO:17); H1520 (SEQ ID NO:39) and L198 (SEQ ID NO:18); H1520 (SEQ ID NO:39) and L314 (SEQ ID NO:33); H1520 (SEQ ID NO:39) and L305 (SEQ ID NO:34); H1520 (SEQ ID NO:39) and L303 (SEQ ID NO:35); H1520 (SEQ ID NO:39) and L298 (SEQ ID NO:36); or H1520 (SEQ ID NO:39) and L321 (SEQ ID NO:37).

[0128] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1521 (SEQ ID NO:40) and L112 (SEQ ID NO:1); H1521 (SEQ ID NO:40) and L151 (SEQ ID NO:2); H1521 (SEQ ID NO:40) and L158 (SEQ ID NO:3); H1521 (SEQ ID NO:40) and L159 (SEQ ID NO:4); H1521 (SEQ ID NO:40) and L164 (SEQ ID NO:5); H1521 (SEQ ID NO:40) and L165 (SEQ ID NO:6); H1521 (SEQ ID NO:40) and L166 (SEQ ID NO:7); H1521 (SEQ ID NO:40) and L167 (SEQ ID NO:8); H1521 (SEQ ID NO:40) and L168 (SEQ ID NO:9); H1521 (SEQ ID NO:40) and L169 (SEQ ID NO:10); H1521 (SEQ ID NO:40) and L170 (SEQ ID NO:11); H1521 (SEQ ID NO:40) and L171 (SEQ ID NO:12); H1521 (SEQ ID NO:40) and L172 (SEQ ID NO:13); H1521 (SEQ ID NO:40) and L173 (SEQ ID NO:14); H1521 (SEQ ID NO:40) and L174 (SEQ ID NO:15); H1521 (SEQ ID NO:40) and L175 (SEQ ID NO:16); H1521 (SEQ ID NO:40) and L189 (SEQ ID NO:17); H1521 (SEQ ID NO:40) and L198 (SEQ ID NO:18); H1521 (SEQ ID NO:40) and L314 (SEQ ID NO:33); H1521 (SEQ ID NO:40) and L305 (SEQ ID NO:34); H1521 (SEQ ID NO:40) and L303 (SEQ ID NO:35); H1521 (SEQ ID NO:40) and L298 (SEQ ID NO:36); or H1521 (SEQ ID NO:40) and L321 (SEQ ID NO:37).

[0129] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1522 (SEQ ID NO:41) and L112 (SEQ ID NO:1); H1522 (SEQ ID NO:41) and L151 (SEQ ID NO:2); H1522 (SEQ ID NO:41) and L158 (SEQ ID NO:3); H1522 (SEQ ID NO:41) and L159 (SEQ ID NO:4); H1522 (SEQ ID NO:41) and L164 (SEQ ID NO:5); H1522 (SEQ ID NO:41) and L165 (SEQ ID NO:6); H1522 (SEQ ID NO:41) and L166 (SEQ ID NO:7); H1522 (SEQ ID NO:41) and L167 (SEQ ID NO:8); H1522 (SEQ ID NO:41) and L168 (SEQ ID NO:9); H1522 (SEQ ID NO:41) and L169 (SEQ ID NO:10); H1522 (SEQ ID NO:41) and L170 (SEQ ID NO:11); H1522 (SEQ ID NO:41) and L171 (SEQ ID NO:12); H1522 (SEQ ID NO:41) and L172 (SEQ ID NO:13); H1522 (SEQ ID NO:41) and L173 (SEQ ID NO:14); H1522 (SEQ ID NO:41) and L174 (SEQ ID NO:15); H1522 (SEQ ID NO:41) and L175 (SEQ ID NO:16); H1522 (SEQ ID NO:41) and L189 (SEQ ID NO:17); H1522 (SEQ ID NO:41) and L198 (SEQ ID NO:18); H1522 (SEQ ID NO:41) and L314 (SEQ ID NO:33); H1522 (SEQ ID NO:41) and L305 (SEQ ID NO:34); H1522 (SEQ ID NO:41) and L303 (SEQ ID NO:35); H1522 (SEQ ID NO:41) and L298 (SEQ ID NO:36); or H1522 (SEQ ID NO:41) and L321 (SEQ ID NO:37).

[0130] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1553 (SEQ ID NO:42) and L112 (SEQ ID NO:1); H1553 (SEQ ID NO:42) and L151 (SEQ ID NO:2); H1553 (SEQ ID NO:42) and L158 (SEQ ID NO:3); H1553 (SEQ ID NO:42) and L159 (SEQ ID NO:4); H1553 (SEQ ID NO:42) and L164 (SEQ ID NO:5); H1553 (SEQ ID NO:42) and L165 (SEQ ID NO:6); H1553 (SEQ ID NO:42) and L166 (SEQ ID NO:7); H1553 (SEQ ID NO:42) and L167 (SEQ ID NO:8); H1553 (SEQ ID NO:42) and L168 (SEQ ID NO:9); H1553 (SEQ ID NO:42) and L169 (SEQ ID NO:10); H1553 (SEQ ID NO:42) and L170 (SEQ ID NO:11); H1553 (SEQ ID NO:42) and L171 (SEQ ID NO:12); H1553 (SEQ ID NO:42) and L172 (SEQ ID NO:13); H1553 (SEQ ID NO:42) and L173 (SEQ ID NO:14); H1553 (SEQ ID NO:42) and L174 (SEQ ID NO:15); H1553 (SEQ ID NO:42) and L175 (SEQ ID NO:16); H1553 (SEQ ID NO:42) and L189 (SEQ ID NO:17); H1553 (SEQ ID NO:42) and L198 (SEQ ID NO:18); H1553 (SEQ ID NO:42) and L314 (SEQ ID NO:33); H1553 (SEQ ID NO:42) and L305 (SEQ ID NO:34); H1553 (SEQ ID NO:42) and L303 (SEQ ID NO:35); H1553 (SEQ ID NO:42) and L298 (SEQ ID NO:36); or H1553 (SEQ ID NO:42) and L321 (SEQ ID NO:37).

[0131] The invention also includes anti-IL-6 antibodies comprising any one of the following combinations of VH regions and VL regions: H1579 (SEQ ID NO:43) and L112 (SEQ ID NO:1); H1579 (SEQ ID NO:43) and L151 (SEQ ID NO:2); H1579 (SEQ ID NO:43) and L158 (SEQ ID NO:3); H1579 (SEQ ID NO:43) and L159 (SEQ ID NO:4); H1579 (SEQ ID NO:43) and L164 (SEQ ID NO:5); H1579 (SEQ ID NO:43) and L165 (SEQ ID NO:6); H1579 (SEQ ID NO:43) and L166 (SEQ ID NO:7); H1579 (SEQ ID NO:43) and L167 (SEQ ID NO:8); H1579 (SEQ ID NO:43) and L168 (SEQ ID NO:9); H1579 (SEQ ID NO:43) and L169 (SEQ ID NO:10); H1579 (SEQ ID NO:43) and L170 (SEQ ID NO:11); H1579 (SEQ ID NO:43) and L171 (SEQ ID NO:12); H1579 (SEQ ID NO:43) and L172 (SEQ ID NO:13); H1579 (SEQ ID NO:43) and L173 (SEQ ID NO:14); H1579 (SEQ ID NO:43) and L174 (SEQ ID NO:15); H1579 (SEQ ID NO:43) and L175 (SEQ ID NO:16); H1579 (SEQ ID NO:43) and L189 (SEQ ID NO:17); H1579 (SEQ ID NO:43) and L198 (SEQ ID NO:18); H1579 (SEQ ID NO:43) and L314 (SEQ ID NO:33); H1579 (SEQ ID NO:43) and L305 (SEQ ID NO:34); H1579 (SEQ ID NO:43) and L303 (SEQ ID NO:35); H1579 (SEQ ID NO:43) and L298 (SEQ ID NO:36); or H1579 (SEQ ID NO:43) and L321 (SEQ ID NO:37).

[0132] It will be understood by person of ordinary skill in the art that any of the aforementioned antibodies comprising a combination of a VH region and a VL region, may include one or more additional regions (or "domains") that are normally found in antibody molecules, such as, *e.g.*, one or more constant heavy chain regions (*e.g.*, CH1, CH2 and/or CH3), and/or a constant light chain region (CL). Preferably, an antibody comprising a combination of a VH region and a VL region, as set forth herein, will bind specifically to an IL-6 antigen.

NUCLEIC ACID MOLECULES, VECTORS AND CELLS

[0133] The present invention includes nucleic acid molecules that encode an anti-IL-6 antibody heavy chain comprising any one of the VH regions set forth herein, including any amino acid variants of the VH regions. The invention also includes nucleic acid molecules that encode an anti-IL-6 antibody light chain comprising any one of the VL regions set forth herein, including any amino acid variants of the VL regions. In certain embodiments, the nucleic acid molecules encode a portion of an anti-IL-6 antibody heavy chain or a portion of an anti-IL-6 antibody light chain. For example, the invention includes nucleic acid molecules that encode a polypeptide comprising one or more CDR of an anti-IL-6 VH set forth herein, including any one of the CDRs represented by SEQ ID NOs:51 to 73. The invention also includes nucleic acid molecules that encode a polypeptide comprising one or more CDR of an anti-IL-6 VL set forth herein, including any one of the CDRs represented by SEQ ID NOs:74 to 96.

[0134] The present invention also includes nucleic acid molecules that encode any of the VH regions set forth herein, including any one of the VH regions represented by SEQ ID NOs:19 to 32 and 38 to 43. The invention includes nucleic acid molecules that encode a VH region having an amino acid sequence that is at least at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to any one of SEQ ID NOs:19 to 32 and 38 to 43, wherein an antibody comprising the VH region specifically binds to IL-6.

[0135] The present invention also includes nucleic acid molecules that encode any of the VL regions set forth herein, including any one of the VL regions represented by SEQ ID NOs:1 to 18 and 33 to 37. The invention includes nucleic acid molecules that encode a VL region having an amino acid sequence that is at least at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to any one of SEQ ID NOs:1 to 18 and 33 to 37, wherein an antibody comprising the VL region specifically binds to IL-6.

[0136] The invention also includes expression vectors comprising any of the nucleic acid molecules described herein. Exemplary vectors include plasmids, phagemids, cosmids, viruses and phage nucleic acids or other nucleic acid molecules that are able to replicate autonomously or to be replicated in a prokaryotic or eukaryotic cell. In certain embodiments, the vectors are able to be replicated in a mammalian cell. Typical expression vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the nucleic acid molecules of the invention. The vectors may also comprise genetic expression cassettes containing at least one independent terminator sequence, sequences permitting replication of the vector in both eukaryotes and prokaryotes, i.e., shuttle vectors, and selection markers for both prokaryotic and eukaryotic systems. The vectors preferably contain a marker to provide a phenotypic trait for selection of transformed host cells such as conferring resistance to antibiotics such as ampicillin or neomycin.

[0137] The nucleic acid molecules of the invention can be under the control of one or more promoters. For example, the nucleic acid molecules can be under the control of a constitutive promoter or an inducible promoter. Exemplary promoters include promoters derived from the human cytomegalovirus, metallothionine promoter, SV-40 early promoter, SV-40 later promoter, murine mammary tumor virus promoter, Rous sarcoma virus promoter, polyhedrin promoter, or other promoters shown effective for expression in eukaryotic cells.

[0138] The invention also includes host cells comprising a nucleic acid molecule or a vector of the invention. By "host cell" is meant a cell or population of cells into which a

nucleic acid molecule or vector of the invention is introduced. A host cell of the present invention is preferably a eukaryotic cell or cell line, preferably a plant, animal, vertebrate, mammalian, rodent, mouse, primate, or human cell or cell line. By "a population of host cells" is meant a group of cultured cells into which a nucleic acid molecule or vector of the present invention can be introduced and expressed. Any host cells which will support expression from a nucleic acid molecule or vector of the invention is intended. Although it is preferred that a population of host cells be a monoculture, *i.e.*, where each cell in the population is of the same cell type, mixed cultures of cells are also contemplated. Host cells of the present invention may be adherent, *i.e.*, host cells which grow attached to a solid substrate, or, alternatively, the host cells may be in suspension. Host cells may be cells derived from primary tumors, cells derived from metastatic tumors, primary cells, cells which have lost contact inhibition, transformed primary cells, immortalized primary cells, cells which may undergo apoptosis, and cell lines derived therefrom.

[0139] The invention also includes methods of producing an antibody of the present invention, the method comprising: (i) culturing a host cell expressing one or more nucleic acid sequences encoding an antibody of the present invention, and (ii) recovering the antibody from the culture medium.

PHARMACEUTICAL COMPOSITIONS

[0140] The anti-IL-6 antibodies of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody or antibody portion of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents,

preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

[0141] The pharmaceutical compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

[0142] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.*, antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0143] The anti-IL-6 antibodies of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred

route/mode of administration is intravenous injection or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. *See, e.g.*, Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[0144] In certain embodiments, an anti-IL-6 antibody of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

[0145] Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an antibody or antibody portion of the invention is coformulated with and/or coadministered with one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents is an agent or agents for the treatment of a disease or condition as described herein, in particular a disease or disorder as described in the section entitled "Therapeutic Uses of Anti-IL-6 Antibodies of the Invention." For example, an anti-IL-6 antibody of the invention may be coformulated and/or coadministered with one or more additional antibodies that bind IL-6 or other targets, *e.g.*, antibodies that bind to the IL-6 receptor.

[0146] As used herein, the terms "treat" and "treatment" refer to therapeutic treatment, including prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change associated with a disease or disorder. Beneficial or desired clinical results include, but are not limited to, alleviation of

symptoms, diminishment of the extent of a disease or disorder, stabilization of a disease or disorder (*i.e.*, where the disease or disorder does not worsen), delay or slowing of the progression of a disease or disorder, amelioration or palliation of the disease or disorder, and remission (whether partial or total) of the disease or disorder, whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the disease or disorder as well as those prone to having the disease or disorder or those in which the disease or disorder is to be prevented.

[0147] The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an anti-IL-6 antibody of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0148] Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the

particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[0149] An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an anti-IL-6 antibody of the invention is 0.1-20 mg/kg, more preferably 1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

THERAPEUTIC USES OF ANTI-IL-6 ANTIBODIES OF THE INVENTION

[0150] The antibodies of the present invention can be used to treat any disease or disorder mediated by, associated with, or caused by the action of IL-6. For example, the antibodies of the invention can be used to treat a disease or disorder that results from the binding of IL-6 to an IL-6 receptor. The antibodies of the invention may be used to treat a disease or disorder caused by an intracellular signaling event that results, directly or indirectly, from the binding of IL-6 to an IL-6 receptor. Exemplary intracellular IL-6 signaling pathways are illustrated in FIG. 11. The antibodies of the present invention can be used to treat any disease or disorder that is caused by or is associated with the activity of any of the molecules illustrated in FIG. 11, the activities of which are influenced by the binding of IL-6 to an IL-6 receptor.

[0151] Thus, the present invention includes methods for treating a disease or disorder mediated by, associated with, or caused by the action of IL-6. The methods comprise administering to a patient in need thereof an anti-IL-6 antibody as disclosed herein. The expression "an anti-IL-6 antibody as disclosed herein" is intended to mean any anti-IL-6 antibody comprising any of the VH regions and/or VL regions set forth herein, as well as any anti-IL-6 antibody comprising a variant of any of the VH regions set forth herein and/or a variant of any of the VL regions set forth herein. An "anti-IL-6 antibody as disclosed herein" is also intended to mean any anti-IL-6 antibody comprising one or more

VH CDRs (*e.g.*, CDR1, CDR2, and/or CDR3) and/or one or more VL CDRs (*e.g.*, CDR1, CDR2, and/or CDR3) disclosed herein. Preferably, the antibodies bind specifically to an IL-6 antigen.

[0152] In some embodiments, the disease or disorder to be treated is selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenile arthritis, and fibrotic conditions.

[0153] In one exemplary embodiment, the invention provides a method for treating an autoimmune disease or disorder, wherein the method comprises administering to a patient in need thereof an anti-IL-6 antibody as disclosed herein. Exemplary autoimmune diseases and disorders that can be treated with an anti-IL-6 antibody of the invention include, *e.g.*, allograft rejection, autoimmune thyroid disease (*e.g.*, Graves' disease and Hashimoto's thyroiditis), autoimmune uveoretinitis, giant cell arteritis, inflammatory bowel diseases (including, *e.g.*, Crohn's disease, ulcerative colitis, regional enteritis, granulomatous enteritis, distal ileitis, regional ileitis, and terminal ileitis), insulin-dependent diabetes mellitus, multiple sclerosis, pernicious anemia, psoriasis, arthritis, rheumatoid arthritis, sarcoidosis, scleroderma, and systemic lupus erythematosus.

[0154] The invention includes methods of treating diseases and disorders associated with aberrant or inappropriate angiogenesis, wherein the method comprises administering to a patient in need thereof an anti-IL-6 antibody as disclosed herein. Exemplary diseases and disorders associated with aberrant or inappropriate angiogenesis that can be treated with an anti-IL-6 antibody of the invention include, *e.g.*, cardiovascular diseases such as angioma, angiofibroma, vascular deformity, atherosclerosis, synechia and edemic sclerosis, and opthalmological diseases such as neovascularization after cornea implantation, neovascular glaucoma, diabetic retinopathy, angiogenic corneal disease, macular degeneration, pterygium, retinal degeneration, retrolental fibroplasias, and granular conjunctivitis. Inflammatory diseases that are associated with inappropriate angiogenesis that can be treated with an anti-IL-6 antibody of the invention include, *e.g.*, arthritis, dermatological diseases such as psoriasis, telangiectasis, pyogenic granuloma, seborrheic dermatitis, venous ulcers, acne, rosacea (acne rosacea or erythematosa), warts (verrucas), eczema, hemangiomas, and lymphangiogenesis.

[0155] The invention includes methods of treating a cancer, wherein the method comprises administering to a patient in need thereof an anti-IL-6 antibody as disclosed herein. Exemplary cancers that can be treated with an anti-IL-6 antibody of the invention include, *e.g.*, cancers arising from immune cell abnormalities, including myeloid cancers such as multiple myeloma, and myelogenous leukemia (CML), as well as lymphocytic leukemia (CLL and ALL) and lymphomas, particularly Non-Hodgkin's Lymphoma (NHL). The antibodies of the invention can also be used to treat, *e.g.*, renal carcinoma, breast cancer, prostate cancer, lymphoma, post-transplant lymphoma, and post-transplant lymphoproliferative disease (also termed posttransplantation lymphoproliferative disorder).

[0156] Additional conditions that can be treated with the anti-IL-6 antibodies of the invention include, *e.g.*, osteoarthritis, idiopathic juvenile arthritis, rheumatoid arthritis, and fibrotic conditions (such as internal and external organ scarring).

[0157] The invention also includes use of an antibody of the present invention for the manufacture of a medicament for the treatment of a disease or disorder as described herein.

[0158] It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions, methods and applications described herein are obvious and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

Examples

Example 1

FIRST GENERATION OF HUMAN MONOCLONAL ANTIBODIES THAT BIND SPECIFICALLY TO IL-6

[0159] The purpose of this Example was to make human anti-IL-6 monoclonal antibodies starting from the murine IL-6 antibody known as B-E8 (also known as Elsilimomab).

[0160] A screening process was carried out using a vaccinia virus based antibody selection platform in order to identify human VH and VK regions that, when paired with the VK or VH regions of the murine B-E8 antibody, formed antibodies that bound specifically to IL-6. The selected human VH and VK were then used to select human VK and VH, respectively, that bound specifically to IL-6. The details of the vaccinia virus based screening platform are disclosed, *e.g.*, in U.S. Patent Appl. Publication No. 2005/0196755. From this screening process, using either murine B-E8 or human VH, 18 different human VK genes were identified. The nucleic acid sequences of the identified human VK genes and their corresponding amino acid sequences were determined. The amino acid sequences of the identified human VK genes is set forth in Table 8, below:

Table 8: amino acid sequences of human VK regions identified

VK	Amino Acid Sequence	SEQ ID NO:
L112	DIVMTQSPATLSVTPGDRVSLSCRASQSISDYLHWYQQKSHESPRL LIKSVSQSISGIPSRFSGSGSGSDFTLSINSVEPEDVGVYYCQNGHSF PLTFGAGTKLELK	1
L151	EIVLTQSPGTLSLSPGERATLSCRASQTIDSSYLAWYQQKPGQAPR LLVYGASSRATGIPDRFSDSGSGTDFTLTISRLEPEDFAVYYCQQY AKSPITFGQGTKLE	2
L158	DVVMTQSPSSVSASVGDRVTITCRASQDIDNFLAWYQQKPGKAPN LLIYKVSSLRSGVPSRFSGSRSGTDFTLTITSLQPEDFATYFCQQTRR FPLTFGPGTKLE	3
L159	DIVMTQSPSSLSASVGDRVTITCRASQTISSYLNWYQQKPGKPPKL LIYAASSLESGVPSRFSGSGSGTEFTLTISSLQPEDLATYYCQQANS FPLTFGGGTKLE	4
L164	DIQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKLGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQSYR PLTFGGGTKLEIK	5
L165	DIQMTQSPSSLSASVGDSVTITCRASQSISIYLNWYQQKPGKAPDLL IYATSTLQSGVPSRFSGRGSGTHFTLTIDSLQPEDFATYYCQQTYRN LFTFGQGTKLE	6
L166	DIQMTQSPSSLSASVGDSVTVTCRASQKMRTYLHWYQQKPGKAP KLLIYDVSFLQNGVPSRFSGRASGTEFTLTISDLQPEDFATYYCQQS YDTPLTFGQGTKLEIK	7

VK	Amino Acid Sequence	SEQ ID NO:
L167	DVVMTQSPSSVSASVGDRVTITCRASQVIDSWLHWYQREPGKAPK ILIYAATTLQRGVPSRFSGSGFGTEFTLTISGLQPEDFATYFCQQGY SFPITFGQGTRLEIK	8
L168	DVVMTQSPSSLSASVGGRVTITCRASQTIGDYLNWYQQKPGKAPR LLIYSASIVQSGVPSRFSASGSGTDFTLTISSLQPEDFATYSCQQSYS FPLTFGGGTKLEIK	9
L169	EIVLTQSPSSLSASAGDTVTIACRASQGIRTALAWYQQKPGRNPKL LISEAYRLQSGVSPKFSGSGFGTDFTLTINSLQPEDFATYYCQQFND FPLTFGGGTKLEIK	10
L170	DIQMTQSPSTLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPK LLISKASSLEYGVPSRFSGSGSGTEFALTISNVQPEDFATYYCQQSF AVPLTFGGGTKLEIK	11
L171	DIQMTQSPSSLSAFVGDGVTMTCWASQSINDYLNWYHQRPGEAP ELLVFAASNLQIGVPSRFRGSGSETYFTLTINSLQPEDSGTYFCQQT SSFPLTFGGGTKLE	12
L172	DIQMTQSPSSLSASVGDSVTITCRASQTISDFLNWYQQKPGKAPKL LIHASSNLQSGVPSRFSGSGSGTDFTLTISDLQPEDFATYSCQQTYS TLGTFGQGTRLE	13
L173	DVVMTQSPSSLSASVGGRVTITCRASQTIGDYLNWYQQRPGKAPR LLIYSASIVQSGVPSRFSGSGSGTHFTLTISSLQPEDFATYSCQQSYS FPLTFGGGTKLEIK	14
L174	DIVMTQSPSSLSASVGDRVTITCRASRNINTYLNWYQQKPGKAPK LLVHSASTLQSGAPSRFSGSGYGTEFTLIISSLQPDDFATYYCQQGY NTLTFGPGTKLE	15
L175	EIVLTQSPSSLSASVGDRVTISCRASQNIIDYLNWYQHKPGKVPTLL ISGTSTLQSGVPSRFSGSGFGTDFTLTISSVQPEDVATYYCQQGHGT PLSFGGGTKLEIK	16
L189	DIQMTQSPSTLSASVGDRVTITCRASQSMSDYLNWYQQKPGKAPK LLIYSASGLQSGVPSRFSGSGSGTDFTLTIINLQPEDVAAYYCQQSF SFPLTFGPGTKLEIK	17
L198	DIQMTQSPSSLSAFVGDGVTMTCWASQSINDYLNWYHQRPGEAP ELLVFAASNLQIGVPSRFRGSGSETYFTLTINSLQPEDSGTYFCQNG HSFPLTFGGGTKLEI	18

The underlined sequences represent CDRs 1-3, respectively.

[0161] In addition, using either the murine B-E8 or human VK, 7 different human VH genes were identified. The nucleic acid sequences of the identified human VH genes and their corresponding amino acid sequences were determined. The amino acid sequences of the identified human VH genes is set forth in Table 9, below:

Table 9: amino acid sequences of human VH regions identified

VH	Amino Acid Sequence	SEQ ID NO:
H415	QVTLKESGPALVKPTQTLTLTCTFSGFSLTTSGMCVSWIRQPPGK ALEWLALIYWDDDKRYNPSLRSRLTITKDTSKNQVVLTMTNMD PVDTATYYCARSYDDYLYYALDYWGQGTLVT	19
H884	QVTLKESGPALVKPTQTLTLTCTFSGFSLTTSGMCVSWIRQPPGK ALEWLALIYWDDDKRYNPSLRSRLTITKDTSKNQVVLTMTNMD PVDTATYYCARSHDDYLYYALDYWGQGTLVT	20
H1077	QVTLKESGPTLVKPTQTLTLTCTFSGFSLRTSGVSVGWFRQPPGK ALEWLALVYWDDDRRYNPSLKNRLTITRDTSKNQVVLTMTNM DPVDTATYYCARSYDDYLYYALDYWGQGTLVT	21
H1078	QVTLKESGPTLVKPTQTLTLTCIFSGFSFKTSGVSVGWIRQPPGK ALEWLALIYWDDDKRYSPSLKNRLTITRDTSKNQVVLTMTNMD PVDTATYYCARSYDDYLYYALDYWGQGTLVT	22
H1079	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTSGVGVGWVRQPPG KALEWLAFIFWDDDKYYSPSLESRLTITKDTSKNQVVLTMTNM DPVDTATYYCARSYDDYLYYALDYWGQGTLVT	23
H1081	QVTLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVAVGWIRQPPGK ALEWLALIFWDDDKHYSPSLKSRLTITKDTSKNQVVLTMTNMD PVDTATYYCARSYDDYLYYALDYWGQGTLVTVSS	24
H1089	QVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGMCVSWIRQPPGK ALEWLTLIYWDDDKRYSPSLETRLTITKDTSKNQVVLTMTNMD PVDTATYYCARSYDDYLYYALDYWGQGTLVT	25

The underlined sequences represent CDRs 1-3, respectively.

[0162] The amino acid sequences of the human VH regions identified exhibited significant sequence identity to one another as illustrated in Table 10, below:

Table 10: amino acid sequence identities among the human VHs

	H1079	H415	H1081	H1078	H1089	H1077
H1079		89	94	90	90	89
H415	89		92	90	95	90
H1081	94	92		93	92	91
H1078	90	90	93		90	94
H1089	90	95	92	90		89
H1077	89	90	91	94	89	

[0163] An alignment of the identified human VH regions is depicted in FIG. 1.

[0164] All of the identified human VKs were cross-paired with all of the identified human VHs. The antibodies resulting from these cross-pairings were tested for their ability to bind IL-6 by ELISA. The antibodies were also tested for functional activity in blocking assays of IL-6-induced cell proliferation or of IL-6 binding to IL-6R.

[0165] The affinity of the selected antibodies for IL-6 was measured by ELISA, based on the procedure set forth in *J. of Immunology Methods 77* (1985) 305-319. Briefly, plates were coated with 2 μg/ml of mBE4 capture antibody in coating buffer, 100 μl per well. The plates were incubated overnight. Next, the plates were washed 3 times and tapped dry. The plates were then blocked with 200 μl per well of Assay Diluent or 10% FBS in PBS and incubated for 2 hours. While the plates were blocking, the competition reaction was set up in solution by pre-incubating 65 μl of Ab at about 2 ng/ml concentration with 65 μl of various concentrations of rhIL6 (from 5.12 μg/ml to 5 ng/ml at 1:2 serial dilutions for total 12 different concentrations including one without IL-6). The reaction was left at RT for 3-4 hours. Therefore, final rhIL6 in competition solution was from 98.46, 49.23, 24.62, 12.31, 6.15, 3.08, 1.54, 0.77, 0.38, 0.19, 0.10 and 0 nM, according IL-6 as monomer. Next, the plates were washed 3 times and tapped dry. 50 ng/ml of recombinant human IL-6 in 100 μl was added to each well to BE4 coated plates. The plates were incubated for 1- 2 hours. The plates were washed 3 times and tapped dry. Next, 100 μl of mAb samples from above were added to IL-6 captured plates. The plates were incubated at RT for 2 hours. (Therefore, any unbound mAb at this point will be measured by ELISA). Plates were then washed 5 times and tapped dry. 100 μl of detection Ab goat anti-human IgG F(ab)'2-HRP (Jackson lab) was added at 1:20,000 dilutions or 1:40,000 dilutions (depending on lot) and the plates were incubated for 1-2 hours. The plates were washed 7 times and tapped dry. Next, the Developer Substrate

(equal parts of each reagent in the kit) was pre-mixed and allowed to warm to room temperature before use. Then 100 µl of Developer was added to each well. The plates were allowed to develop for 15 minutes un-sealed in a drawer in the dark. Finally, developing was stopped by adding 100 µl of 2N H_2SO_4 to each well and plates were read as Endpoint at 450 nm – 570 nm.

[0166] The blocking assay was conducted as described elsewhere herein.

[0167] From the VH/VK cross-pairings, thirty-three first generation mAbs were identified. These first generation mAbs are listed in Table 11, below:

Table 11: Summary of first generation human anti-IL-6 antibodies

mAb	VH	VK	Affinity (IC50 in nM)	Blocking Activity on IL-6-Induced Cell Proliferation
88*	H383	L112	0.5	++++
123	H884	L112	1.1	
179	H415	L112	0.85 – 4.2	++
181	H415	L159	12.9	
182	H415	L164	6.3	
183	H415	L165	1.75	++
184	H415	L166	2.4	
185	H415	L167	1.5	
186	H415	L168	2.0	
187	H415	L169	2.4	
188	H415	L170	1.4	
189	H415	L171	0.72	
190	H415	L172	1.9	++
191	H415	L173	1.5	
192	H415	L174	2.3	
193	H415	L175	2.7	
197	H884	L167	3.7	
201	H884	L171	2.0	
202	H884	L172	2.4	

mAb	VH	VK	Affinity (IC50 in nM)	Blocking Activity on IL-6-Induced Cell Proliferation
205	H884	L175	7.4	
237	H1077	L158	6.5	
239	H1078	L158	9.6	
241	H1079	L158	6.5	
242	H1079	L159	2.2	++
246	H1081	L151	5.5	
247	H1081	L158	4.0	
248	H1081	L159	2.0	
265	H415	L189	6.2	
273	H884	L171		
275	H415	L198	0.7	++
285	H1089	L158	2.5	
286	H1089	L159	2.5	
297	H1081	L172	11.5	+
416	H1079	L198	0.6	+++

*mAb 88 is a chimeric B-E8 control antibody

[0168] As the above Table shows, all of the first generation human anti-IL-6 antibodies obtained exhibited some degree of affinity for IL-6 and functional activity in a blocking assay. Briefly, biotinylated human recombinant IL-6 at 12.5 ng/ml was incubated with anti-IL-6 antibodies at the indicated concentrations for 20 min. on ice. FcR-blocked U266 cells (about 250,000 cells) were then added and co-incubated for another 30 min on ice. After washing, streptavidin-PE was added to reveal IL-6 bound to the cell surface. After washing, the cells were analyzed by flow cytometry.

[0169] The ability of certain exemplary first generation mAbs to block IL-6 binding to the IL-6 receptor on U266 cells is depicted in FIG. 2.

[0170] This Example therefore demonstrates the production of several biologically functional, human anti-IL-6 monoclonal antibodies.

Example 2

AFFINITY IMPROVEMENT OF HUMAN ANTI-IL-6 ANTIBODIES

[0171] Mutagenesis was used to further improve the functional activity of first generation human mAbs identified in Example 1. In particular, PCR-based mutagenesis was used to introduce amino acid sequence changes in the CDR3 of VH (H1079) and VK (L198), of mAb 416.

[0172] In order to introduce variability, the sequence NNK was introduced at specific positions in the VH and VK genes, where N can be A, T, G, or C, and K is T or G. Using NNK, all 20 amino acids and 1 stop codon can be introduced at each position (there are 32 possible combinations 4 x 4 x 2 with the NNK sequence).

[0173] All of the CDR3 residues in both H1079 and L198 were changed, one residue at a time. The light chain (VK) CDR3 has 9 amino acids, and the heavy chain (VH) CDR3 has 12 amino acids. Selected residues in CDR1 and CDR2 of H1079 were changed using this process as well.

[0174] To create the mutations, an anti-sense primer that encodes one amino acid replaced with NNK and amplifies CDR3 and Framework Region 4 was paired with a sense primer that hybridizes in Framework Region 1 of the chain of interest for a PCR reaction. Each PCR product encodes the entire VK or VH chain and has one amino acid position converted to NNK.

[0175] The PCR products were cloned into a mammalian expression vector containing the constant domain of human gamma I (for VH mutants), or kappa (for VK mutants), thereby generating the full length heavy or light chains.

[0176] Clones were dispatched in 96 well plate format, with 1 clone per well. Plasmid DNA was purified from each clone and then each clone was expressed with the complementary chain (*e.g.*, a mutated VK would be expressed with a VH) by transfection in CHO cells. Higher affinity binders were selected and characterized. A summary of this procedure is shown in FIG. 3.

[0177] When higher affinity mutants were identified, the mutants were sequenced, the resulting mAb was produced by transfection in CHO cells and then tested for specificity, affinity and function in a flow cytometry-based IL-6 blocking assay.

[0178] By this process, the following H1079 and L198 variants were obtained:

Table 12: H1079 variants obtained by PCR-based mutagenesis

Amino Acid Change*	Sequence§	SEQ ID NO:	New VH Designation
S95F	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARFYDDYLYYALDYWGQGTLVT	26	H1511
Y96A	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSADDYLYYALDYWGQGTLVT	27	H1420
Y96G	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSGDDYLYYALDYWGQGTLVT	28	H1432
Y100aM	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSYDDYLMYALDYWGQGTLVT	29	H1515
A100cS	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSYDDYLYYSLDYWGQGTLVT	30	H1362
L100dF	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSYDDYLYYAFDYWGQGTLVT	31	H1437
Y102T	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSYDDYLYYALDTWGQGTLVT	32	H1461

* The amino acid number represents the Kabat number.

§ The boxed residue is the residue that has been changed relative to the sequence of H1079. The underlined sequences represent CDRs 1-3, respectively.

Table 13: L198 variants obtained by PCR-based mutagenesis

Amino Acid Change*	Sequence§	SEQ ID NO:	New VK Designation
N90S	DIQMTQSPSSLSAFVGDGVTMTCWASQSIND YLNWYHQRPGEAPELLVFAASNLQIGVPSRF RGSGSETYFTLTINSLQPEDSGTYFCQSGHSF PLTFGGGTKLEI	33	L314
N90H	DIQMTQSPSSLSAFVGDGVTMTCWASQSIND YLNWYHQRPGEAPELLVFAASNLQIGVPSRF RGSGSETYFTLTINSLQPEDSGTYFCQHGHSF PLTFGGGTKLEI	34	L305
N90L	DIQMTQSPSSLSAFVGDGVTMTCWASQSIND YLNWYHQRPGEAPELLVFAASNLQIGVPSRF RGSGSETYFTLTINSLQPEDSGTYFCQLGHSF PLTFGGGTKLEI	35	L303
G91A	DIQMTQSPSSLSAFVGDGVTMTCWASQSIND YLNWYHQRPGEAPELLVFAASNLQIGVPSRF RGSGSETYFTLTINSLQPEDSGTYFCQNAHSF PLTFGGGTKLEI	36	L298
H92W	DIQMTQSPSSLSAFVGDGVTMTCWASQSIND YLNWYHQRPGEAPELLVFAASNLQIGVPSRF RGSGSETYFTLTINSLQPEDSGTYFCQNGWS FPLTFGGGTKLEI	37	L321

* The amino acid number represents the Kabat number.
§ The boxed residue is the residue that has been changed relative to the sequence of L198. The underlined sequences represent CDRs 1-3, respectively.

[0179] The following antibodies were made using the H1079 variants set forth in Table 12 paired with L198:

Table 14: mAbs made by pairing H1079 variants with L198

mAb designation	H1079 variant	VK	Affinity (IC50 in nM)
1123	H1511	L198	0.11
926	H1420	L198	0.07
963	H1432	L198	0.09
1127	H1515	L198	0.09

mAb designation	H1079 variant	VK	Affinity (IC50 in nM)
810	H1362	L198	0.22
968	H1437	L198	0.053
992	H1461	L198	0.065

[0180] Monoclonal antibodies 416, 926, 810, 963, 968 and 992 were tested, along with control mAb 88, for the ability to block IL-6 binding to IL-6R-expressing cells. Briefly, human recombinant IL-6 at 1 nM was incubated with anti-IL-6 antibodies at 1 μg/ml - 0.1 μg/ml - 10 ng/ml - 0 ng/ml for 30 min on ice. FcR-blocked U266 cells (about 250,000 cells) were then added and co-incubated for another 30 min on ice. After washing, a purified IL-6-specific mouse antibody (B-F6) was added and incubated with the cells for 30 min on ice. Finally an APC-conjugated polyclonal goat-anti-mouse Fc gamma was added and incubated for 30 min on ice. After washing, the cells were analyzed by flow cytometry by gating on the population of live cells only. Each sample started out with 250,000 cells. All flow cytometry data is based on a minimum of 10,000 live (PI-negative) cells. The results of these experiments are set forth in FIG. 4.

[0181] The following antibodies were made using the L198 variants set forth in Table 13 paired with H1079:

Table 15: mAbs made by pairing L198 variants with H1079

mAb designation	L198 variant	VH	Affinity (IC50 in nM)
774	L314	H1079	0.16
770	L305	H1079	0.12
765	L298	H1079	0.07
808	L321	H1079	0.08

[0182] Multiple mutations in H1079 were also prepared by the procedure outlined above.

Table 16: H1079 multiple mutants obtained by PCR-based mutagenesis

Amino Acid Changes*	Sequence§	SEQ ID NO:	New VH Designation
Y96A A100cS	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSADDYLYYSLDYWGQGTLVT	38	H1519
Y96A L100dF	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSADDYLYYAFDYWGQGTLVT	39	H1520
Y96A A100cS L100dF	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSADDYLYYSFDYWGQGTLVT	40	H1521
Y96A A100cS L100dF Y102T	QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTS GVGVGWVRQPPGKALEWLAFIFWDDDKYY SPSLESRLTITKDTSKNQVVLTMTNMDPVDT ATYYCARSADDYLYYSFDTWGQGTLVT	41	H1522

* The amino acid number represents the Kabat number.
§ The boxed residues are the residues that have been changed relative to the sequence of H1079.
The underlined sequences represent CDRs 1-3, respectively.

[0183] In addition, a variant heavy chain, designated H1553, was created by making a single amino acid change (F52W) in CDR2 of H1079. H1553 has the following amino acid sequence:

[0184] QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTSGVGVGWVRQPPGKALEWL AFIWWDDDKYYSPSLESRLTITKDTSKNQVVLTMTNMDPVDTATYYCARSYDD YLYYALDYWGQGTLVT (SEQ ID NO:42).

[0185] Furthermore, the amino acid change found in the CDR2 of H1553 was combined with the four CDR3 amino acid substitutions in H1522 to create H1579, having the following amino acid sequence:

[0186] QVTLKESGPTLVKPTQTLTLTCSFSGFSLSTSGVGVGWVRQPPGKALEWL AFIWWDDDKYYSPSLESRLTITKDTSKNQVVLTMTNMDPVDTATYYCARSADD YLYYSFDTWGQGTLVT (SEQ ID NO:43).

[0187] The following mAbs were obtained by combining VH and VK variants, as shown in Table 17, below:

Table 17: mAbs created by combining VH and VK variants:

mAb designation	VH variant	VK variant	Affinity (IC50 in nM)
1154	H1522	L198	0.027
1155	H1522	L305	0.032
1156	H1522	L314	0.023
1192	H1553	L198	0.029
1259	H1579	L198	0.028
1337	H1579	L305	0.047
1338	H1579	L314	0.031
1339	H1579	L298	0.026
1340	H1579	L321	0.028

[0188] The affinity of exemplary mAbs for IL-6 was determined by IC50 ELISA and by Biacore, as shown in Table 18, below. IC50 ELISA was performed as described above. Affinity analysis by Biacore was performed according to manufacturer protocols using HBS-EP buffer (Biacore AB). Briefly, 100 μg/ml goat anti-human IgG (Sigma-Aldrich Co.) was immobilized on the surface of a CM5 sensor chip (Biacore AB) with affinity for each IL-6 mAb determined by injection of 15 μl of 5 μg/ml of the mAb at a flow rate of 5 μl/min followed by injection of 100 μl of 40 nM to 1.25 nM human IL-6 (Strathmann Biotec GmbH & Co.KG) at a flow rate of 30 μl/min on a Biacore 2000 system (Biacore AB).

Table 18: Affinity of mAbs by IC50 ELISA and Biacore

mAb	Affinity (nM) by IC50 ELISA	Affinity (nM) by Biacore
88 (chimeric B-E8)	0.01	0.02
1339	0.026	0.071
1259	0.028	0.093
1340	0.028	*not determined*
1338	0.031	0.072
1337	0.047	*not determined*
926	0.033	0.13
416	0.056	0.3

[0189] Monoclonal antibodies 1259, 1337, 1338, 1339 and 1340 are IgG1 kappa. All of the constant domains are the same. The constant domains are in the expression plasmids and therefore do not vary from mAb to mAb. Only the VH and VK domains were selected from the library.

[0190] This Example therefore illustrates the production of several additional human anti-IL-6 monoclonal antibodies comprising variant VH and VK chains obtained by PCR-based mutagenesis.

Example 3

SEQUENCES AND VECTORS

EXEMPLARY HEAVY AND LIGHT CHAIN SEQUENCES

[0191] The nucleotide sequences encoding the murine mAb B-E8 heavy and light chains are depicted in Table 19:

Table 19: heavy and light chain sequences of B-E8

mAb B-E8 heavy chain
GTCGACCCACGCGTCCGGACatggacaggcttacttcttcattcctgctgctgattgtccctgcatatgtctt gtccCAAGTTACTCTAAAAGAGTCTGGCCCTGGGATATTGAAGCCCTCACAG ACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTCACTGAGC**ACTTCTGGT ATGGGTGTAGGC**TGGATTCGTCAGCCTTCAGGGAAGGGTCTGGAGTGGC TGGCA**CACATTTGGTGGGATGATGATAAGTACTATAACCCATCCCTGA AGAGC**CAGCTCACAATCTCCAAGGATACCTCCAGAAACCAGGTATTCCTC AAGATCACCAGTGTGGACACTGCAGATACTGCCACTTACTACTGTGCTCG A**TCCTATGATGACTATCTTTACTATGCTTTGGACTACT**GGGGTCAAGGA ACCTCAGTCACCGTCTCCTCA*GCCAAAACGACACCCCCATCTGTCTATCCACT GGCCCCTGGATCTGC* (SEQ ID NO:44)
Lowercase letters represent the leader sequence Underlined sequences represent CDRs 1-3, respectively Italicized letters represent the mouse Cγ1 sequence

mAb B-E8 light chain
GTCGACCCACGCGTCCGGAAAATTTGAAGatggtgtccacttctcagctccttggacttttgctttt ctggacttcagcctccagatgtGACATTGTGATGACTCAGTCTCCAGCCACCCTGTCTGT GACTCCAGGAGATAGAGTCTCTCTTTCCTGC**AGGGCCAGCCAGAGTATT** **AGCGACTACTTACAC**TGGTATCAACAAAAATCACATGAGTCTCCAAGGC TTCTCATCAAA**TCTGTTTCCCAATCCATCTCT**GGGATCCCCTCC AGGTTCAGTGGCAGTGGATCAGGGTCAGATTTCACTCTCAGTATC AACAGTGTGGAACCTGAAGATGTTGGAGTGTATTACTGT**CAAAATGGTCACAG** **CTTTCCGCTCACG**TTCGGTGCTGGGACCAAGCTGGAGCTGAAA*CGGGCTGATGCTGC* *ACCAACTGTATCCATCTTCCCACCATCATGCGAGATTCGAACATCT* (SEQ ID NO:45)
Lowercase letters represent the leader sequence Underlined sequences represent CDRs 1-3, respectively Italicized letters represent the mouse Cκ sequence

[0192] The amino acid sequences of the human mAb 926 heavy and light chains are depicted in Table 20:

Table 20: heavy and light chain sequences of mAb 926

mAb 926 heavy chain
MGWSCIILFLVATATGAHSQVTLKESGPTLVKPTQTLTLTCSFSGFSLSTSGVG VGWVRQPPGKALEWLAFIFWDDDKYYSPSLESRLTITKDTSKNQVVLTMTN MDPVDTATYYCARSADDYLYYALDYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO:46)
mAb 926 light chain
MGWSCIILFLVATATGVHSDIQMTQSPSSLSAFVGDGVTMTCWASQSINDYL NWYHQRPGEAPELLVFAASNLQIGVPSRFRGSGSETYFTLTINSLQPEDSGTYF CQNGHSFPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:47)

[0193] The amino acid sequences of the human mAb 1339 heavy and light chains are depicted in Table 21:

Table 21: heavy and light chain sequences of mAb 1339

mAb 1339 heavy chain
MGWSCIILFLVATATGAHSQVTLKESGPTLVKPTQTLTLTCSFSGFSLSTSGVG VGWVRQPPGKALEWLAFIWWDDDKYYSPSLESRLTITKDTSKNQVVLTMTN MDPVDTATYYCARSADDYLYYSFDTWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV

TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO:48)
mAb 1339 light chain MGWSCIILFLVATATGVHSDIQMTQSPSSLSAFVGDGVTMTCWASQSINDYL NWYHQRPGEAPELLVFAASNLQIGVPSRFRGSGSETYFTLTINSLQPEDSGTYF CQNAHSFPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:49)

CONSTRUCTION OF DOUBLE GENE VECTOR EXPRESSING THE HEAVY AND LIGHT CHAINS OF MAB 1339

CLONING HEAVY CHAIN H1579 INTO pCONG1

[0194] H1579 was subcloned from the original expression vector by digesting the variable region with BssHII and BstEII restriction enzymes into pACeL heavy vector. H1579pAcEL-H was digested with HindIII/ApaI and ligated into HindIII/ApaI-cut pConG1. H1579.pConG1 clone was sequence verified.

CLONING LIGHT CHAIN L298 INTO pCONK2

[0195] L298 was subcloned from the original expression vector by digesting variable region with ApaL1/XhoI and ligating into a vaccinia transfer vector VKE to provide compatible sequence encoding necessary restriction sites for subsequent dual gene cloning. Variable sequence was PCR amplified to add HindIII site at 5' end and BsiWI site at 3' end. PCR product was cloned into TOPO to facilitate complete digestion with HindIII and BsiWI in subsequent cloning reaction. L298.TOPO was sequence verified, digested with HindIII/BsiWI and ligated into HindIII/BsiWI- cut pConK2. L298.pConK2 was sequence verified.

CREATION OF DOUBLE GENE VECTOR

[0196] Heavy chain expression cassette was released as a NotI/ PvuI fragment with a 24 hour digestion of H1579.pConG1. L298.pConK2 was digested with AviII to prevent re-formation of parental clones, and L298 variable region cassette was released with PvuI

and NotI digestion. Following gel purification, Heavy and Light chain cassettes were ligated at a 1:1 ratio in an overnight ligation reaction at 14°C. Colonies were screened for presence of both heavy and light chain inserts by whole-cell PCR, positive clones were confirmed by sequencing. A map of the double gene vector is depicted in FIG. 9. The sequence of the double gene vector is set forth in Table 22:

Table 22: nucleotide sequence of mAb 1339 double gene vector

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1     GCTTTCTCAT AGCTCACGCT GTAGGTATCT CAGTTCGGTG TAGGTCGTTC GCTCCAAGCT
61    GGGCTGTGTG CACGAACCCC CCGTTCAGCC CGACCGCTGC GCCTTATCCG GTAACTATCG
121   TCTTGAGTCC AACCCGGTAA GACACGACTT ATCGCCACTG GCAGCAGCCA CTGGTAACAG
181   GATTAGCAGA GCGAGGTATG TAGGCGGTGC TACAGAGTTC TTGAAGTGGT GGCCTAACTA
241 CGGCTACACT AGAAGAACAG TATTTGGTAT CTGCGCTCTG CTGAAGCCAG TTACCTTCGG
301 AAAAAGAGTT GGTAGCTCTT GATCCGGCAA ACAAACCACC GCTGGTAGCG GTGGTTTTTT
361 TGTTTGCAAG CAGCAGATTA CGCGCAGAAA AAAAGGATCT CAAGAAGATC CTTTGATCTT
421 TTCTACGGGG TCTGACGCTC AGTGGAACGA AAACTCACGT TAAGGGATTT TGGTCATGAG
481 ATTATCAAAA AGGATCTTCA CCTAGATCCT TTTAAATTAA AAATGAAGTT TTAAATCAAT
541 CTAAAGTATA TATGAGTAAA CTTGGTCTGA CAGTTACCAA TGCTTAATCA GTGAGGCACC
601 TATCTCAGCG ATCTGTCTAT TTCGTTCATC CATAGTTGCC TGACTCCCCG TCGTGTAGAT
661 AACTACGATA CGGGAGGGCT TACCATCTGG CCCCAGTGCT GCAATGATAC CGCGAGACCC
721 ACGCTCACCG GCTCCAGATT TATCAGCAAT AAACCAGCCA GCCGGAAGGG CCGAGCGCAG
781 AAGTGGTCCT GCAACTTTAT CCGCCTCCAT CCAGTCTATT AATTGTTGCC GGGAAGCTAG
841 AGTAAGTAGT TCGCCAGTTA ATAGTTTGCG CAACGTTGTT GCCATTGCTA CAGGCATCGT
901 GGTGTCACGC TCGTCGTTTG GTATGGCTTC ATTCAGCTCC GGTTCCCAAC GATCAAGGCG
961 AGTTACATGA TCCCCCATGT TGTGCAAAAA AGCGGTTAGC TCCTTCGGTC CTCCGATCGT
1021 TGTCAGAAGT AAGTTGGCCG CAGTGTTATC ACTCATGGTT ATGGCAGCAC TGCATAATTC
1081 TCTTACTGTC ATGCCATCCG TAAGATGCTT TTCTGTGACT GGTGAGTACT CAACCAAGTC
1141 ATTCTGAGAA TAGTGTATGC GGCGACCGAG TTGCTCTTGC CCGGCGTCAA CACGGGATAA
1201 TACCGCGCCA CATAGCAGAA CTTTAAAAGT GCTCATCATT GGAAAACGTT CTTCGGGGCG
1261 AAAACTCTCA AGGATCTTAC CGCTGTTGAG ATCCAGTTCG ATGTAACCCA CTCGTGCACC
1321 CAACTGATCT TCAGCATCTT TTACTTTCAC CAGCGTTTCT GGGTGAGCAA AAACAGGAAG
1381 GCAAAATGCC GCAAAAAAGG GAATAAGGGC GACACGGAAA TGTTGAATAC TCATACTCTT
1441 CCTTTTTCAA TATTATTGAA GCATTTATCA GGGTTATTGT CTCATGAGCG GATACATATT
1501 TGAATGTATT TAGAAAAATA AACAAATAGG GGTTCCGCGC ACATTTCCCC GAAAAGTGCC
1561 ACCTGACGTC TAAGAAACCA TTATTATCAT GACATTAACC TATAAAAATA GGCGTATCAC
1621 GAGGCCCTGA TGGCTCTTTG CGGCACCCAT CGTTCGTAAT GTTCCGTGGC ACCGAGGACA
1681 ACCCTCAAGA GAAAATGTAA TCACACTGGC TCACCTTCGG GTGGGCCTTT CTGCGTTTAT
1741 AAGGAGACAC TTTATGTTTA AGAAGGTTGG TAAATTCCTT GCGGCTTTGG CAGCCAAGCT
1801 AGATCCGGCT GTGGAATGTG TGTCAGTTAG GGTGTGGAAA GTCCCCAGGC TCCCCAGCAG
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1861 GCAGAAGTAT GCAAAGCATG CATCTCAATT AGTCAGCAAC CAGGTGTGGA AAGTCCCCAG
1921 GCTCCCCAGC AGGCAGAAGT ATGCAAAGCA TGCATCTCAA TTAGTCAGCA ACCATAGTCC
1981 CGCCCCTAAC TCCGCCCATC CCGCCCCTAA CTCCGCCCAG TTCCGCCCAT TCTCCGCCCC
2041 ATGGCTGACT AATTTTTTTT ATTTATGCAG AGGCCGAGGC CGCCTCGGCC TCTGAGCTAT
2101 TCCAGAAGTA GTGAGGAGGC TTTTTTGGAG GCCTAGGCTT TTGCAAAAAG CTAGCTTGGG
2161 GCCACCGCTC AGAGCACCTT CCACCATGGC CACCTCAGCA AGTTCCCACT TGAACAAAAA
2221 CATCAAGCAA ATGTACTTGT GCCTGCCCCA GGGTGAGAAA GTCCAAGCCA TGTATATCTG
2281 GGTTGATGGT ACTGGAGAAG GACTGCGCTG CAAAACCCGC ACCCTGGACT GTGAGCCCAA
2341 GTGTGTAGAA GAGTTACCTG AGTGGAATTT TGATGGCTCT AGTACCTTTC AGTCTGAGGG
2401 CTCCAACAGT GACATGTATC TCAGCCCTGT TGCCATGTTT CGGGACCCCT TCCGCAGAGA
2461 TCCCAACAAG CTGGTGTTCT GTGAAGTTTT CAAGTACAAC CGGAAGCCTG CAGAGACCAA
2521 TTTAAGGCAC TCGTGTAAAC GGATAATGGA CATGGTGAGC AACCAGCACC CCTGGTTTGG
2581 AATGGAACAG GAGTATACTC TGATGGGAAC AGATGGGCAC CCTTTTGGTT GGCCTTCCAA
2641 TGGCTTTCCT GGGCCCCAAG GTCCGTATTA CTGTGGTGTG GGCGCAGACA AAGCCTATGG
2701 CAGGGATATC GTGGAGGCTC ACTACCGCGC CTGCTTGTAT GCTGGGGTCA AGATTACAGG
2761 AACAAATGCT GAGGTCATGC CTGCCCAGTG GGAACTCCAA ATAGGACCCT GTGAAGGAAT
2821 CCGCATGGGA GATCATCTCT GGGTGGCCCG TTTCATCTTG CATCGAGTAT GTGAAGACTT
2881 TGGGGTAATA GCAACCTTTG ACCCCAAGCC CATTCCTGGG AACTGGAATG GTGCAGGCTG
2941 CCATACCAAC TTTAGCACCA AGGCCATGCG GGAGGAGAAT GGTCTGAAGC ACATCGAGGA
3001 GGCCATCGAG AAACTAAGCA AGCGGCACCG GTACCACATT CGAGCCTACG ATCCCAAGGG
3061 GGGCCTGGAC AATGCCCGTG GTCTGACTGG GTTCCACGAA ACGTCCAACA TCAACGACTT
3121 TTCTGCTGGT GTCGCCAATC GCAGTGCCAG CATCCGCATT CCCCGGACTG TCGGCCAGGA
3181 GAAGAAAGGT TACTTTGAAG ACCGCGGCCC CTCTGCCAAT TGTGACCCCT TTGCAGTGAC
3241 AGAAGCCATC GTCCGCACAT GCCTTCTCAA TGAGACTGGC GACGAGCCCT TCCAATACAA
3301 AAACTAATTA GACTTTGAGT GATCTTGAGC CTTTCCTAGT TCATCCCACC CCGCCCCAGA
3361 GAGATCTTTG TGAAGGAACC TTACTTCTGT GGTGTGACAT AATTGGACAA ACTACCTACA
3421 GAGATTTAAA GCTCTAAGGT AAATATAAAA TTTTTAAGTG TATAATGTGT TAAACTACTG
3481 ATTCTAATTG TTTGTGTATT TTAGATTCCA ACCTATGGAA CTGATGAATG GGAGCAGTGG
3541 TGGAATGCCT TTAATGAGGA AAACCTGTTT TGCTCAGAAG AAATGCCATC TAGTGATGAT
3601 GAGGCTACTG CTGACTCTCA ACATTCTACT CCTCCAAAAA AGAAGAGAAA GGTAGAAGAC
3661 CCCAAGGACT TTCCTTCAGA ATTGCTAAGT TTTTTGAGTC ATGCTGTGTT TAGTAATAGA
3721 ACTCTTGCTT GCTTTGCTAT TTACACCACA AAGGAAAAAG CTGCACTGCT ATACAAGAAA
3781 ATTATGGAAA AATATTCTGT AACCTTTATA AGTAGGCATA ACAGTTATAA TCATAACATA
3841 CTGTTTTTTC TTACTCCACA CAGGCATAGA GTGTCTGCTA TTAATAACTA TGCTCAAAAA
3901 TTGTGTACCT TTAGCTTTTT AATTTGTAAA GGGGTTAATA AGGAATATTT GATGTATAGT
3961 GCCTTGACTA GAGATCATAA TCAGCCATAC CACATTTGTA GAGGTTTTAC TTGCTTTAAA
4021 AAACCTCCCA CACCTCCCCC TGAACCTGAA ACATAAAATG AATGCAATTG TTGTTGTTAA
4081 CTTGTTTATT GCAGCTTATA ATGGTTACAA ATAAAGCAAT AGCATCACAA ATTTCACAAA

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4141 TAAAGCATTT TTTTCACTGC ATTCTAGTTG TGGTTTGTCC AAACTCATCA ATGTATCTTA
4201 TCATGTCTGG ATCTCTAGCT TCGTGTCAAG GACGGTGACT GCAGTGAATA ATAAAATGTG
4261 TGTTTGTCCG AAATACGCGT TTTGAGATTT CTGTCGCCGA CTAAATTCAT GTCGCGCGAT
4321 AGTGGTGTTT ATCGCCGATA GAGATGGCGA TATTGGAAAA ATCGATATTT GAAAATATGG
4381 CATATTGAAA ATGTCGCCGA TGTGAGTTTC TGTGTAACTG ATATCGCCAT TTTTCCAAAA
4441 GTGATTTTTG GGCATACGCG ATATCTGGCG ATAGCGCTTA TATCGTTTAC GGGGGATGGC
4501 GATAGACGAC TTTGGTGACT TGGGCGATTC TGTGTGTCGC AAATATCGCA GTTTCGATAT
4561 AGGTGACAGA CGATATGAGG CTATATCGCC GATAGAGGCG ACATCAAGCT GGCACATGGC
4621 CAATGCATAT CGATCTATAC ATTGAATCAA TATTGGCCAT TAGCCATATT ATTCATTGGT
4681 TATATAGCAT AAATCAATAT TGGCTATTGG CCATTGCATA CGTTGTATCC ATATCATAAT
4741 ATGTACATTT ATATTGGCTC ATGTCCAACA TTACCGCCAT GTTGACATTG ATTATTGACT
4801 AGTTATTAAT AGTAATCAAT TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC
4861 GTTACATAAC TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG
4921 ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA TTGACGTCAA
4981 TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC ATCAAGTGTA TCATATGCCA
5041 AGTACGCCCC CTATTGACGT CAATGACGGT AAATGGCCCG CCTGGCATTA TGCCCAGTAC
5101 ATGACCTTAT GGGACTTTCC TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC
5161 ATGGTGATGC GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA
5221 TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA AAATCAACGG
5281 GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC AAATGGGCGG TAGGCGTGTA
5341 CGGTGGGAGG TCTATATAAG CAGAGCTCGT TTAGTGAACC GTCAGATCGC CTGGAGACGC
5401 CATCCACGCT GTTTTGACCT CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG
5461 GAACGGTGCA TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA
5521 GTCTATAGGC CCACCCCCTT GGCTTCTTAT GCATGCTATA CTGTTTTTGG CTTGGGGTCT
5581 ATACACCCCC GCTTCCTCAT GTTATAGGTG ATGGTATAGC TTAGCCTATA GGTGTGGGTT
5641 ATTGACCATT ATTGACCACT CCCCTATTGG TGACGATACT TTCCATTACT AATCCATAAC
5701 ATGGCTCTTT GCCACAACTC TCTTTATTGG CTATATGCCA ATACACTGTC CTTCAGAGAC
5761 TGACACGGAC TCTGTATTTT TACAGGATGG GGTCTCATTT ATTATTTACA AATTCACATA
5821 TACAACACCA CCGTCCCCAG TGCCCGCAGT TTTTATTAAA CATAACGTGG GATCTCACGC
5881 GAATCTCGGG TACGTGTTCC GGACATGGGC TCTTCTCCGG TAGCGGCGGA GCTTCTACAT
5941 CCGAGCCCTG CTCCCATGCC TCCAGCGACT CATGGTCGCT CGGCAGCTCC TTGCTCCTAA
6001 CAGTGGAGGC CAGACTTAGG CACAGCACGA TGCCCACCAC CACCAGTGTG CCGCACAAGG
6061 CCGTGGCGGT AGGGTATGTG TCTGAAAATG AGCTCGGGGA GCGGGCTTGC ACCGCTGACG
6121 CATTTGGAAG ACTTAAGGCA GCGGCAGAAG AAGATGCAGG CAGCTGAGTT GTTGTGTTCT
6181 GATAAGAGTC AGAGGTAACT CCCGTTGCGG TGCTGTTAAC GGTGGAGGGC AGTGTAGTCT
6241 GAGCAGTACT CGTTGCTGCC GCGCGCGCCA CCAGACATAA TAGCTGACAG ACTAACAGAC
6301 TGTTCCTTTC CATGGGTCTT TTCTGCAGTC ACCGTCCTTG ACACGAAGCT TAAGCCGCCA
6361 CCATGGGATG GAGCTGTATC ATCCTCTTCT TGGTAGCAAC AGCTACAGGC GTGCACTCCG
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6421 ACATCCAGAT GACCCAGTCT CCGTCCTCCC TGTCTGCTTT TGTGGGAGAC GGAGTCACCA
6481 TGACTTGTTG GGCAAGTCAG AGTATCAACG ACTATTTAAA TTGGTATCAC CAGAGGCCAG
6541 GGGAGGCCCC TGAGCTCCTG GTCTTTGCTG CCTCCAATTT GCAAATTGGA GTCCCGTCAA
6601 GGTTCAGGGG CAGTGGATCT GAGACGTATT TCACTTTAAC TATCAACAGT CTGCAACCTG
6661 AAGATAGTGG CACATACTTC TGTCAGAATG CTCACTCTTT CCCGCTTACT TTCGGCGGAG
6721 GGACCAAGCT CGAGATCAAA CGTACGGTGG CTGCACCATC TGTCTTCATC TTCCCGCCAT
6781 CTGATGAGCA GTTGAAATCT GGAACTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC
6841 CCAGAGAGGC CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG
6901 AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC ACCCTGACGC
6961 TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC CATCAGGGCC
7021 TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG TTAGGAATTC ATTGATCATA
7081 ATCAGCCATA CCACATTTGT AGAGGTTTTA CTTGCTTTAA AAAACCTCCC ACACCTCCCC
7141 CTGAACCTGA AACATAAAAT GAATGCAATT GTTGTTGTTA ACTTGTTTAT TGCAGCTTAT
7201 AATGGTTACA AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG
7261 CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG GCGGCCGCCG
7321 ATATTTGAAA ATATGGCATA TTGAAAATGT CGCCGATGTG AGTTTCTGTG TAACTGATAT
7381 CGCCATTTTT CCAAAAGTGA TTTTTGGGCA TACGCGATAT CTGGCGATAG CGCTTATATC
7441 GTTTACGGGG GATGGCGATA GACGACTTTG GTGACTTGGG CGATTCTGTG TGTCGCAAAT
7501 ATCGCAGTTT CGATATAGGT GACAGACGAT ATGAGGCTAT ATCGCCGATA GAGGCGACAT
7561 CAAGCTGGCA CATGGCCAAT GCATATCGAT CTATACATTG AATCAATATT GGCCATTAGC
7621 CATATTATTC ATTGGTTATA TAGCATAAAT CAATATTGGC TATTGGCCAT TGCATACGTT
7681 GTATCCATAT CATAATATGT ACATTTATAT TGGCTCATGT CCAACATTAC CGCCATGTTG
7741 ACATTGATTA TTGACTAGTT ATTAATAGTA ATCAATTACG GGGTCATTAG TTCATAGCCC
7801 ATATATGGAG TTCCGCGTTA CATAACTTAC GGTAAATGGC CCGCCTGGCT GACCGCCCAA
7861 CGACCCCCGC CCATTGACGT CAATAATGAC GTATGTTCCC ATAGTAACGC CAATAGGGAC
7921 TTTCCATTGA CGTCAATGGG TGGAGTATTT ACGGTAAACT GCCCACTTGG CAGTACATCA
7981 AGTGTATCAT ATGCCAAGTA CGCCCCCTAT TGACGTCAAT GACGGTAAAT GGCCCGCCTG
8041 GCATTATGCC CAGTACATGA CCTTATGGGA CTTTCCTACT TGGCAGTACA TCTACGTATT
8101 AGTCATCGCT ATTACCATGG TGATGCGGTT TTGGCAGTAC ATCAATGGGC GTGGATAGCG
8161 GTTTGACTCA CGGGGATTTC CAAGTCTCCA CCCCATTGAC GTCAATGGGA GTTTGTTTTG
8221 GCACCAAAAT CAACGGGACT TTCCAAAATG TCGTAACAAC TCCGCCCCAT TGACGCAAAT
8281 GGGCGGTAGG CGTGTACGGT GGGAGGTCTA TATAAGCAGA GCTCGTTTAG TGAACCGTCA
8341 GATCGCCTGG AGACGCCATC CACGCTGTTT TGACCTCCAT AGAAGACACC GGGACCGATC
8401 CAGCCTCCGC GGCCGGGAAC GGTGCATTGG AACGCGGATT CCCCGTGCCA AGAGTGACGT
8461 AAGTACCGCC TATAGAGTCT ATAGGCCCAC CCCCTTGGCT TCTTATGCAT GCTATACTGT
8521 TTTTGGCTTG GGGTCTATAC ACCCCCGCTT CCTCATGTTA TAGGTGATGG TATAGCTTAG
8581 CCTATAGGTG TGGGTTATTG ACCATTATTG ACCACTCCCC TATTGGTGAC GATACTTTCC
8641 ATTACTAATC CATAACATGG CTCTTTGCCA CAACTCTCTT TATTGGCTAT ATGCCAATAC

8701 ACTGTCCTTC AGAGACTGAC ACGGACTCTG TATTTTTACA GGATGGGGTC TCATTTATTA
8761 TTTACAAATT CACATATACA ACACCACCGT CCCCAGTGCC CGCAGTTTTT ATTAAACATA
8821 ACGTGGGATC TCCACGCGAA TCTCGGGTAC GTGTTCCGGA CATGGGCTCT TCTCCGGTAG
8881 CGGCGGAGCT TCTACATCCG AGCCCTGCTC CCATGCCTCC AGCGACTCAT GGTCGCTCGG
8941 CAGCTCCTTG CTCCTAACAG TGGAGGCCAG ACTTAGGCAC AGCACGATGC CCACCACCAC
9001 CAGTGTGCCG CACAAGGCCG TGGCGGTAGG GTATGTGTCT GAAAATGAGC TCGGGGAGCG
9061 GGCTTGCACC GCTGACGCAT TTGGAAGACT TAAGGCAGCG GCAGAAGAAG ATGCAGGCAG
9121 CTGAGTTGTT GTGTTCTGAT AAGAGTCAGA GGTAACTCCC GTTGCGGTGC TGTTAACGGT
9181 GGAGGGCAGT GTAGTCTGAG CAGTACTCGT TGCTGCCGCG CGCGCCACCA GACATAATAG
9241 CTGACAGACT AACAGACTGT TCCTTTCCAT GGGTCTTTTC TGCAGTCACC GTCCTTGACA
9301 CGAAGCTTAA GCCGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC
9361 TACAGGCGCG CACTCCCAAG TCACTTTGAA GGAGTCTGGT CCTACGCTGG TGAAACCCAC
9421 ACAGACCCTC ACGCTGACCT GCAGCTTCTC TGGGTTCTCA CTCAGCACTA GTGGAGTGGG
9481 TGTGGGCTGG GTCCGTCAGC CCCCAGGAAA GGCCCTGGAG TGGCTTGCAT TCATTTGGTG
9541 GGATGATGAT AAGTACTACA GCCCGTCTCT GGAGAGCAGG CTCACCATCA CCAAGGACAC
9601 CTCCAAAAAC CAGGTGGTCC TTACAATGAC CAACATGGAC CCTGTGGACA CAGCCACATA
9661 TTACTGTGCA CGATCCGCTG ATGACTATCT TTACTATTCT TTTGACACGT GGGGCCAGGG
9721 AACCCTGGTC ACCGTCTCCT CAGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC
9781 CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA AGGACTACTT
9841 CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT
9901 CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA CCGTGCCCTC
9961 CAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA
10021 GGTGGACAAG AGAGTTGGTG AGAGGCCAGC ACAGGGAGGG AGGGTGTCTG CTGGAAGCCA
10081 GGCTCAGCGC TCCTGCCTGG ACGCATCCCG GCTATGCAGT CCCAGTCCAG GGCAGCAAGG
10141 CAGGCCCCGT CTGCCTCTTC ACCCGGAGGC CTCTGCCCGC CCCACTCATG CTCAGGGAGA
10201 GGGTCTTCTG GCTTTTTCCC CAGGCTCTGG GCAGGCACAG GCTAGGTGCC CCTAACCCAG
10261 GCCCTGCACA CAAAGGGGCA GGTGCTGGGC TCAGACCTGC CAAGAGCCAT ATCCGGGAGG
10321 ACCCTGCCCC TGACCTAAGC CCACCCCAAA GGCCAAACTC TCCACTCCCT CAGCTCGGAC
10381 ACCTTCTCTC CTCCCAGATT CCAGTAACTC CCAATCTTCT CTCTGCAGAG CCCAAATCTT
10441 GTGACAAAAC TCACACATGC CCACCGTGCC CAGGTAAGCC AGCCCAGGCC TCGCCCTCCA
10501 GCTCAAGGCG GGACAGGTGC CCTAGAGTAG CCTGCATCCA GGGACAGGCC CCAGCCGGGT
10561 GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
10621 TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA
10681 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
10741 GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC
10801 CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
10861 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
10921 GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC CGGCTCGGCC CACCCTCTGC

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10981 CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG CAGCCCCGAG AACCACAGGT
11041 GTACACCCTG CCCCCATCCC GGGAGGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT
11101 GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG GAGAGCAATG GGCAGCCGGA
11161 GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT TCCTCTATAG
11221 CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT
11281 GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAATA
11341 GGAATTCATT GATCATAATC AGCCATACCA CATTTGTAGA GGTTTTACTT GCTTTAAAAA
11401 ACCTCCCACA CCTCCCCCTG AACCTGAAAC ATAAAATGAA TGCAATTGTT GTTGTTAACT
11461 TGTTTATTGC AGCTTATAAT GGTTACAAAT AAAGCAATAG CATCACAAAT TTCACAAATA
11521 AAGCATTTTT TTCACTGCAT TCTAGTTGTG GTTTGTCCAA ACTCATCAAT GTATCTTATC
11581 ATGTCTGGAT CCTCTACGCC GGACGCATCG TGGCCGGCAT CACCGGCGCC ACAGGTGCGG
11641 TTGCTGGCGC CTATATCGCC GACATCACCG ATGGGGAAGA TCGGGCTCGC CACTTCGGGC
11701 TCATGAGCGC TTGTTTCGGC GTGGGTATGG TGGCAGGCCC CGTGGCCGGG GGACTGTTGG
11761 GCGCCATCTC CTTGCATGCA CCATTCCTTG CGGCGGCGGT GCTCAACGGC CTCAACCTAC
11821 TACTGGGCTG CTTCCTAATG CAGGAGTCGC ATAAGGGAGA GCGTCGACCT CGGGCCGCGT
11881 TGCTGGCGTT TTTCCATAGG CTCCGCCCCC CTGACGAGCA TCACAAAAAT CGACGCTCAA
11941 GTCAGAGGTG GCGAAACCCG ACAGGACTAT AAAGATACCA GGCGTTTCCC CCTGGAAGCT
12001 CCCTCGTGCG CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC
12061 CTTCGGGAAG CGTGGC  (SEQ ID NO:50)
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Example 4

CREATION OF A CHO CELL LINE EXPRESSING MAB 1339

[0197] CHO-K1 HD, a cell line that was adapted to grow in high density suspension culture, was transfected with mAb 1339 dual gene vector (as described in Example 3, above). CHO-K1 HD cells were carried in suspension until time of transfection. The day before the transfection, suspension lines were seeded into 6-well plates in presence of serum to allow attachment of the cells.

[0198] Four separate transfections were performed, each separated by 7 days, using subsequent passages of CHO-K1 HD cells and freshly purified and digested DNA from separate plasmid DNA preps. Each week, cells were seeded into two 6-well plates, one plate for a 2.5:1 DNA: lipofectamine ratio, and the other for a 3.0:1 ratio. Therefore, a total of 48 pools were transfected over the course of 4 weeks. Each pool was followed for growth and antibody production levels; not every pool survived drug selection. Pools are denoted by the following nomenclature: mAb name/transfection number,

DNA:lipofectamine ratio, letter of transfected well, and dish number. (Example: mAb 1339/1 2.5 B2 pool).

[0199] Productivity was measured using a 3-day secretion assay. Data is presented in mAb titer (μg/ml) and specific productivity (μg/million cells/day). Antibody titer and specificity are determined by ELISA. Results of secretion assays from all tested 1339 pools are set forth in Table 23.

Table 23: productivity of transfected CHO cells

IL-6 mAb Pool	mAb conc. (in μg/ml)	SPR (μg/E6 cells/day)	μg/E6 cells	final cell no. (x 10^6)
TRANSFECTION 1				
mAb 1339/1 2.5 A1 pool (2E+05)	6.34	3.019	9.057	1.400
mAb 1339/1 2.5 A1 pool (2E+05)	7.15	2.020	6.059	2.360
mAb 1339/1 2.5 A1 (5E+05)	10.10	3.367	10.100	2.000
mAb 1339/1 2.5 A1 (1E+06)	17.68	3.274	9.822	3.600
mAb 1339/1 2.5 A1 #D2	1.60	3.048	9.143	0.350
mAb 1339/1 2.5 A2 pool	0.40	0.437	1.311	0.610
mAb 1339/1 2.5 B1 pool	0.78	0.765	2.294	0.680
mAb 1339/1 2.5 B2 pool	10.18	18.244	54.731	0.372
mAb 1339/1 2.5 B2 (2E+05)	28.81	27.166	81.499	0.707
mAb 1339/1 2.5 B2 (2E+05)	23.95	20.790	62.370	0.768
mAb 1339/1 2.5 B2 (2E+05)	10.58	21.374	64.121	0.330
mAb 1339/1 2.5 B2 (5E+05)	54.21	24.255	72.765	1.490
mAb 1339/1 2.5 B2 (5E+05)	37.23	20.683	62.050	1.200
mAb 1339/1 2.5 B2 (1E+06)	77.50	24.603	73.810	2.100
mAb 1339/1 2.5 C1 pool	4.29	9.226	27.677	0.310
mAb 1339/1 2.5 C2 pool	0.26	0.231	0.692	0.737
mAb 1339/1 2.5 C2 #D1	0.00	0.000	0.000	1.180
mAb 1339/1 2.5 C2 #D2	0.48	0.281	0.842	1.140
TRANSFECTION 2				
mAb 1339/2 2.5 C1 pool	5.89	3.812	11.437	1.030
mAb b 1339/2 pool 2.5 C2	2.95	0.624	1.873	3.150
TRANSFECTION 3				
mAb 1339/3 2.5 A1 pool	0	0.000	0.000	1.160
mAb 1339/3 2.5 A2 pool	0.56	0.213	0.640	1.750
mAb 1339/3 2.5 B1 pool	0	0.000	0.000	1.340

IL-6 mAb Pool	mAb conc. (in µg/ml)	SPR (µg/E6 cells/day)	µg/E6 cells	final cell no. (x 10^6)
mAb 1339/3 2.5 B2 pool	0.35	0.175	0.526	1.330
mAb 1339/3 2.5 C1 pool	0	0.000	0.000	2.040
mAb 1339/3 2.5 C2 pool	0.71	0.601	1.802	0.788
mAb 1339/3 3.0 A1 pool	0.80	0.368	1.103	1.450
mAb 1339/3 3.0 A2 pool	0	0.000	0.000	0.110
mAb 1339/3 3.0 A2 pool	0	0.000	0.000	0.220
mAb 1339/3 3.0 B1 pool	0	0.000	0.000	2.730
mAb 1339/3 3.0 B2 pool	0.89	0.436	1.309	1.360
mAb 1339/3 3.0 C2 pool	0	0.000	0.000	1.130

[0200] The mAb yields from small scale secretion experiments is depicted in FIG. 10.

Example 5

ANTIBODY SPECIFICITY AND BIOLOGICAL ACTIVITY

ANTIBODY SPECIFICITY

[0201] Purified mAb 1339 was tested to confirm specificity for IL-6. Purified mAb 1339 was tested by ELISA for binding to a panel of control antigens, including human insulin, human serum albumin, human hemoglobin, and bovine serum albumin. No non-specific binding was seen to these antigens. (Data not shown).

[0202] In addition, purified mAb 1339 and control mAb 88 were tested by ELISA for binding to a panel of IL-6 superfamily members: CNFT, oncostatin M, IL-11, and NNT-1. As shown in FIGs. 5A and 5B, neither mAb 1339 nor mAb 88 bound to any of these cytokines in the ELISA.

INHIBITION OF IL-6-INDUCED MURINE AND HUMAN CELL PROLIFERATION

[0203] In order to assess the biological activity of the human anti-IL-6 mAbs, their ability to inhibit IL-6-induced murine B9 myeloma cell proliferation (FIG. 12) and IL-6-induced human U266 cell proliferation (FIG. 13) was assessed. The murine B9 cell line is human IL-6 sensitive.

[0204] As shown in FIG. 12, mAbs 926, 1259, 1337, 1338, 1339 and 1340 all showed a dose-dependent inhibitory effect on IL-6-induced murine myeloma cell proliferation. For example, at mAb concentrations of 100 ng/ml, the inhibition level observed with mAbs 926, 1337, 1338 and 1339 is very close to the inhibition level observed with the murine mAb B-E8.

[0205] As shown in FIG. 13, mAbs 416, 926, and 1339 showed a dose-dependent inhibitory effect on IL-6-induced human myeloma cell proliferation.

INHIBITION OF THE INTERACTION BETWEEN IL-6 AND IL-6R

[0206] To further assess the biological activity of the human anti-IL-6 mAbs, their ability to inhibit the interaction between IL-6 and the IL-6 receptor was assessed using flow cytometry.

[0207] Flow cytometry was carried out using standard methods. First, Fc-receptor blocking on U266 cells was carried out. U266 is an IgE and IL-6 producing human plasmacytoma line. U266 cells were harvested and spun down. Cells were counted and washed twice in flow buffer (FB) and adjusted to roughly 120% of the final cell number needed for the assay, calculating 150,000 cells per well of a 96 well plate. Cells were resuspended in FB at 5x10e6 cells/ml and adjusted to 0.1 mg huIgG/ml. Cells were mixed and incubated on ice for 20-30 min. Next, 15 volumes FB was added and the cells were spun down. The supernatant was discarded and the cells were washed two more times with 20 ml FB. The cells were then resuspended to a density of 1.5x10e6 cells/ml and 100 µl was added per well to the preincubation plate. Next, recombinant human IL-6 and anti-human IL-6 mAbs were coincubated. All of the necessary dilutions of mAbs and IL-6 in FB were first prepared. Next 50 µl of mAb was preincubated with 50 µl of IL-6 (preferrably at 1 nM final) for 30 minutes on ice after mixing the plate on a plate vortex for 30 s at medium power. Control wells for each mAb were included with either no IL-6 or IL-6 in the absence of antibody. Next, U266 cells were coincubated with IL-6 and anti-IL6 mAbs. The blocked and washed cells were added in 100 µl FB to the IL6/MAb mix from above. The final incubation volume was 200 µl. The cells were incubated for 30 min on ice. The wash steps between incubations were carried out as follows: Initially the incubation plate was spun at 250xg for 4 min in a centrifuge set to 4°C. The plates

were carefully flipped and wiped without dislocating the pellets. Next, the cells were resuspended by vortexing the plate for 10 s at highest power. 220 µl FB was added and the plate was spun again. This wash step was repeated one more time and the vortexed cell pellets were finally resuspended in 100 µl of the respective antibody dilution. Then the cells were incubated with the mouse anti IL-6 antibody B-F6. 100 µl of the antibody [5 µg/ml in FB] was added directly to the washed cell pellets from above which were loosened up by brief vortexing and then carefully vortexed again at medium power for 15 s. The cells were incubated for 30 min on ice and washed. Next the cells were incubated with APC coupled goat anti-mouse IgG1. The loosened, washed cell pellets were resuspended in 100 µl of the labeled antibody [2.5 µg allophycocyanin/ml]. Cells were kept in the dark and vortexed and incubated on ice for 30 min. The cells were washed and resuspended in 200 to 400 µl FB. Analysis by flow cytometry was then conducted. First, propidium iodide (PI) was added using a 150-fold dilution of the PI stock. A live gate based on the exclusion of PI by looking at Fl-3 vs. FSC was set. PI was added only for the next samples of cells to avoid extended incubation of cells with PI.

[0208] As shown in FIGs. 6A and 6B, mAbs 926, 1259, 1337, 1338, 1339 and 1340 all showed an inhibitory effect on IL-6 binding to IL-6 receptor on U266 cells under increasing concentrations of IL-6 with the antibody concentration held constant at 0.5 µg/ml. A notably high level of inhibition was observed with mAb 1339. Similarly, FIGs. 7A and 7B show an inhibitory effect of mAbs 242, 416, 926 and 1339 on IL-6 binding to IL-6 receptor on U266 cells under increasing concentrations of mAb with the IL-6 concentration held constant at 500 ng/ml.

[0209] The inhibitory effect of the mAbs was also demonstrated when biotinylated IL-6 was used (data not shown).

[0210] These results show that mAbs 242, 416, 926, 1259, 1337, 1338, 1339 and 1340 are capable of inhibiting the interaction between IL-6 and its receptor and therefore confirm the biological activity of these mAbs.

[0211] Finally, a competition assay as described in Example 2 for FIG. 4 was performed using mAbs 416, 926, 1259, 1337, 1338, 1339 and 1340, along with control mAb 88. As

shown in FIG. 8, all of the mAbs tested exhibited a dose-dependent inhibitory effect on recombinant human IL-6 binding to the IL-6 receptor.

Example 6

MAB SPECIFICITY OF MABS 926 AND 1339

[0212] Cross-reactivity with murine and rat IL-6 was determined for mAbs 926 and 1339 by ELISA as described above. Wells were coated with 100 ng/ml murine or rat IL-6 (R&D Systems) at 100 µl/well. For experiments using human monoclonal antibodies, IgG1 Kappa (human myeloma IgG1; Sigma-Aldrich Co.) mAb was used as a control. Rabbit anti-human IgG-HRP (Dako) was added at a dilution of 1/10,000 at 100 µl/well for detection of mAbs. Polyclonal antibody (pAb) controls included biotinylated goat anti-human IL-6 (Peprotech), biotinylated goat anti-murine IL-6 (Peprotech), and biotinylated goat anti-human Il-2 (Peprotech). For pAbs, Streptavidin-HRP (Prozyme) was added for detection at 100 µl/well. Antibodies were applied at concentrations of 12.5, 25, 50, and 100 ng/ml. As shown in FIGs. 14 and 15, respectively, mAbs 926 and 1339 do not detect coated recombinant murine or rat IL-6 by ELISA.

Example 7

DETECTION OF NATURAL HUMAN AND MONKEY IL-6

[0213] The ability of mAbs 926 and 1339 to detect natural human IL-6 was analyzed in activated human monocytes. Monocytes from peripheral blood mononuclear cells were activated for 24 hours with lipopolysaccharide (LPS; 20 µg/ml; Sigma-Aldrich Co.) in order to induce intracytoplasmic expression of IL-6 (data not shown). Cells were treated with 1 µg/ml Brefeldin A (Sigma-Aldrich Co.) 6 hours before the end of LPS treatment to inhibit transport of IL-6 to the supernatant. Activated cells were analyzed by flow cytometry as previously described with 0.8 µg/ml biotinylated mAbs 88, 1339, 926, B-E8 (anti-murine-IL-6; Diaclone), B-Z1 (mouse IgG1; Diaclone), and human IgG1 Kappa (Sigma-Aldrich Co.). Three independent experiments were performed for each antibody.

Representative experiments are shown in FIG. 16, showing that mAbs 926 and 1339 recognize natural intracytoplasmic IL-6.

[0214] Additionally, the ability of mAbs 926 and 1339 to detect natural human IL-6 from human serum was determined by ELISA using the Diaclone High Sensitivity human IL-6 ELISA kit according to manufacturer protocols. Using the latter kit, the detection of human IL-6 was determined by mAb competition (5 μg/ml) with the IL-6 antibody coated on the ELISA plate wells. Addition of serum containing IL-6 (Serum AB batch 5; Blood Center, Besançon, France) in the absence of a competitor antibody results in detection of IL-6 by the ELISA kit. Addition of serum containing IL-6 in the presence of a competitor antibody results in a reduction in the ability of the ELISA kit to detect IL-6 in the serum. Control antibodies included B-E8 (anti-murine-IL-6; Diaclone), B-Z1 (mouse IgG1; Diaclone), and human IgG1 Kappa (Sigma-Aldrich Co.). As shown in FIG. 17, mAbs 926 and 1339 detect natural IL-6 from healthy donor serum.

[0215] The ability of mAb 1339 to detect natural monkey IL-6 from rhesus monkey serum (BPRC, The Netherlands) was determined by ELISA using the U-Cytech Monkey IL-6 ELISA kit (U-Cytech biosciences) according to manufacturer protocols. Using the latter kit, the detection of monkey IL-6 was determined by mAb competition (5 μg/ml) with the IL-6 antibody coated on the ELISA plate wells. Addition of serum containing IL-6 in the absence of a competitor antibody results in detection of IL-6 by the ELISA kit. Addition of serum containing IL-6 in the presence of a competitor antibody results in a reduction in the ability of the ELISA kit to detect IL-6 in the serum. Monkey IgG1 Kappa served as a control antibody. As shown in FIG. 18, mAb 1339 detects natural IL-6 from monkey serum.

[0216] Having now fully described the present invention in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious to one of ordinary skill in the art that the same can be performed by modifying or changing the invention within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any specific embodiment thereof, and that such modifications or changes are intended to be encompassed within the scope of the appended claims.

[0217] All publications, patents and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention

pertains, and are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody comprising:

(a) a variable heavy chain region (VH) comprising:

(i) a VH-CDR1 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and an amino acid sequence that is identical to any one of SEQ ID NOs:51-55 except for 1 to 5 amino acid substitutions;

(ii) a VH-CDR2 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:97, and an amino acid sequence that is identical to any one of SEQ ID NOs:56 to 61 or 97 except for 1 to 5 amino acid substitutions;

(iii) a VH-CDR3 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:98, and an amino acid sequence that is identical to any one of SEQ ID NOs:62 to 73 or 98 except for 1 to 5 amino acid substitutions; and

(b) a variable light chain region (VL) comprising:

(i) a VL-CDR1 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, and an amino acid sequence that is identical to any one of SEQ ID NOs:74-79 except for 1 to 5 amino acid substitutions;

(ii) a VL-CDR2 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:80, SEQ ID NO:81, SEQ ID

NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and an amino acid sequence that is identical to any one of SEQ ID NOs:80-85 except for 1 to 5 amino acid substitutions;

(iii) a VL-CDR3 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, and an amino acid sequence that is identical to any one of SEQ ID NOs:86-96 except for 1 to 5 amino acid substitutions;

wherein said antibody binds specifically to an IL-6 antigen.

2. An isolated human monoclonal antibody comprising a variable heavy chain CDR1 (VH-CDR1) having the amino acid sequence T-S-G-X_1-X_2-V-X_3 (SEQ ID NO:99), wherein X_1, X_2 and X_3 can be any amino acid, and wherein said antibody binds specifically to an IL-6 antigen.

3. The antibody of claim 2, wherein X_1 is methionine (M) or valine (V).

4. The antibody of claim 3, wherein X_1 is valine (V).

5. The antibody of claim 2, wherein X_2 is cysteine (C), alanine (A), serine (S) or glycine (G).

6. The antibody of claim 2, wherein X_3 is serine (S) or glycine (G).

7. An isolated human monoclonal antibody comprising a variable heavy chain CDR2 (VH-CDR2) having the amino acid sequence X_1-X_2-X_3-W-D-D-D-X_4-X_5-Y-X_6-P-S-L-X_7-X_8 (SEQ ID NO:100), wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7 and X_8 can be any amino acid, and wherein said antibody binds specifically to an IL-6 antigen.

8. The antibody of claim 7, wherein X_1 is leucine (L), phenylalanine (F) or valine (V).

9. The antibody of claim 8, wherein X_1 is leucine (L).

10. The antibody of claim 7, wherein X_2 is isoleucine (I) or valine (V).

11. The antibody of claim 10, wherein X_2 is isoleucine (I).

12. The antibody of claim 7, wherein X_3 is tyrosine (Y) or phenyalanine (F).

13. The antibody of claim 7, wherein X_4 is lysine (K) or arginine (R).

14. The antibody of claim 7, wherein X_5 is arginine (R), tyrosine (Y), or histidine (H).

15. The antibody of claim 7, wherein X_6 is serine (S) or asparagine (N).

16. The antibody of claim 15, wherein X_6 is serine (S).

17. The antibody of claim 7, wherein X_7 is arginine (R), lysine (K), glutamic acid (E) or serine (S).

18. The antibody of claim 17, wherein X_7 is lysine (K).

19. The antibody of claim 7, wherein X_8 is serine (S) or asparagine (N).

20. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable heavy chain CDR1 (VH-CDR1) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and an amino acid sequence that is identical to any one of SEQ ID NOs:51-55 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VH-CDR1 binds specifically to an IL-6 antigen.

21. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable heavy chain CDR2 (VH-CDR2) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:97, and an amino acid sequence that is identical to any one of SEQ ID NOs:56 to 61 or 97 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VH-CDR2 binds specifically to an IL-6 antigen.

22. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable heavy chain CDR3 (VH-CDR3) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:98, and an amino acid sequence that is identical to any one of SEQ ID NOs:62 to 73 or 98 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VH-CDR3 binds specifically to an IL-6 antigen.

23. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable light chain CDR1 (VL-CDR1) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, and an amino acid sequence that is identical to any one of SEQ ID NOs:74-79 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VL-CDR1 binds specifically to an IL-6 antigen.

24. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable light chain CDR2 (VL-CDR2) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, and an amino acid sequence that is identical to any one of SEQ ID NOs:80-85 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VL-CDR2 binds specifically to an IL-6 antigen.

25. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a variable light chain CDR3 (VL-CDR3) comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID

NO:94, SEQ ID NO:95, SEQ ID NO:96, and an amino acid sequence that is identical to any one of SEQ ID NOs:86-96 except for 1 to 5 amino acid substitutions;

wherein an antibody molecule comprising said VL-CDR3 binds specifically to an IL-6 antigen.

26. An isolated monoclonal antibody comprising:

(a) a variable heavy chain region (VH) comprising an amino acid sequence selected from the group consisting of:

(1) H415 (SEQ ID NO:19);

(2) H884 (SEQ ID NO:20);

(3) H1077 (SEQ ID NO:21)

(4) H1078 (SEQ ID NO:22);

(5) H1079 (SEQ ID NO:23);

(6) H1081 (SEQ ID NO:24);

(7) H1089 (SEQ ID NO:25); and

(8) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs:19 to 25; and

(b) a variable light chain region (VL) comprising an amino acid sequence selected from the group consisting of:

(9) L112 (SEQ ID NO:1);

(10) L151 (SEQ ID NO:2);

(11) L158 (SEQ ID NO:3);

(12) L159 (SEQ ID NO:4);

(13) L164 (SEQ ID NO:5);

(14) L165 (SEQ ID NO:6);

(15) L166 (SEQ ID NO:7);

(16) L167 (SEQ ID NO:8);

(17) L168 (SEQ ID NO:9);

(18) L169 (SEQ ID NO:10);

(19) L170 (SEQ ID NO:11);

(20) L171 (SEQ ID NO:12)

(21) L172 (SEQ ID NO:13);

(22) L173 (SEQ ID NO:14);

(23) L174 (SEQ ID NO:15);

(24) L175 (SEQ ID NO:16);

(25) L189 (SEQ ID NO:17);

(26) L198 (SEQ ID NO:18); and

(27) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs: 1 to 18; and

wherein said antibody binds specifically to an IL-6 antigen.

27. The antibody of claim 26, wherein said VH comprises H415 (SEQ ID NO:19) or an amino acid sequence that is at least 80% identical thereto.

28. The antibody of claim 26, wherein said VH comprises H884 (SEQ ID NO:20) or an amino acid sequence that is at least 80% identical thereto.

29. The antibody of claim 26, wherein said VH comprises H1077 (SEQ ID NO:21) or an amino acid sequence that is at least 80% identical thereto.

30. The antibody of claim 26, wherein said VH comprises H1078 (SEQ ID NO:22) or an amino acid sequence that is at least 80% identical thereto.

31. The antibody of claim 26, wherein said VH comprises H1079 (SEQ ID NO:23) or an amino acid sequence that is at least 80% identical thereto.

32. The antibody of claim 26, wherein said VH comprises H1081 (SEQ ID NO:24) or an amino acid sequence that is at least 80% identical thereto.

33. The antibody of claim 26, wherein said VH comprises H1089 (SEQ ID NO:25) or an amino acid sequence that is at least 80% identical thereto.

34. The antibody of claim 26, wherein said VH comprises H415 (SEQ ID NO:19) and said VL comprises L112 (SEQ ID NO:1).

35. The antibody of claim 26, wherein said VH comprises H415 (SEQ ID NO:19) and said VL comprises L165 (SEQ ID NO:6).

36. The antibody of claim 26, wherein said VH comprises H415 (SEQ ID NO:19) and said VL comprises L172 (SEQ ID NO:13).

37. The antibody of claim 26, wherein said VH comprises H1079 (SEQ ID NO:23) and said VL comprises L159 (SEQ ID NO:4).

38. The antibody of claim 26, wherein said VH comprises H415 (SEQ ID NO:19) and said VL comprises L198 (SEQ ID NO:18).

39. The antibody of claim 26, wherein said VH comprises H1079 (SEQ ID NO:23) and said VL comprises L198 (SEQ ID NO:18).

40. The antibody of claim 26, wherein said VH comprises H1081 (SEQ ID NO:24) and said VL comprises L172 (SEQ ID NO:13).

41. The antibody of claim 26, wherein said VH comprises H1077 (SEQ ID NO:21) and said VL comprises L158 (SEQ ID NO:3).

42. The antibody of claim 26, wherein said VH comprises H1078 (SEQ ID NO:22) and said VL comprises L158 (SEQ ID NO:3).

43. The antibody of claim 26, wherein said VH comprises H1081 (SEQ ID NO:24) and said VL comprises L159 (SEQ ID NO:4).

44. The antibody of claim 26, wherein said VH is a variant of H1079.

45. The antibody of claim 44, wherein said variant of H1079 comprises one or more amino acid differences in the CDR1, CDR2 or CDR3 of H1079.

46. The antibody of claim 45, wherein said variant of H1079 comprises one or more amino acid differences in CDR3 of H1079.

47. The antibody of claim 46, wherein said variant of H1079 is selected from the group consisting of H1511 (SEQ ID NO:26); H1420 (SEQ ID NO:27); H1432 (SEQ ID NO:28); H1515 (SEQ ID NO:29); H1362 (SEQ ID NO:30); H1437 (SEQ ID NO:31); and H1461 (SEQ ID NO:32).

48. The antibody of claim 46, wherein said variant of H1079 is selected from the group consisting of H1519 (SEQ ID NO:38); H1520 (SEQ ID NO:39); H1521 (SEQ ID NO:40); and H1522 (SEQ ID NO:41).

49. The antibody of claim 26, wherein said VL is a variant of L198.

50. The antibody of claim 49, wherein said variant of L198 comprises one or more amino acid differences in the CDR1, CDR2 or CDR3 of L198.

51. The antibody of claim 50, wherein said variant of L198 comprises one or more amino acid differences in the CDR3 of L198.

52. The antibody of claim 51, wherein said variant of L198 is selected from the group consisting of L314 (SEQ ID NO:33); L305 (SEQ ID NO:34); L303 (SEQ ID NO:35); L298 (SEQ ID NO:36); and L321 (SEQ ID NO:37).

53. The antibody of claim 44, wherein said variant of H1079 is H1553 (SEQ ID NO:42) or H1579 (SEQ ID NO:43).

54. An isolated monoclonal antibody comprising:

(a) a variable heavy chain region (VH) comprising an amino acid sequence selected from the group consisting of:

(1) H1522 (SEQ ID NO:41);

(2) H1553 (SEQ ID NO:42);

(3) H1579 (SEQ ID NO:43); and

(4) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs:41 to 43; and

(b) a variable light chain region (VL) comprising an amino acid sequence selected from the group consisting of:

(5) L198 (SEQ ID NO:18)

(6) L305 (SEQ ID NO:34)

(7) L314 (SEQ ID NO:33)

(8) L298 (SEQ ID NO:36)

(9) L321 (SEQ ID NO:37); and

(10) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs: 18, 33, 34, 36 or 37; and

wherein said antibody binds specifically to an IL-6 antigen.

55. The antibody of claim 54, wherein said VH comprises H1522 (SEQ ID NO:41) or an amino acid sequence that is at least 80% identical thereto.

56. The antibody of claim 54, wherein said VH comprises H1553 (SEQ ID NO:42) or an amino acid sequence that is at least 80% identical thereto.

57. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) or an amino acid sequence that is at least 80% identical thereto.

58. The antibody of claim 54, wherein said VH comprises H1522 (SEQ ID NO:41) and said VL comprises L198 (SEQ ID NO:18).

59. The antibody of claim 54, wherein said VH comprises H1522 (SEQ ID NO:41) and said VL comprises L305 (SEQ ID NO:34).

60. The antibody of claim 54, wherein said VH comprises H1522 (SEQ ID NO:41) and said VL comprises L314 (SEQ ID NO:33).

61. The antibody of claim 54, wherein said VH comprises H1553 (SEQ ID NO:42) and said VL comprises L198 (SEQ ID NO:18).

62. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) and said VL comprises L198 (SEQ ID NO:18).

63. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) and said VL comprises L305 (SEQ ID NO:34).

64. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) and said VL comprises L314 (SEQ ID NO:33).

65. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) and said VL comprises L298 (SEQ ID NO:36).

66. The antibody of claim 54, wherein said VH comprises H1579 (SEQ ID NO:43) and said VL comprises L321 (SEQ ID NO:37).

67. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes an anti-IL-6 antibody variable heavy chain region (VH), wherein said VH comprises an amino acid sequence selected from the group consisting of:

(1) H415 (SEQ ID NO:19);

(2) H884 (SEQ ID NO:20);

(3) H1077 (SEQ ID NO:21)

(4) H1078 (SEQ ID NO:22);

(5) H1079 (SEQ ID NO:23);

(6) H1081 (SEQ ID NO:24);

(7) H1089 (SEQ ID NO:25); and

(8) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs:19 to 25.

68. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes an anti-IL-6 antibody variable light chain region (VL), wherein said VL comprises an amino acid sequence selected from the group consisting of:

(1) L112 (SEQ ID NO:1);

(2) L151 (SEQ ID NO:2);

(3) L158 (SEQ ID NO:3);

(4) L159 (SEQ ID NO:4);

(5) L164 (SEQ ID NO:5);

(6) L165 (SEQ ID NO:6);

(7) L166 (SEQ ID NO:7);

(8) L167 (SEQ ID NO:8);

(9) L168 (SEQ ID NO:9);

(10) L169 (SEQ ID NO:10);

(11) L170 (SEQ ID NO:11);

(12) L171 (SEQ ID NO:12)

(13) L172 (SEQ ID NO:13);

(14) L173 (SEQ ID NO:14);

(15) L174 (SEQ ID NO:15);

(16) L175 (SEQ ID NO:16);

(17) L189 (SEQ ID NO:17);

(18) L198 (SEQ ID NO:18); and

(19) an amino acid sequence that is at least 80% identical to any one of SEQ ID NOs: 1 to 18.

69. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a complementary determining region (CDR) of an anti-IL-6 antibody variable heavy chain region (VH) selected from the group consisting of:

(1) H415 (SEQ ID NO:19);

(2) H884 (SEQ ID NO:20);

(3) H1077 (SEQ ID NO:21)

(4) H1078 (SEQ ID NO:22);

(5) H1079 (SEQ ID NO:23);

(6) H1081 (SEQ ID NO:24); and

(7) H1089 (SEQ ID NO:25).

70. The nucleic acid molecule of claim 69, wherein said nucleotide sequence encodes a CDR3 of an anti-IL-6 antibody variable heavy chain region (VH) selected from the group consisting of::

(1) H415 (SEQ ID NO:19);

(2) H884 (SEQ ID NO:20);

(3) H1077 (SEQ ID NO:21)

(4) H1078 (SEQ ID NO:22);

(5) H1079 (SEQ ID NO:23);

(6) H1081 (SEQ ID NO:24); and

(7) H1089 (SEQ ID NO:25).

71. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a complementary determining region (CDR) of an anti-IL-6 antibody variable light chain region (VL) selected from the group consisting of:

(1) L112 (SEQ ID NO:1);

(2) L151 (SEQ ID NO:2);

(3) L158 (SEQ ID NO:3);

(4) L159 (SEQ ID NO:4);

(5) L164 (SEQ ID NO:5);

(6) L165 (SEQ ID NO:6);

(7) L166 (SEQ ID NO:7);

(8) L167 (SEQ ID NO:8);

(9) L168 (SEQ ID NO:9);

(10) L169 (SEQ ID NO:10);

(11) L170 (SEQ ID NO:11);

(12) L171 (SEQ ID NO:12)

(13) L172 (SEQ ID NO:13);

(14) L173 (SEQ ID NO:14);

(15) L174 (SEQ ID NO:15);

(16) L175 (SEQ ID NO:16);

(17) L189 (SEQ ID NO:17); and

(18) L198 (SEQ ID NO:18).

72. The nucleic acid molecule of claim 71, wherein said nucleotide sequence encodes a CDR3 of an anti-IL-6 antibody variable light chain region (VL) selected from the group consisting of:

(1) L112 (SEQ ID NO:1);

(2) L151 (SEQ ID NO:2);

(3) L158 (SEQ ID NO:3);

(4) L159 (SEQ ID NO:4);

(5) L164 (SEQ ID NO:5);

(6) L165 (SEQ ID NO:6);

(7) L166 (SEQ ID NO:7);

(8) L167 (SEQ ID NO:8);

(9) L168 (SEQ ID NO:9);

(10) L169 (SEQ ID NO:10);

(11) L170 (SEQ ID NO:11);

(12) L171 (SEQ ID NO:12)

(13) L172 (SEQ ID NO:13);

(14) L173 (SEQ ID NO:14);

(15) L174 (SEQ ID NO:15);

(16) L175 (SEQ ID NO:16);

(17) L189 (SEQ ID NO:17); and

(18) L198 (SEQ ID NO:18).

73. An expression vector comprising a nucleic acid molecule of claim 67.

74. An expression vector comprising a nucleic acid molecule of claim 68.

75. An expression vector comprising a nucleic acid molecule of claim 69.

76. An expression vector comprising a nucleic acid molecule of claim 71.

77. A host cell comprising an expression vector of claim 73.

78. A host cell comprising an expression vector of claim 74.

79. A host cell comprising an expression vector of claim 75.

80. A host cell comprising an expression vector of claim 76.

81. A method for treating an inflammatory disease, said method comprising administering an antibody of any one of claims 1-19 or 26-66 to a patient in need thereof.

82. A method for treating an autoimmune disease, said method comprising administering an antibody of any one of claims 1-19 or 26-66 to a patient in need thereof.

83. The method of claim 82, wherein the autoimmune disease is rheumatoid arthritis.

84. A method for treating a cancer, said method comprising administering an antibody of any one of claims 1-19 or 26-66 to a patient in need thereof.

85. The method of claim 84, wherein said cancer is multiple myeloma.

86. The method of claim 84, wherein said cancer is selected from the group consisting of renal carcinoma, breast cancer, prostate cancer, lymphoma and post-transplant lymphoma.

87. A method for treating idiopathic juvenile arthritis, said method comprising administering an antibody of any one of claims 1-19 or 26-66 to a patient in need thereof.

88. A method for producing the isolated monoclonal antibody of any one of claims 1-19 or 26-66, said method comprising: (i) culturing a host cell expressing one or more nucleic acid sequences encoding said antibody and (ii) recovering said antibody from the culture medium.

89. Use of the isolated monoclonal antibody of any one of claims 1-19 or 26-66 for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenille arthritis, and fibrotic conditions.

90. A pharmaceutical composition comprising the isolated monoclonal antibody of any one of claims 1-19 or 26-66 and a pharmaceutically acceptable carrier.

91. The isolated monoclonal antibody of any one of claims 1-19 or 26-66 for use as a medicament in the treatment of a disease or disorder selected from the group consisting of an autoimmune disease or disorder, a disease or disorder associated with aberrant or inappropriate angiogenesis, cancer, osteoarthritis, idiopathic juvenile arthritis, and fibrotic conditions.

92. The isolated monoclonal antibody of any one of claims 1-19 or 26-66, wherein said antibody inhibits IL-6-induced proliferation of cells such as murine B9 (ECACC) or human U266 myeloma cells at a level of 80% or greater inhibition.

93. The isolated monoclonal antibody of any one of claims 1-19 or 26-66, wherein said antibody binds specifically to IL-6, inhibiting the binding of IL-6 to its receptor at a level of 80% or greater inhibition.