ANTIBODIES TO IL-6 AND USE THEREOF

This application claims priority to U.S. provisional patent application no. 60/924,550, filed May 21, 2007, the disclosure of which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention pertains to antibodies and fragments thereof having binding specificity to IL-6. The invention also pertains to methods of screening for diseases and disorders associated with IL-6, and methods of preventing or treating diseases or disorders associated with IL-6 by administering said antibodies or fragments thereof.

Description of Related Art

[0002] Interleukin-6 (hereinafter "IL-6") (also known as interferon-β_2; B-cell differentiation factor; B-cell stimulatory factor-2; hepatocyte stimulatory factor; hybridoma growth factor; and plasmacytoma growth factor) is a multifunctional cytokine involved in numerous biological processes such as the regulation of the acute inflammatory response, the modulation of specific immune responses including B- and T-cell differentiation, bone metabolism, thrombopoiesis, epidermal proliferation, menses, neuronal cell differentiation, neuroprotection, aging, cancer, and the inflammatory reaction occurring in Alzheimer's disease. *See* A. Papassotiropoulos, *et al*, Neurobiology of Aging, 22:863-871 (2001).

[0003] IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor ("IL-6R")(also known as gp80). The IL-6R may also be present in a soluble form ("sIL-6R"). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130. *See* Jones, SA, J. Immunology, 175:3463-3468 (2005).

[0004] In humans, the gene encoding for IL-6 is organized in five exons and four introns, and maps to the short arm of chromosome 7 at 7p21. Translation of IL-6 RNA and

post-translational processing result in the formation of a 21 to 28 kDa protein with 184 amino acids in its mature form. *See* A. Papassotiropoulos, *et al*, Neurobiology of Aging, 22:863-871 (2001).

[0005] As set forth in greater detail below, IL-6 is believed to play a role in the development of a multitude of diseases and disorders, including but not limited to fatigue, cachexia, autoimmune diseases, diseases of the skeletal system, cancer, heart disease, obesity, diabetes, asthma, alzheimer's disease and multiple sclerosis. Due to the perceived involvement of IL-6 in a wide range of diseases and disorders, there remains a need in the art for compositions and methods useful for preventing or treating diseases associated with IL-6, as well as methods of screening to identify patients having diseases or disorders associated with IL-6. Particularly preferred anti-IL-6 compositions are those having minimal or minimizing adverse reactions when administered to the patient. Compositions or methods that reduce or inhibit diseases or disorders associated with IL-6 are beneficial to the patient in need thereof.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention is directed to specific antibodies and fragments thereof having binding specificity for IL-6, in particular antibodies having specific epitopic specificity and/or functional properties. One embodiment of the invention encompasses specific humanized antibodies and fragments thereof capable of binding to IL-6 and/or the IL-6/IL-6R complex. These antibodies may bind soluble IL-6 or cell surface expressed IL-6. Also, these antibodies may inhibit the formation or the biological effects of of one or more of IL-6, IL-6/IL-6R complexes, IL-6/IL-6R/gp130 complexes and/or multimers of IL-6/IL-6R/gp130.

[0007] Another embodiment of this invention relates to the antibodies described herein, comprising the sequences of the V_H, V_L and CDR polypeptides described herein, and the polynucleotides encoding them. In more specific embodiments of the invention these antibodies will block gp130 activation and/or possess binding affinities (Kds) less than 50 picomolar and/or K_{off} values less than or equal to 10^{-4} S^{-1}.

[0008] In another embodiment of the invention these antibodies and humanized versions will be derived from rabbit immune cells (B lymphocytes) and may be selected based on their homology (sequence identity) to human germ line sequences. These antibodies may require minimal or no sequence modifications, thereby facilitating retention of functional properties after humanization.

[0009] In another embodiment of the invention the subject antibodies may be selected based on their activity in functional assays such as IL-6 driven T1165 proliferation assays, IL-6 simulated HepG2 haptoglobin production assays, and the like. A further embodiment of the invention is directed to fragments from anti-IL-6 antibodies encompassing V_H, V_L and CDR polypeptides, e.g., derived from rabbit immune cells and the polynucleotides encoding the same, as well as the use of these antibody fragments and the polynucleotides encoding them in the creation of novel antibodies and polypeptide compositions capable of recognizing IL-6 and/or IL-6/IL-6R complexes or IL-6/IL-6R/gp130 complexes and/or multimers thereof.

[0010] The invention also contemplates conjugates of anti-IL-6 antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates methods of making said humanized anti-IL-6 or anti-IL-6/IL-6R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv and scFv fragments.

[0011] Embodiments of the invention pertain to the use of anti-IL-6 antibodies for the diagnosis, assessment and treatment of diseases and disorders associated with IL-6 or aberrant expression thereof. The invention also contemplates the use of fragments of anti-IL-6 antibodies for the diagnosis, assessment and treatment of diseases and disorders associated with IL-6 or aberrant expression thereof. Preferred usages of the subject antibodies are the treatment and prevention of cancer associated fatigue, and/or cachexia and rheumatoid arthritis.

[0012] Other embodiments of the invention relate to the production of anti-IL-6 antibodies in recombinant host cells, preferably diploid yeast such as diploid Pichia and other yeast strains.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0013] Fig. 1 shows that a variety of unique epitopes were recognized by the collection of anti-IL-6 antibodies prepared by the antibody selection protocol. Epitope variability was confirmed by antibody-IL-6 binding competition studies (ForteBio Octet).

[0014] Fig. 2 shows alignments of variable light and variable heavy sequences between a rabbit antibody variable light and variable heavy sequences and homologous human sequences and the final humanized sequences. Framework regions are identified FR1-FR4. Complementarity determining regions are identified as CDR1-CDR3. Amino acid residues are numbered as shown. The initial rabbit sequences are called RbtVL and RbtVH for the variable light and variable heavy sequences respectively. Three of the most similar human germline antibody sequences, spanning from Framework 1 through to the end of Framework 3, are aligned below the rabbit sequences. The human sequence that is considered the most similar to the rabbit sequence is shown first. In this example those most similar sequences are L12A for the light chain and 3-64-04 for the heavy chain. Human CDR3 sequences are not shown. The closest human Framework 4 sequence is aligned below the rabbit Framework 4 sequence. The vertical dashes indicate a residue where the rabbit residue is identical with one or more of the human residues at the same position. The bold residues indicate that the human residue at that position is identical to the rabbit residue at the same position. The final humanized sequences are called VLh and VHh for the variable light and variable heavy sequences respectively. The underlined residues indicate that the residue is the same as the rabbit residue at that position but different than the human residues at that position in the three aligned human sequences.

[0015] Fig. 3 demonstrates the high correlation between the IgG produced and antigen specificity for an exemplary IL-6 protocol. 9 of 11 wells showed specific IgG correlation with antigen recognition.

[0016] Fig. 4 provides the α-2-macroglobulin (A2M) dose response curve for antibody Ab1 administered intravenously at different doses one hour after a 100μg/kg s.c. dose of human IL-6.

[0017] Fig. 5 provides survival data for the antibody Ab1 progression groups versus control groups.

[0018] Fig. 6 provides additional survival data for the antibody Ab1 regression groups versus control groups.

[0019] Fig. 7 provides survival data for polyclonal human IgG at 10mg/kg i.v. every three days (270-320mg tumor size) versus antibody Ab1 at 10mg/kg i.v. every three days (270-320mg tumor size).

[0020] Fig. 8 provides survival data for polyclonal human IgG at 10mg/kg i.v. every three days (400-527mg tumor size) versus antibody Ab1 at 10mg/kg i.v. every three days (400-527mg tumor size).

[0021] Fig. 9 provides a pharamcokinetic profile of antibody Ab1. Plasma levels of antibody Ab1 were quantitated through antigen capture ELISA. This protein displays a half life of between 12 and 17 days consistent with other full length humanized antibodies.

[0022] Figs. 10 A-D provide binding data for antibodies Ab4, Ab3, Ab8 and Ab2, respectively. Fig. 10 E provides binding data for antibodies Ab1, Ab6 and Ab7.

[0023] Fig. 11 summarizes the binding data of Figures 10 A-E in tabular form.

[0024] Fig. 12 presents the sequences of the 15 amino acid peptides used in the peptide mapping experiment of Example 14.

[0025] Fig. 13 presents the results of the blots prepared in Example 14.

[0026] Fig. 14 presents the results of the blots prepared in Example 14.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

[0027] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0028] As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0029] *Interleukin-6 (IL-6)*: As used herein, interleukin-6 (IL-6) encompasses not only the following 212 amino acid sequence available as GenBank Protein Accession No. NP_000591:

MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEDSKDVAAPHRQPLTSSERIDKQI
RYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDGCFQSGFNEETCLV
KIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFLQKKAKNLDAITTPDPT
TNASLLTKLQAQNQWLQDMTTHLILRSFKEFLQSSLRALRQM (SEQ ID NO: 1), but also any pre-pro, pro- and mature forms of this IL-6 amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0030] *Mating competent yeast species*: In the present invention this is intended to broadly encompass any diploid or tetraploid yeast which can be grown in culture. Such species of yeast may exist in a haploid, diploid, or tetraploid form. The cells of a given ploidy may, under appropriate conditions, proliferate for indefinite number of generations in that form. Diploid cells can also sporulate to form haploid cells. Sequential mating can result in tetraploid strains through further mating or fusion of diploid strains. In the present invention the diploid or polyploidal yeast cells are preferably produced by mating or spheroplast fusion.

[0031] In one embodiment of the invention, the mating competent yeast is a member of the *Saccharomycetaceae* family, which includes the genera *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*. Other types of yeast potentially useful in the invention include *Yarrowia*, *Rhodosporidium*,

Candida, *Hansenula*, *Filobasium*, *Filobasidellla*, *Sporidiobolus*, *Bullera*, *Leucosporidium* and *Filobasidella*.

[0032] In a preferred embodiment of the invention, the mating competent yeast is a member of the genus *Pichia*. In a further preferred embodiment of the invention, the mating competent yeast of the genus *Pichia* is one of the following species: *Pichia pastoris*, *Pichia methanolica*, and *Hansenula polymorpha* (*Pichia angusta*). In a particularly preferred embodiment of the invention, the mating competent yeast of the genus *Pichia* is the species *Pichia pastoris*.

[0033] *Haploid Yeast Cell*: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0034] *Polyploid Yeast Cell*: A cell having more than one copy of its normal genomic (chromosomal) complement.

[0035] *Diploid Yeast Cell*: A cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells.

[0036] *Tetraploid Yeast Cell*: A cell having four copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells. Tetraploids may carry two, three, four, or more different expression cassettes. Such tetraploids might be obtained in *S. cerevisiae* by selective mating homozygotic heterothallic a/a and alpha/alpha diploids and in *Pichia* by sequential mating of haploids to obtain auxotrophic diploids. For example, a [met his] haploid can be mated with [ade his] haploid to obtain diploid [his]; and a [met arg] haploid can be mated with [ade arg] haploid to obtain diploid [arg]; then the diploid [his] x diploid [arg] to obtain a tetraploid prototroph. It will be understood by those of skill in the art that reference to the benefits and uses of diploid cells may also apply to tetraploid cells.

[0037] *Yeast Mating*: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0038] *Meiosis*: The process by which a diploid yeast cell undergoes reductive division to form four haploid spore products. Each spore may then germinate and form a haploid vegetatively growing cell line.

[0039] *Selectable Marker*: A selectable marker is a gene or gene fragment that confers a growth phenotype (physical growth characteristic) on a cell receiving that gene as, for example through a transformation event. The selectable marker allows that cell to survive and grow in a selective growth medium under conditions in which cells that do not receive that selectable marker gene cannot grow. Selectable marker genes generally fall into several types, including positive selectable marker genes such as a gene that confers on a cell resistance to an antibiotic or other drug, temperature when two ts mutants are crossed or a ts mutant is transformed; negative selectable marker genes such as a biosynthetic gene that confers on a cell the ability to grow in a medium without a specific nutrient needed by all cells that do not have that biosynthetic gene, or a mutagenized biosynthetic gene that confers on a cell inability to grow by cells that do not have the wild type gene; and the like. Suitable markers include but are not limited to: ZEO; G418; LYS3; MET1; MET3a; ADE1; ADE3; URA3; and the like.

[0040] *Expression Vector*: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, *e.g. E. coli,* and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0041] Expression vectors for use in the methods of the invention will further include yeast specific sequences, including a selectable auxotrophic or drug marker for identifying

transformed yeast strains. A drug marker may further be used to amplify copy number of the vector in a yeast host cell.

[0042] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in yeast cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome.

[0043] In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0044] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway^{R} Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0045] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to

some change in culture conditions, *e.g.*, the presence or absence of a nutrient or a change in temperature.

[0046] The yeast promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the yeast genome; alternatively a selectable marker is used as the site for homologous recombination. *Pichia* transformation is described in Cregg *et al.* (1985) Mol. Cell. Biol. **5**:3376-3385.

[0047] Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg *et al.* (1989) Mol. Cell. Biol. **9**:1316-1323); ICL1 promoter (Menendez *et al.* (2003) Yeast **20**(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham *et al.* (1997) Gene **186**(1):37-44); and FLD1 promoter (Shen *et al.* (1998) Gene **216**(1):93-102). The *GAP* promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[0048] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile , amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0049] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, *e.g.* a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be

engineered to provide for enhanced secretion in diploid yeast expression systems. Other secretion signals of interest also include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, *e.g.*, K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto *et. al.* Protein Eng 11(2) 75 (1998); and Kobayashi *et. al.* Therapeutic Apheresis 2(4) 257 (1998).

[0050] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[0051] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0052] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0053] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) Ann.Rev.Biochem. 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E.coli* –encoded recombination proteins. Recombination occurs between specific attachment (*att*) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp.211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the *att* sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[0054] *Att* sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing *att* B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

[0055] *Folding*, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. While non-covalent interactions are important in determining structure, usually the proteins of interest will have intra- and/or intermolecular covalent disulfide bonds formed by two cysteine residues. For naturally occurring proteins and polypeptides or derivatives and variants thereof, the proper folding is typically the arrangement that results in optimal biological activity, and can conveniently be monitored by assays for activity, *e.g.* ligand binding, enzymatic activity, *etc.*

[0056] In some instances, for example where the desired product is of synthetic origin, assays based on biological activity will be less meaningful. The proper folding of such molecules may be determined on the basis of physical properties, energetic considerations, modeling studies, and the like.

[0057] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, *i.e.*

foldases, chaperonins, *etc.* Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, *etc.* as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[0058] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, *e.g.* one strain may express BIP, and the other strain may express PDI or combinations thereof.

[0059] The terms "*desired protein*" or "*target protein*" are used interchangeably and refer generally to a humanized antibody or a binding portion thereof described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies such as scFvs, camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', $F(ab')_2$ and the like. *See* Streltsov VA, *et al.*, Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, Protein Sci. 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, *et al.*, A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, Nature. 1995 Mar

9;374(6518):168-73; Nuttall SD, *et al.*, Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, Mol Immunol. 2001 Aug;38(4):313-26; Hamers-Casterman C, *et al.*, Naturally occurring antibodies devoid of light chains, Nature. 1993 Jun 3;363(6428):446-8; Gill DS, *et al.*, Biopharmaceutical drug discovery using novel protein scaffolds, Curr Opin Biotechnol. 2006 Dec;17(6):653-8. Epub 2006 Oct 19.

[0060] For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0061] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (*e.g.*, a functional domain, catalytic amino acid residues, *etc*). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains.

Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[0062] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[0063] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, e.g., U.S. Patent No. 6,187,287, incorporated fully herein by reference.

[0064] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', $F(ab')_2$, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, *e.g.* diabodies, which comprise two distinct Fv specificities. In another

embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0065] Immunoglobulins and fragments thereof may be modified post-translationally, *e.g.* to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided *infra*.

[0066] The term "polyploid yeast that stably expresses or expresses a desired secreted heterologous polypeptide for prolonged time" refers to a yeast culture that secretes said polypeptide for at least several days to a week, more preferably at least a month, still more preferably at least 1-6 months, and even more preferably for more than a year at threshold expression levels, typically at least 10-25 mg/liter and preferably substantially greater.

[0067] The term "polyploidal yeast culture that secretes desired amounts of recombinant polypeptide" refers to cultures that stably or for prolonged periods secrete at least 10-25 mg/liter of heterologous polypeptide, more preferably at least 50-500 mg/liter, and most preferably 500-1000 mg/liter or more.

[0068] A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0069] A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different

than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0070] A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[0071] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypepide encoded by said polynucleotide sequence.

[0072] "Amplification" of polynucleotide sequences is the *in vitro* production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in

the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, Bio/Technol., 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0073] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the F_C region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0074] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ, μ, α, δ, and ε (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., *et al.*, Clinical Immunobiology, pp 1-18, W. B. Sanders (1980); Kohl, S., *et al.*, Immunology, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be paired with either kappa or lambda light chain. The light and heavy chains are covalently

bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0075] The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0076] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., *et al.*, US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, J Mol. Biol. 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the anibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)).

[0077] The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

Anti-IL-6 Antibodies and Binding Fragments Thereof

[0078] The invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below: MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQASQSINNEL SWYQQKPGQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDLECADAATYYCQ QGYSLRNIDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN (SEQ ID NO: 2).

[0079] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYVTWV RQAPGKGLEWIGIIYGSDETAYATWAIGRFTISKTSTTVDLKMTSLTAADTATYFC ARDDSSDWDAKFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK (SEQ ID NO: 3).

[0080] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0081] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID

NO: 3, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0082] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 2. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 3.

[0083] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 2.

[0084] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3.

[0085] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 2; the variable heavy chain region of SEQ ID NO: 3; the complementarity-determining regions (SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6) of the variable light chain region of SEQ ID NO: 2; and the complementarity-determining regions (SEQ ID NO: 7; SEQ ID NO: 8; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 3.

[0086] The invention also contemplates variants wherein either of the heavy chain polypeptide sequences of SEQ ID NO: 18 or SEQ ID NO: 19 is substituted for the heavy chain polypeptide sequence of SEQ ID NO: 3; the light chain polypeptide sequence of SEQ

ID NO: 20 is substituted for the light chain polypeptide sequence of SEQ ID NO: 2; and the heavy chain CDR sequence of SEQ ID NO: 120 is substituted for the heavy chain CDR sequence of SEQ ID NO: 8.

[0087] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab1, comprising SEQ ID NO: 2 and SEQ ID NO: 3, or the alternative SEQ ID NOs set forth in paragraph [0083] above, and having at least one of the biological activities set forth herein.

[0088] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTINCQASETIYSWL
SWYQQKPGQPPKLLIYQASDLASGVPSRFSGSGAGTEYTLTISGVQCDDAATYYC
QQGYSGSNVDNVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
(SEQ ID NO: 21)

[0089] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:
METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTASGFSLNDHAMG
WVRQAPGKGLEYIGFINSGGSARYASWAEGRFTISRTSTTVDLKMTSLTTEDTATY
FCVRGGAVWSIHSFDPWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
K (SEQ ID NO: 22).

[0090] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0091] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21, and/or one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0092] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 21. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 22.

[0093] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21.

[0094] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 22.

[0095] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the

variable light chain region of SEQ ID NO: 21; the variable heavy chain region of SEQ ID NO: 22; the complementarity-determining regions (SEQ ID NO: 23; SEQ ID NO: 24; and SEQ ID NO: 25) of the variable light chain region of SEQ ID NO: 21; and the complementarity-determining regions (SEQ ID NO: 26; SEQ ID NO: 27; and SEQ ID NO: 28) of the variable heavy chain region of SEQ ID NO: 22.

[0096] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab2, comprising SEQ ID NO: 21 and SEQ ID NO: 22, and having at least one of the biological activities set forth herein.

[0097] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQASQSVYDNN
YLSWFQQKPGQPPKLLIYGASTLASGVPSRFVGSGSGTQFTLTITDVQCDDAATYY
CAGVYDDDSDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
(SEQ ID NO: 37)

[0098] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:
METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSVYYMNW
VRQAPGKGLEWIGFITMSDNINYASWAKGRFTISKTSTTVDLKMTSPTTEDTATYF
CARSRGWGTMGRLDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
K (SEQ ID NO: 38).

[0099] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the

invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0100] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37, and/or one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0101] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 37. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 38.

[0102] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 37.

[0103] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 38.

[0104] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention,

fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 37; the variable heavy chain region of SEQ ID NO: 38; the complementarity-determining regions (SEQ ID NO: 39; SEQ ID NO: 40; and SEQ ID NO: 41) of the variable light chain region of SEQ ID NO: 37; and the complementarity-determining regions (SEQ ID NO: 42; SEQ ID NO: 43; and SEQ ID NO: 44) of the variable heavy chain region of SEQ ID NO: 38.

[0105] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab3, comprising SEQ ID NO: 37 and SEQ ID NO: 38, and having at least one of the biological activities set forth herein.

[0106] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0107] MDTRAPTQLLGLLLLWLPGAICDPVLTQTPSPVSAPVGGTVSISCQASQS VYENNYLSWFQQKPGQPPKLLIYGASTLDSGVPSRFKGSGSGTQFTLTITDVQCDD AATYYCAGVYDDDSDDAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNN (SEQ ID NO: 53)

[0108] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQEQLKESGGGLVTPGGTLTLTCTASGFSLNAYYMN WVRQAPGKGLEWIGFITLNNNVAYANWAKGRFTFSKTSTTVDLKMTSPTPEDTAT YFCARSRGWGAMGRLDLWGHGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVK (SEQ ID NO: 54).

[0109] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53, and/or one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54, or combinations of these

polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0110] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53, and/or one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0111] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 53. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 54.

[0112] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 53.

[0113] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 54.

[0114] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 53; the variable heavy chain region of SEQ ID NO: 54; the complementarity-determining regions (SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57) of the variable light chain region of SEQ ID NO: 53; and the complementarity-determining regions (SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60) of the variable heavy chain region of SEQ ID NO: 54.

[0115] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab4, comprising SEQ ID NO: 53 and SEQ ID NO: 54, and having at least one of the biological activities set forth herein.

[0116] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0117] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSAAVGGTVTINCQASQ SVDDNNWLGWYQQKRGQPPKYLIYSASTLASGVPSRFKGSGSGTQFTLTISDLECD DAATYYCAGGFSGNIFAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNF (SEQ ID NO: 69)

[0118] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWV RQAPGKGLEWIGIIGGFGTTYYATWAKGRFTISKTSTTVDLRITSPTTEDTATYFCA RGGPGNGGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD (SEQ ID NO: 70).

[0119] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0120] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69, and/or one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0121] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 69. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 70.

[0122] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 69.

[0123] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 70.

[0124] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 69; the variable heavy chain region of SEQ ID NO: 70; the complementarity-determining regions (SEQ ID NO: 71; SEQ ID NO: 72; and SEQ ID NO: 73) of the variable light chain region of SEQ ID NO: 69; and the complementarity-determining regions (SEQ ID NO: 74; SEQ ID NO: 75; and SEQ ID NO: 76) of the variable heavy chain region of SEQ ID NO: 70.

[0125] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab5, comprising SEQ ID NO: 69 and SEQ ID NO: 70, and having at least one of the biological activities set forth herein.

[0126] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0127] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSVPVGGTVTIKCQSSQS VYNNFLSWYQQKPGQPPKLLIYQASKLASGVPDRFSGSGSGTQFTLTISGVQCDDA ATYYCLGGYDDDADNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNF (SEQ ID NO: 85)

[0128] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGIDLSDYAMSWV RQAPGKGLEWIGIIYAGSGSTWYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFC ARDGYDDYGDFDRLDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKD (SEQ ID NO: 86).

[0129] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions)

of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0130] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85, and/or one or more of the polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 86, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0131] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 85. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 86.

[0132] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 85.

[0133] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the

polypeptide sequences of SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variableheavy chain sequence of SEQ ID NO: 86.

[0134] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 85; the variable heavy chain region of SEQ ID NO: 86; the complementarity-determining regions (SEQ ID NO: 87; SEQ ID NO: 88; and SEQ ID NO: 89) of the variable light chain region of SEQ ID NO: 85; and the complementarity-determining regions (SEQ ID NO: 90; SEQ ID NO: 91; and SEQ ID NO: 92) of the variable heavy chain region of SEQ ID NO: 86.

[0135] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab6, comprising SEQ ID NO: 85 and SEQ ID NO: 86, and having at least one of the biological activities set forth herein.

[0136] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0137] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVSAAVGGTVTIKCQAS QSINNELSWYQQKSGQRPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDLECADA ATYYCQQGYSLRNIDNAFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNF (SEQ ID NO: 101)

[0138] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLSGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLSNYYMTWV RQAPGKGLEWIGMIYGSDETAYANWAIGRFTISKTSTTVDLKMTSLTAADTATYF CARDDSSDWDAKFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV K (SEQ ID NO: 102).

[0139] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0140] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101, and/or one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0141] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 101. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 102.

[0142] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101.

[0143] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 102.

[0144] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 101; the variable heavy chain region of SEQ ID NO: 102; the complementarity-determining regions (SEQ ID NO: 103; SEQ ID NO: 104; and SEQ ID NO: 105) of the variable light chain region of SEQ ID NO: 101; and the complementarity-determining regions (SEQ ID NO: 106; SEQ ID NO: 107; and SEQ ID NO: 108) of the variable heavy chain region of SEQ ID NO: 102.

[0145] The invention also contemplates variants wherein either of the heavy chain polypeptide sequences of SEQ ID NO: 117 or SEQ ID NO: 118 is substituted for the heavy chain polypeptide sequence of SEQ ID NO: 102; the light chain polypeptide sequence of SEQ ID NO: 119 is substituted for the light chain polypeptide sequence of SEQ ID NO: 101; and the heavy chain CDR sequence of SEQ ID NO: 121 is substituted for the heavy chain CDR sequence of SEQ ID NO: 107.

[0146] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab7, comprising SEQ ID NO: 101 and SEQ ID NO: 102, or the alternative SEQ ID NOs set forth in paragraph [0138] above, and having at least one of the biological activities set forth herein.

[0147] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0148] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQSSQS VGNNQDLSWFQQRPGQPPKLLIYEISKLESGVPSRFSGSGSGTHFTLTISGVQCDDA ATYYCLGGYDDDADNA (SEQ ID NO: 122)

[0149] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCHSVEESGGRLVTPGTPLTLTCTVSGFSLSSRTMSWV RQAPGKGLEWIGYIWSGGSTYYATWAKGRFTISKTSTTVDLKITSPTTEDTATYFC ARLGDTGGHAYATRLNL (SEQ ID NO: 123).

[0150] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0151] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0152] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

122. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 123.

[0153] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122.

[0154] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123.

[0155] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 122; the variable heavy chain region of SEQ ID NO: 123; the complementarity-determining regions (SEQ ID NO: 124; SEQ ID NO: 125; and SEQ ID NO: 126) of the variable light chain region of SEQ ID NO: 122; and the complementarity-determining regions (SEQ ID NO: 127; SEQ ID NO: 128; and SEQ ID NO: 129) of the variable heavy chain region of SEQ ID NO: 123.

[0156] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab8, comprising SEQ ID NO: 122 and SEQ ID NO: 123, and having at least one of the biological activities set forth herein.

[0157] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0158] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVSISCQSSQS VYSNKYLAWYQQKPGQPPKLLIYWTSKLASGAPSRFSGSGSGTQFTLTISGVQCDD AATYYCLGAYDDDADNA (SEQ ID NO: 138)

[0159] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTASGFSLEGGYMTW VRQAPGKGLEWIGISYDSGSTYYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATY FCVRSLKYPTVTSDDL (SEQ ID NO: 139).

[0160] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0161] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138, and/or one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0162] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

138. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 139.

[0163] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 138.

[0164] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 139.

[0165] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 138; the variable heavy chain region of SEQ ID NO: 139; the complementarity-determining regions (SEQ ID NO: 140; SEQ ID NO: 141; and SEQ ID NO: 142) of the variable light chain region of SEQ ID NO: 138; and the complementarity-determining regions (SEQ ID NO: 143; SEQ ID NO: 144; and SEQ ID NO: 145) of the variable heavy chain region of SEQ ID NO: 139.

[0166] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab9, comprising SEQ ID NO: 138 and SEQ ID NO: 139, and having at least one of the biological activities set forth herein.

[0167] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0168] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQSSQS VYNNNDLAWYQQKPGQPPKLLIYYASTLASGVPSRFKGSGSGTQFTLTISGVQCD DAAAYYCLGGYDDDADNA (SEQ ID NO: 154)

[0169] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGLSLSSNTINWV RQAPGKGLEWIGYIWSGGSTYYASWVNGRFTISKTSTTVDLKITSPTTEDTATYFC ARGGYASGGYPYATRLDL (SEQ ID NO: 155).

[0170] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0171] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154, and/or one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0172] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

154. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 155.

[0173] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 154.

[0174] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 155.

[0175] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 154; the variable heavy chain region of SEQ ID NO: 155; the complementarity-determining regions (SEQ ID NO: 156; SEQ ID NO: 157; and SEQ ID NO: 158) of the variable light chain region of SEQ ID NO: 154; and the complementarity-determining regions (SEQ ID NO: 159; SEQ ID NO: 160; and SEQ ID NO: 161) of the variable heavy chain region of SEQ ID NO: 155.

[0176] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab10, comprising SEQ ID NO: 154 and SEQ ID NO: 155, and having at least one of the biological activities set forth herein.

[0177] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0178] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSSVSAAVGGTVTINCQSSQ SVYNNDYLSWYQQRPGQRPKLLIYGASKLASGVPSRFKGSGSGKQFTLTISGVQC DDAATYYCLGDYDDDADNT (SEQ ID NO: 170)

[0179] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFTLSTNYYLSW VRQAPGKGLEWIGIIYPSGNTYCAKWAKGRFTISKTSSTTVDLKMTSPTTEDTATY FCARNYGGDESL (SEQ ID NO: 171).

[0180] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0181] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170, and/or one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0182] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

170. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 171.

[0183] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 170.

[0184] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 171.

[0185] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 170; the variable heavy chain region of SEQ ID NO: 171; the complementarity-determining regions (SEQ ID NO: 172; SEQ ID NO: 173; and SEQ ID NO: 174) of the variable light chain region of SEQ ID NO: 170; and the complementarity-determining regions (SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177) of the variable heavy chain region of SEQ ID NO: 171.

[0186] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab11, comprising SEQ ID NO: 170 and SEQ ID NO: 171, and having at least one of the biological activities set forth herein.

[0187] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0188] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQAS ETIGNALAWYQQKSGQPPKLLIYKASKLASGVPSRFKGSGSGTEYTLTISDLECAD AATYYCQWCYFGDSV (SEQ ID NO: 186)

[0189] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVTVLKGVQCQEQLVESGGGLVQPEGSLTLTCTASGFDFSSGYYM CWVRQAPGKGLEWIACIFTITTNTYYASWAKGRFTISKTSSTTVTLQMTSLTAADT ATYLCARGIYSDNNYYAL (SEQ ID NO: 187).

[0190] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0191] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186, and/or one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0192] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

186. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 187.

[0193] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 186.

[0194] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 187.

[0195] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 186; the variable heavy chain region of SEQ ID NO: 187; the complementarity-determining regions (SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190) of the variable light chain region of SEQ ID NO: 186; and the complementarity-determining regions (SEQ ID NO: 191; SEQ ID NO: 192; and SEQ ID NO: 193) of the variable heavy chain region of SEQ ID NO: 187.

[0196] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab12, comprising SEQ ID NO: 186 and SEQ ID NO: 187, and having at least one of the biological activities set forth herein.

[0197] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0198] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQAS ESIGNALAWYQQKPGQPPKLLIYKASTLASGVPSRFSGSGSGTEFTLTISGVQCADA AAYYCQWCYFGDSV (SEQ ID NO: 202)

[0199] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQQQLVESGGGLVKPGASLTLTCKASGFSFSSGYYM CWVRQAPGKGLESIACIFTITDNTYYANWAKGRFTISKPSSPTVTLQMTSLTAADT ATYFCARGIYSTDNYYAL (SEQ ID NO: 203).

[0200] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0201] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202, and/or one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0202] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

202. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 203.

[0203] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 202.

[0204] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 203.

[0205] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 202; the variable heavy chain region of SEQ ID NO: 203; the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 205; and SEQ ID NO: 206) of the variable light chain region of SEQ ID NO: 202; and the complementarity-determining regions (SEQ ID NO: 207; SEQ ID NO: 208; and SEQ ID NO: 209) of the variable heavy chain region of SEQ ID NO: 203.

[0206] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab13, comprising SEQ ID NO: 202 and SEQ ID NO: 203, and having at least one of the biological activities set forth herein.

[0207] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0208] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQAS QSVSSYLNWYQQKPGQPPKLLIYRASTLESGVPSRFKGSGSGTEFTLTISDLECADA ATYYCQCTYGTSSSYGAA (SEQ ID NO: 218)

[0209] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGISLSSNAISWVR QAPGKGLEWIGIISYSGTTYYASWAKGRFTISKTSSTTVDLKITSPTTEDTATYFCA RDDPTTVMVMLIPFGAGMDL (SEQ ID NO: 219).

[0210] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0211] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218, and/or one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0212] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

218. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 219.

[0213] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 218.

[0214] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 219.

[0215] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 218; the variable heavy chain region of SEQ ID NO: 219; the complementarity-determining regions (SEQ ID NO: 220; SEQ ID NO: 221; and SEQ ID NO: 222) of the variable light chain region of SEQ ID NO: 218; and the complementarity-determining regions (SEQ ID NO: 223; SEQ ID NO: 224; and SEQ ID NO: 225) of the variable heavy chain region of SEQ ID NO: 219.

[0216] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab14, comprising SEQ ID NO: 218 and SEQ ID NO: 219, and having at least one of the biological activities set forth herein.

[0217] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0218] MDTRAPTQLLGLLLLWLPGATFAQVLTQTASPVSAAVGGTVTINCQASQ SVYKNNYLSWYQQKPGQPPKGLIYSASTLDSGVPLRFSGSGSGTQFTLTISDVQCD DAATYYCLGSYDCSSGDCYA (SEQ ID NO: 234)

[0219] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCTASGFSFSSYWMCW VRQAPGKGLEWIACIVTGNGNTYYANWAKGRFTISKTSSTTVTLQMTSLTAADTA TYFCAKAYDL (SEQ ID NO: 235).

[0220] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0221] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234, and/or one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0222] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

234. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 235.

[0223] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 234.

[0224] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 235.

[0225] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 234; the variable heavy chain region of SEQ ID NO: 235; the complementarity-determining regions (SEQ ID NO: 236; SEQ ID NO: 237; and SEQ ID NO: 238) of the variable light chain region of SEQ ID NO: 234; and the complementarity-determining regions (SEQ ID NO: 239; SEQ ID NO: 240; and SEQ ID NO: 241) of the variable heavy chain region of SEQ ID NO: 235.

[0226] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab15, comprising SEQ ID NO: 234 and SEQ ID NO: 235, and having at least one of the biological activities set forth herein.

[0227] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0228] MDTRAPTQLLGLLLLWLPGSTFAAVLTQTPSPVSAAVGGTVSISCQASQS VYDNNYLSWYQQKPGQPPKLLIYGASTLASGVPSRFKGTGSGTQFTLTITDVQCD DAATYYCAGVFNDDSDDA (SEQ ID NO: 250)

[0229] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVPKGVQCQSLEESGGRLVTPGTPLTLTCTLSGFSLSAYYMSWV RQAPGKGLEWIGFITLSDHISYARWAKGRFTISKTSTTVDLKMTSPTTEDTATYFCA RSRGWGAMGRLDL (SEQ ID NO: 251).

[0230] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0231] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250, and/or one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0232] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

250. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 251.

[0233] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 250.

[0234] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 251.

[0235] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 250; the variable heavy chain region of SEQ ID NO: 251; the complementarity-determining regions (SEQ ID NO: 252; SEQ ID NO: 253; and SEQ ID NO: 254) of the variable light chain region of SEQ ID NO: 250; and the complementarity-determining regions (SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257) of the variable heavy chain region of SEQ ID NO: 251.

[0236] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab16, comprising SEQ ID NO: 250 and SEQ ID NO: 251, and having at least one of the biological activities set forth herein.

[0237] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0238] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVTISCQASQ SVYNNKNLAWYQQKSGQPPKLLIYWASTLASGVSSRFSGSGSGTQFTLTVSGVQC DDAATYYCLGVFDDDADNA (SEQ ID NO: 266)

[0239] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYSMTWV RQAPGKGLEYIGVIGTSGSTYYATWAKGRFTISRTSTTVALKITSPTTEDTATYFCV RSLSSITFL (SEQ ID NO: 267).

[0240] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0241] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266, and/or one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0242] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

266. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 267.

[0243] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 266.

[0244] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 267.

[0245] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 266; the variable heavy chain region of SEQ ID NO: 267; the complementarity-determining regions (SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270) of the variable light chain region of SEQ ID NO: 266; and the complementarity-determining regions (SEQ ID NO: 271; SEQ ID NO: 272; and SEQ ID NO: 273) of the variable heavy chain region of SEQ ID NO: 267.

[0246] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab17, comprising SEQ ID NO: 266 and SEQ ID NO: 267, and having at least one of the biological activities set forth herein.

[0247] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0248] MDTRAPTQLLGLLLLWLPGARCAFELTQTPASVEAAVGGTVTINCQASQ NIYRYLAWYQQKPGQPPKFLIYLASTLASGVPSRFKGSGSGTEFTLTISDLECADAA TYYCQSYYSSNSVA (SEQ ID NO: 282)

[0249] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQEQLVESGGDLVQPEGSLTLTCTASELDFSSGYWIC WVRQVPGKGLEWIGCIYTGSSGSTFYASWAKGRFTISKTSSTTVTLQMTSLTAADT ATYFCARGYSGFGYFKL (SEQ ID NO: 283).

[0250] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0251] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282, and/or one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0252] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

282. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 283.

[0253] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 282.

[0254] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 283.

[0255] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 282; the variable heavy chain region of SEQ ID NO: 283; the complementarity-determining regions (SEQ ID NO: 284; SEQ ID NO: 285; and SEQ ID NO: 286) of the variable light chain region of SEQ ID NO: 282; and the complementarity-determining regions (SEQ ID NO: 287; SEQ ID NO: 288; and SEQ ID NO: 289) of the variable heavy chain region of SEQ ID NO: 283.

[0256] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab18, comprising SEQ ID NO: 282 and SEQ ID NO: 283, and having at least one of the biological activities set forth herein.

[0257] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0258] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQAS EDIYRLLAWYQQKPGQPPKLLIYDSSDLASGVPSRFKGSGSGTEFTLAISGVQCDD AATYYCQQAWSYSDIDNA (SEQ ID NO: 298)

[0259] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTASGFSLSSYYMSWV RQAPGKGLEWIGIITTSGNTFYASWAKGRLTISRTSTTVDLKITSPTTEDTATYFCAR TSDIFYYRNL (SEQ ID NO: 299).

[0260] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0261] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298, and/or one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0262] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

298. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 299.

[0263] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 298.

[0264] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 299.

[0265] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 298; the variable heavy chain region of SEQ ID NO: 299; the complementarity-determining regions (SEQ ID NO: 300; SEQ ID NO: 301; and SEQ ID NO: 302) of the variable light chain region of SEQ ID NO: 298; and the complementarity-determining regions (SEQ ID NO: 303; SEQ ID NO: 304; and SEQ ID NO: 305) of the variable heavy chain region of SEQ ID NO: 299.

[0266] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab19, comprising SEQ ID NO: 298 and SEQ ID NO: 299, and having at least one of the biological activities set forth herein.

[0267] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0268] MDTRAPTQLLGLLLLWLPGATFAAVLTQTASPVSAAVGATVTINCQSSQ SVYNDMDLAWFQQKPGQPPKLLIYSASTLASGVPSRFSGSGSGTEFTLTISGVQCD DAATYYCLGAFDDDADNT (SEQ ID NO: 314)

[0269] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLTRHAITWV RQAPGKGLEWIGCIWSGGSTYYATWAKGRFTISKTSTTVDLRITSPTTEDTATYFC ARVIGDTAGYAYFTGLDL (SEQ ID NO: 315).

[0270] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0271] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314, and/or one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0272] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

314. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 315.

[0273] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 314.

[0274] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 315.

[0275] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 314; the variable heavy chain region of SEQ ID NO: 315; the complementarity-determining regions (SEQ ID NO: 316; SEQ ID NO: 317; and SEQ ID NO: 318) of the variable light chain region of SEQ ID NO: 314; and the complementarity-determining regions (SEQ ID NO: 319; SEQ ID NO: 320; and SEQ ID NO: 321) of the variable heavy chain region of SEQ ID NO: 315.

[0276] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab20, comprising SEQ ID NO: 314 and SEQ ID NO: 315, and having at least one of the biological activities set forth herein.

[0277] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0278] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQAS QSVYNWLSWYQQKPGQPPKLLIYTASSLASGVPSRFSGSGSGTEFTLTISGVECAD AATYYCQQGYTSDVDNV (SEQ ID NO: 330)

[0279] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEEAGGRLVTPGTPLTLTCTVSGIDLSSYAMGW VRQAPGKGLEYIGIISSSGSTYYATWAKGRFTISQASSTTVDLKITSPTTEDSATYFC ARGGAGSGGVWLLDGFDP (SEQ ID NO: 331).

[0280] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0281] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330, and/or one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0282] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

330. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 331.

[0283] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 330.

[0284] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 331.

[0285] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 330; the variable heavy chain region of SEQ ID NO: 331; the complementarity-determining regions (SEQ ID NO: 332; SEQ ID NO: 333; and SEQ ID NO: 334) of the variable light chain region of SEQ ID NO: 330; and the complementarity-determining regions (SEQ ID NO: 335; SEQ ID NO: 336; and SEQ ID NO: 337) of the variable heavy chain region of SEQ ID NO: 331.

[0286] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab21, comprising SEQ ID NO: 330 and SEQ ID NO: 331, and having at least one of the biological activities set forth herein.

[0287] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0288] MDTRAPTQLLGLLLLWLPGAKCADVVMTQTPASVSAAVGGTVTINCQA SENIYNWLAWYQQKPGQPPKLLIYTVGDLASGVSSRFKGSGSGTEFTLTISDLECA DAATYYCQQGYSSSYVDNV (SEQ ID NO: 346)

[0289] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQEQLKESGGRLVTPGTPLTLTCTVSGFSLNDYAVG WFRQAPGKGLEWIGYIRSSGTTAYATWAKGRFTISATSTTVDLKITSPTTEDTATYF CARGGAGSSGVWILDGFAP (SEQ ID NO: 347).

[0290] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346, and/or one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0291] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346, and/or one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0292] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

346. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 347.

[0293] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 346.

[0294] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

[0295] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 346; the variable heavy chain region of SEQ ID NO: 347; the complementarity-determining regions (SEQ ID NO: 348; SEQ ID NO: 349; and SEQ ID NO: 350) of the variable light chain region of SEQ ID NO: 346; and the complementarity-determining regions (SEQ ID NO: 351; SEQ ID NO: 352; and SEQ ID NO: 353) of the variable heavy chain region of SEQ ID NO: 347.

[0296] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab22, comprising SEQ ID NO: 346 and SEQ ID NO: 347, and having at least one of the biological activities set forth herein.

[0297] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0298] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSSVSAAVGGTVTINCQASQ SVYQNNYLSWFQQKPGQPPKLLIYGAATLASGVPSRFKGSGSGTQFTLTISDLECD DAATYYCAGAYRDVDS (SEQ ID NO: 362)

[0299] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTASGFSFTSTYYIYW VRQAPGKGLEWIACIDAGSSGSTYYATWVNGRFTISKTSSTTVTLQMTSLTAADTA TYFCAKWDYGGNVGWGYDL (SEQ ID NO: 363).

[0300] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0301] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362, and/or one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0302] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

362. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 363.

[0303] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 362.

[0304] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 363.

[0305] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 362; the variable heavy chain region of SEQ ID NO: 363; the complementarity-determining regions (SEQ ID NO: 364; SEQ ID NO: 365; and SEQ ID NO: 366) of the variable light chain region of SEQ ID NO: 362; and the complementarity-determining regions (SEQ ID NO: 367; SEQ ID NO: 368; and SEQ ID NO: 369) of the variable heavy chain region of SEQ ID NO: 363.

[0306] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab23, comprising SEQ ID NO: 362 and SEQ ID NO: 363, and having at least one of the biological activities set forth herein.

[0307] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0308] MDTRAPTQLLGLLLLWLPGARCAFELTQTPSSVEAAVGGTVTIKCQASQ SISSYLAWYQQKPGQPPKFLIYRASTLASGVPSRFKGSGSGTEFTLTISDLECADAA TYYCQSYYDSVSNP (SEQ ID NO: 378)

[0309] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGDLVKPEGSLTLTCKASGLDLGTYWFMC WVRQAPGKGLEWIACIYTGSSGSTFYASWVNGRFTISKTSSTTVTLQMTSLTAADT ATYFCARGYSGYGYFKL (SEQ ID NO: 379).

[0310] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0311] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378, and/or one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0312] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

378. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 379.

[0313] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 378.

[0314] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 379.

[0315] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 378; the variable heavy chain region of SEQ ID NO: 379; the complementarity-determining regions (SEQ ID NO: 380; SEQ ID NO: 381; and SEQ ID NO: 382) of the variable light chain region of SEQ ID NO: 378; and the complementarity-determining regions (SEQ ID NO: 383; SEQ ID NO: 384; and SEQ ID NO: 385) of the variable heavy chain region of SEQ ID NO: 379.

[0316] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab24, comprising SEQ ID NO: 378 and SEQ ID NO: 379, and having at least one of the biological activities set forth herein.

[0317] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0318] MDTRAPTQLLGLLLLWLPGVTFAIEMTQSPFSVSAAVGGTVSISCQASQS VYKNNQLSWYQQKSGQPPKLLIYGASALASGVPSRFKGSGSGTEFTLTISDVQCDD AATYYCAGAITGSIDTDG (SEQ ID NO: 394)

[0319] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGDLVKPGASLTLTCTTSGFSFSSSYFICWV RQAPGKGLEWIACIYGGDGSTYYASWAKGRFTISKTSSTTVTLQMTSLTAADTAT YFCAREWAYSQGYFGAFDL (SEQ ID NO: 395).

[0320] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0321] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394, and/or one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0322] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

394. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 395.

[0323] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 394.

[0324] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 395.

[0325] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 394; the variable heavy chain region of SEQ ID NO: 395; the complementarity-determining regions (SEQ ID NO: 396; SEQ ID NO: 397; and SEQ ID NO: 398) of the variable light chain region of SEQ ID NO: 394; and the complementarity-determining regions (SEQ ID NO: 399; SEQ ID NO: 400; and SEQ ID NO: 401) of the variable heavy chain region of SEQ ID NO: 395.

[0326] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab25, comprising SEQ ID NO: 394 and SEQ ID NO: 395, and having at least one of the biological activities set forth herein.

[0327] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0328] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVEAAVGGTVTIKCQAS EDISSYLAWYQQKPGQPPKLLIYAASNLESGVSSRFKGSGSGTEYTLTISDLECADA ATYYCQCTYGTISISDGNA (SEQ ID NO: 410)

[0329] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMTWV RQAPGEGLEYIGFINPGGSAYYASWVKGRFTISKSSTTVDLKITSPTTEDTATYFCA RVLIVSYGAFTI (SEQ ID NO: 411).

[0330] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0331] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410, and/or one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0332] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

410. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 411.

[0333] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 410.

[0334] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 411.

[0335] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 410; the variable heavy chain region of SEQ ID NO: 411; the complementarity-determining regions (SEQ ID NO: 412; SEQ ID NO: 413; and SEQ ID NO: 414) of the variable light chain region of SEQ ID NO: 410; and the complementarity-determining regions (SEQ ID NO: 415; SEQ ID NO: 416; and SEQ ID NO: 417) of the variable heavy chain region of SEQ ID NO: 411.

[0336] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab26, comprising SEQ ID NO: 410 and SEQ ID NO: 411, and having at least one of the biological activities set forth herein.

[0337] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0338] MDTRAPTQLLGLLLLWLPGARCDVVMTQTPASVSAAVGGTVTIKCQAS EDIESYLAWYQQKPGQPPKLLIYGASNLESGVSSRFKGSGSGTEFTLTISDLECADA ATYYCQCTYGIISISDGNA (SEQ ID NO: 426)

[0339] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMTWV RQAPGEGLEYIGFMNTGDNAYYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFC ARVLVVAYGAFNI (SEQ ID NO: 427).

[0340] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0341] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426, and/or one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0342] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

426. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 427.

[0343] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 426.

[0344] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427.

[0345] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 426; the variable heavy chain region of SEQ ID NO: 427; the complementarity-determining regions (SEQ ID NO: 428; SEQ ID NO: 429; and SEQ ID NO: 430) of the variable light chain region of SEQ ID NO: 426; and the complementarity-determining regions (SEQ ID NO: 431; SEQ ID NO: 432; and SEQ ID NO: 433) of the variable heavy chain region of SEQ ID NO: 427.

[0346] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab27, comprising SEQ ID NO: 426 and SEQ ID NO: 427, and having at least one of the biological activities set forth herein.

[0347] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0348] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSEPVGGTVSISCQSSKS VMNNNYLAWYQQKPGQPPKLLIYGASNLASGVPSRFSGSGSGTQFTLTISDVQCD DAATYYCQGGYTGYSDHGT (SEQ ID NO: 442)

[0349] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVKPDETLTLTCTVSGIDLSSYPMNWV RQAPGKGLEWIGFINTGGTIVYASWAKGRFTISKTSTTVDLKMTSPTTEDTATYFC ARGSYVSSGYAYYFNV (SEQ ID NO: 443).

[0350] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0351] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442, and/or one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0352] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

442. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 443.

[0353] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 442.

[0354] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 443.

[0355] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 442; the variable heavy chain region of SEQ ID NO: 443; the complementarity-determining regions (SEQ ID NO: 444; SEQ ID NO: 445; and SEQ ID NO: 446) of the variable light chain region of SEQ ID NO: 442; and the complementarity-determining regions (SEQ ID NO: 447; SEQ ID NO: 448; and SEQ ID NO: 449) of the variable heavy chain region of SEQ ID NO: 443.

[0356] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab28, comprising SEQ ID NO: 442 and SEQ ID NO: 443, and having at least one of the biological activities set forth herein.

[0357] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0358] MDTRAPTQLLGLLLLWLPGATFAAVLTQTPSPVSAAVGGTVSISCQSSQS VYNNNWLSWFQQKPGQPPKLLIYKASTLASGVPSRFKGSGSGTQFTLTISDVQCDD VATYYCAGGYLDSVI (SEQ ID NO: 458)

[0359] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSTYSINWV RQAPGKGLEWIGIIANSGTTFYANWAKGRFTVSKTSTTVDLKITSPTTEDTATYFCA RESGMYNEYGKFNI (SEQ ID NO: 459).

[0360] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0361] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458, and/or one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0362] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

458. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 459.

[0363] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 458.

[0364] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 459.

[0365] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 458; the variable heavy chain region of SEQ ID NO: 459; the complementarity-determining regions (SEQ ID NO: 460; SEQ ID NO: 461; and SEQ ID NO: 462) of the variable light chain region of SEQ ID NO: 458; and the complementarity-determining regions (SEQ ID NO: 463; SEQ ID NO: 464; and SEQ ID NO: 465) of the variable heavy chain region of SEQ ID NO: 459.

[0366] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab29, comprising SEQ ID NO: 458 and SEQ ID NO: 459, and having at least one of the biological activities set forth herein.

[0367] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0368] MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINCQASE NIYSFLAWYQQKPGQPPKLLIFKASTLASGVSSRFKGSGSGTQFTLTISDLECDDAA TYYCQQGATVYDIDNN (SEQ ID NO: 474)

[0369] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAMIWV RQAPGEGLEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTEDTATYFCA RDAESSKNAYWGYFNV (SEQ ID NO: 475).

[0370] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0371] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474, and/or one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0372] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

474. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 475.

[0373] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 474.

[0374] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 475.

[0375] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 474; the variable heavy chain region of SEQ ID NO: 475; the complementarity-determining regions (SEQ ID NO: 476; SEQ ID NO: 477; and SEQ ID NO: 478) of the variable light chain region of SEQ ID NO: 474; and the complementarity-determining regions (SEQ ID NO: 479; SEQ ID NO: 480; and SEQ ID NO: 481) of the variable heavy chain region of SEQ ID NO: 475.

[0376] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab30, comprising SEQ ID NO: 474 and SEQ ID NO: 475, and having at least one of the biological activities set forth herein.

[0377] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0378] MDTRAPTQLLGLLLLWLPGARCASDMTQTPSSVSAAVGGTVTINCQASE NIYSFLAWYQQKPGQPPKLLIFRASTLASGVSSRFKGSGSGTQFTLTISDLECDDAA TYYCQQGATVYDIDNN (SEQ ID NO: 490)

[0379] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGIDLSAYAMIWV RQAPGEGLEWITIIYPNGITYYANWAKGRFTVSKTSTAMDLKITSPTTEDTATYFCA RDAESSKNAYWGYFNV (SEQ ID NO: 491).

[0380] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0381] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490, and/or one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0382] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

490. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 491.

[0383] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 490.

[0384] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 491.

[0385] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 490; the variable heavy chain region of SEQ ID NO: 491; the complementarity-determining regions (SEQ ID NO: 492; SEQ ID NO: 493; and SEQ ID NO: 494) of the variable light chain region of SEQ ID NO: 490; and the complementarity-determining regions (SEQ ID NO: 495; SEQ ID NO: 496; and SEQ ID NO: 497) of the variable heavy chain region of SEQ ID NO: 491.

[0386] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab31, comprising SEQ ID NO: 490 and SEQ ID NO: 491, and having at least one of the biological activities set forth herein.

[0387] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0388] MDTRAPTQLLGLLLLWLPGATFAIEMTQTPSPVSAAVGGTVTINCQASES VFNNMLSWYQQKPGHSPKLLIYDASDLASGVPSRFKGSGSGTQFTLTISGVECDDA ATYYCAGYKSDSNDGDNV (SEQ ID NO: 506)

[0389] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLNRNSITWV RQAPGEGLEWIGIITGSGRTYYANWAKGRFTISKTSTTVDLKMTSPTTEDTATYFC ARGHPGLGSGNI (SEQ ID NO: 507).

[0390] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0391] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506, and/or one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0392] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

506. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 507.

[0393] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 506.

[0394] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 507.

[0395] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 506; the variable heavy chain region of SEQ ID NO: 507; the complementarity-determining regions (SEQ ID NO: 508; SEQ ID NO: 509; and SEQ ID NO: 510) of the variable light chain region of SEQ ID NO: 506; and the complementarity-determining regions (SEQ ID NO: 511; SEQ ID NO: 512; and SEQ ID NO: 513) of the variable heavy chain region of SEQ ID NO: 507.

[0396] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab32, comprising SEQ ID NO: 506 and SEQ ID NO: 507, and having at least one of the biological activities set forth herein.

[0397] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0398] MDTRAPTQLLGLLLLWLPGATFAQVLTQTASSVSAAVGGTVTINCQSSQ SVYNNYLSWYQQKPGQPPKLLIYTASSLASGVPSRFKGSGSGTQFTLTISEVQCDD AATYYCQGYYSGPIIT (SEQ ID NO: 522)

[0399] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTASGFSLNNYYIQWV RQAPGEGLEWIGIIYAGGSAYYATWANGRFTIAKTSSTTVDLKMTSLTTEDTATYF CARGTFDGYEL (SEQ ID NO: 523).

[0400] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0401] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522, and/or one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0402] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

522. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 523.

[0403] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 522.

[0404] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 523.

[0405] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 522; the variable heavy chain region of SEQ ID NO: 523; the complementarity-determining regions (SEQ ID NO: 524; SEQ ID NO: 525; and SEQ ID NO: 526) of the variable light chain region of SEQ ID NO: 522; and the complementarity-determining regions (SEQ ID NO: 527; SEQ ID NO: 528; and SEQ ID NO: 529) of the variable heavy chain region of SEQ ID NO: 523.

[0406] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab33, comprising SEQ ID NO: 522 and SEQ ID NO: 523, and having at least one of the biological activities set forth herein.

[0407] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0408] MDTRAPTQLLGLLLLWLPGATFAQVLTQTPSPVSVPVGDTVTISCQSSES VYSNNLLSWYQQKPGQPPKLLIYRASNLASGVPSRFKGSGSGTQFTLTISGAQCDD AATYYCQGYYSGVINS (SEQ ID NO: 538)

[0409] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSVEESGGRLVTPGTPLTLTCTVSGFSLSSYFMSWV RQAPGEGLEYIGFINPGGSAYYASWASGRLTISKTSTTVDLKITSPTTEDTATYFCA RILIVSYGAFTI (SEQ ID NO: 539).

[0410] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0411] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538, and/or one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0412] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

538. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 539.

[0413] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 538.

[0414] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 539.

[0415] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 538; the variable heavy chain region of SEQ ID NO: 539; the complementarity-determining regions (SEQ ID NO: 540; SEQ ID NO: 541; and SEQ ID NO: 542) of the variable light chain region of SEQ ID NO: 538; and the complementarity-determining regions (SEQ ID NO: 543; SEQ ID NO: 544; and SEQ ID NO: 545) of the variable heavy chain region of SEQ ID NO: 539.

[0416] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab34, comprising SEQ ID NO: 538 and SEQ ID NO: 539, and having at least one of the biological activities set forth herein.

[0417] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0418] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQAT ESIGNELSWYQQKPGQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITGVECDDA ATYYCQQGYSSANIDNA (SEQ ID NO: 554)

[0419] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSKYYMSWV RQAPEKGLKYIGYIDSTTVNTYYATWARGRFTISKTSTTVDLKITSPTSEDTATYFC ARGSTYFTDGGHRLDL (SEQ ID NO: 555).

[0420] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0421] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554, and/or one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0422] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

554. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 555.

[0423] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 554.

[0424] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 555.

[0425] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 554; the variable heavy chain region of SEQ ID NO: 555; the complementarity-determining regions (SEQ ID NO: 556; SEQ ID NO: 557; and SEQ ID NO: 558) of the variable light chain region of SEQ ID NO: 554; and the complementarity-determining regions (SEQ ID NO: 559; SEQ ID NO: 560; and SEQ ID NO: 561) of the variable heavy chain region of SEQ ID NO: 555.

[0426] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab35, comprising SEQ ID NO: 554 and SEQ ID NO: 555, and having at least one of the biological activities set forth herein.

[0427] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth below:

[0428] MDTRAPTQLLGLLLLWLPGARCAYDMTQTPASVEVAVGGTVTIKCQAT ESIGNELSWYQQKPGQAPKLLIYSASTLASGVPSRFKGSGSGTQFTLTITGVECDDA ATYYCQQGYSSANIDNA (SEQ ID NO: 570)

[0429] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below: METGLRWLLLVAVLKGVQCQSLEESGGRLVTPGTPLTLTCTVSGFSLSTYNMGW VRQAPGKGLEWIGSITIDGRTYYASWAKGRFTVSKSSTTVDLKMTSLTTGDTATYF CARILIVSYGAFTI (SEQ ID NO: 571).

[0430] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0431] In another embodiment, the invention contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570, and/or one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention include combinations of the CDRs and the variable heavy and light chain sequences set forth above.

[0432] The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO:

570. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 571.

[0433] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 570.

[0434] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 571.

[0435] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 570; the variable heavy chain region of SEQ ID NO: 571; the complementarity-determining regions (SEQ ID NO: 572; SEQ ID NO: 573; and SEQ ID NO: 574) of the variable light chain region of SEQ ID NO: 570; and the complementarity-determining regions (SEQ ID NO: 575; SEQ ID NO: 576; and SEQ ID NO: 577) of the variable heavy chain region of SEQ ID NO: 571.

[0436] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab36, comprising SEQ ID NO: 570 and SEQ ID NO: 571, and having at least one of the biological activities set forth herein.

[0437] Such antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', $F(ab')_2$, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-IL-6 antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

[0438] VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 586).

[0439] In another preferred embodiment, the anti-IL-6 antibodies described herein further comprises and the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below:

[0440] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 588).

[0441] In another embodiment, the invention contemplates an isolated anti-IL-6 antibody comprising a V_H polypeptide sequence selected from the group consisting of: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571; and further comprising a V_L polypeptide sequence selected from the group consisting of: SEQ ID NO: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570 or a variant thereof wherein one or more of the framework residues (FR residues) in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-IL-6 antibody that specifically binds IL-6. The invention contemplates humanized and chimeric forms of these antibodies. The chimeric antibodies may include an Fc derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[0442] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0443] In another embodiment of the invention, the anti-IL-6 antibodies and fragments thereof have binding specificity for primate homologs of the human IL-6 protein. Non-limiting examples of primate homologs of the human IL-6 protein are IL-6 obtained from *Macaca fascicularis* (also known as the cynomolgus monkey) and the Rhesus monkey. In another embodiment of the invention, the anti-IL-6 antibodies and fragments thereof inhibits the association of IL-6 with IL-6R, and/or the production of IL-6/IL-6R/gp130 complexes and/or the production of IL-6/IL-6R/gp130 multimers and/or antagonizes the biological effects of one or more of the foregoing.

[0444] As stated in paragraph [0062] herein, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0445] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, *beta*-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0446] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclothosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin

(adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimytotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0447] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and *Pseudomonas* toxin may be conjugated to the humanized antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, et al., Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

[0448] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0449] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter *et al*, Nature 144:945 (1962); David *et al*, Biochemistry 13:1014 (1974); Pain *et al*,

J. Immunol. Meth. 40:219 (1981); and Nygren, J., Histochem. and Cytochem. 30:407 (1982).

[0450] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[0451] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0452] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-IL-6 activity. Non-limiting examples of anti-IL-6 activity are set forth herein, for example, in paragraphs [0731] - [0736] *infra*.

[0453] In another embodiment, the invention further contemplates the generation and use of anti-idiotypic antibodies that bind any of the foregoing sequences. In an exemplary embodiment, such an anti-idiotypic antibody could be administered to a subject who has received an anti-IL-6 antibody to modulate, reduce, or neutralize, the effect of the anti-IL-6 antibody. Such anti-idiotypic antibodies could also be useful for treatment of an autoimmune disease characterized by the presence of anti-IL-6 antibodies. A further

exemplary use of such anti-idiotypic antibodies is for detection of the anti-IL-6 antibodies of the present invention, for example to monitor the levels of the anti-IL-6 antibodies present in a subject's blood or other bodily fluids.

[0454] The present invention also contemplates anti-IL-6 antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

Additional Exemplary Embodiments of the Invention

[0455] In another embodiment, the invention contemplates one or more anti-human IL-6 antibodies or antibody fragment which specifically bind to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-human IL-6 antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36. In a preferred embodiment, the anti-human IL-6 antibody or fragment specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as Ab1.

[0456] In another embodiment of the invention, the anti-human IL-6 antibody which specifically binds to the same linear or conformational epitopes on an intact IL-6 polypeptide or fragment thereof that is (are) specifically bound by Ab1 binds to a IL-6 epitope(s) ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide. In one embodiment of the invention, the IL-6 epitope comprises, or alternatively consists of, one or more residues comprised in IL-6 fragments selected from those respectively encompassing amino acid

residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72.

[0457] The invention is also directed to an anti-IL-6 antibody that binds with the same IL-6 epitope and/or competes with an anti-IL-6 antibody for binding to IL-6 as an antibody or antibody fragment disclosed herein, including but not limited to an anti-IL-6 antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36.

[0458] In another embodiment, the invention is also directed to an isolated anti-IL-6 antibody or antibody fragment comprising one or more of the CDRs contained in the V_H polypeptide sequences selected from the group consisting of: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571 and/or one or more of the CDRs contained in the V_L polypeptide sequence consisting of: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570.

[0459] In one embodiment of the invention, the anti-human IL-6 antibody discussed in the two prior paragraphs comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-human IL-6 antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36.

[0460] In a preferred embodiment, the anti-human IL-6 antibody discussed above comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab1. In another embodiment, all of the CDRs of the anti-human IL-6 antibody discussed above are identical to the CDRs contained in an anti-human IL-6 antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13,

Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, and Ab36. In a preferred embodiment of the invention, all of the CDRs of the anti-human IL-6 antibody discussed above are identical to the CDRs contained in Ab1.

[0461] The invention further contemplates that the one or more anti-human IL-6 antibodies discussed above are aglycosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human IL-6 antibody.

[0462] The invention further contemplates one or more anti-human IL-6 antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of at most 2 or 3 human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

[0463] In one embodiment of the invention, the anti-human IL-6 antibody or fragment specifically binds to IL-6 expressing human cells and/or to circulating soluble IL-6 molecules in vivo, including IL-6 expressed on or by human cells in a patient with a disease associated with cells that express IL-6.

[0464] In another embodiment, the disease is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's

syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS). In a preferred embodiment, the disease is selected from a cancer, inflammatory disorder, viral disorder, or autoimmune disorder. In a particularly preferred embodiment, the disease is arthritis, cachexia, and wasting syndrome

[0465] The invention further contemplates anti-human IL-6antibodies or fragments directly or indirectly attached to a detectable label or therapeutic agent.

[0466] The invention also contemplates one or more nucleic acid sequences which result in the expression of an anti-human IL-6 antibody or antibody fragment as set forth above, including those comprising, or alternatively consisting of, yeast or human preferred codons. The invention also contemplates vectors (including plasmids or recombinant viral vectors) comprising said nucleic acid sequence(s). The invention also contemplates host cells or recombinant host cells expressing at least one of the antibodies set forth above, including a mammalian, yeast, bacterial, and insect cells. In a preferred embodiment, the host cell is a yeast cell. In a further preferred embodiment, the yeast cell is a diploidal yeast cell. In a more preferred embodiment, the yeast cell is a Pichia yeast.

[0467] The invention also contemplates a method of treatment comprising administering to a patient with a disease or condition associated with IL-6 expressing cells a therapeutically effective amount of at least one anti-human IL-6 antibody or fragment. The

diseases that may be treated are presented in the non-limiting list set forth above. In a preferred embodiment, the disease is selected from a cancer, autoimmune disease, or inflammatory condition. In a particularly preferred embodiment, the disease is cancer or viral infection. In another embodiment the treatment further includes the administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy.

[0468] The invention further contemplates a method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of at least one anti-human IL-6 antibody. In one embodiment, said administration further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at IL-6 expressing disease sites. In another embodiment of the invention, the method of in vivo imaging is used to detect IL-6 expressing tumors or metastases or is used to detect the presence of sites of autoimmune disorders associated with IL-6 expressing cells. In a further embodiment, the results of said in vivo imaging method are used to facilitate design of an appropriate therapeutic regimen, including therapeutic regimens including radiotherapy, chemotherapy or a combination thereof.

Polynucleotides Encoding Anti-IL-6 Antibody Polypeptides

[0469] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 2:

[0470] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCGGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTCAGAGCATTA
ACAATGAATTATCCTGGTATCAGCAGAAACCAGGGCAGCGTCCCAAGCTCCTG
ATCTATAGGGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGT
GGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGC

TGCCACTTACTACTGTCAACAGGGTTATAGTCTGAGGAATATTGATAATGCTTT
CGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGTCT
TCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTT (SEQ ID NO: 10)

[0471] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 3:

[0472] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACG
TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCATT
TATGGTAGTGATGAAACGGCCTACGCGACCTGGGCGATAGGCCGATTCACCAT
CTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAGCCGCGG
ACACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGCAAAA
TTTAACTTGTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGCGCCTCCACCAA
GGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGG (SEQ ID NO: 11).

[0473] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 2.

[0474] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 3.

[0475] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 10 encoding the light chain variable region of SEQ ID NO: 2; the polynucleotide SEQ ID NO: 11 encoding the heavy chain variable region of SEQ ID NO: 3; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 12; SEQ ID NO: 13; and SEQ ID NO: 14) of the light chain variable region of SEQ ID NO: 10; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17) of the heavy chain variable region of SEQ ID NO: 11.

[0476] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 21:

[0477] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGG
AGGTAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTGAGACCATT
TACAGTTGGTTATCCTGGTATCAGCAGAAGCCAGGGCAGCCTCCCAAGCTCCT
GATCTACCAGGCATCCGATCTGGCATCTGGGGTCCCATCGCGATTCAGCGGCA
GTGGGGCTGGGACAGAGTACACTCTCACCATCAGCGGCGTGCAGTGTGACGAT
GCTGCCACTTACTACTGTCAACAGGGTTATAGTGGTAGTAATGTTGATAATGTT
TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGT
CTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGT
GTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG (SEQ ID NO: 29)

[0478] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 22:

[0479] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTG GGACACCCCTGACACTTACCTGCACAGCCTCTGGATTCTCCCTCAATGACCATG CAATGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGATTC ATTAATAGTGGTGGTAGCGCACGCTACGCGAGCTGGGCAGAAGGCCGATTCAC CATCTCCAGAACCTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCG AGGACACGGCCACCTATTTCTGTGTCAGAGGGGGTGCTGTTTGGAGTATTCATA GTTTTGATCCCTGGGGCCCAGGGACCCTGGTCACCGTCTCGAGCGCCTCCACCA AGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC ACAGCGGCCCTGGGCTGCCTGGTCAAG (SEQ ID NO: 30).

[0480] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 21.

[0481] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 22.

[0482] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 29 encoding the light chain variable region of SEQ ID NO: 21; the polynucleotide SEQ ID NO: 30 encoding the heavy chain variable region of SEQ ID NO: 22; polynucleotides encoding the complementarity-determining regions (SEQ ID

NO: 31; SEQ ID NO: 32; and SEQ ID NO: 33) of the light chain variable region of SEQ ID NO: 29; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 34; SEQ ID NO: 35; and SEQ ID NO: 36) of the heavy chain variable region of SEQ ID NO: 30.

[0483] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 37:

[0484] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTC
TGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTT
ATGACAACAACTACTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAG
CTCCTGATCTATGGTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCGTG
GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCACAGACGTGCAGTGTGA
CGATGCTGCCACTTACTATTGTGCAGGCGTTTATGATGATGATAGTGATAATGC
CTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTG
TCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCT (SEQ ID NO: 45)

[0485] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 38:

[0486] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACCCCTGGGA
CACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTGTCTACTACA
TGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATTCATT
ACAATGAGTGATAATATAAATTACGCGAGCTGGGCGAAAGGCCGATTCACCAT
CTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAACCGAGG
ACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTACAATGGGTCGG
TTGGATCTCTGGGGCCCAGGCACCCTCGTCACCGTCTCGAGCGCCTCCACCAAG

GGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA GCGGCCCTGGGCTGCCTGGTCAAGG (SEQ ID NO: 46).

[0487] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 47; SEQ ID NO: 48; and SEQ ID NO: 49 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 37.

[0488] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 50; SEQ ID NO: 51; and SEQ ID NO: 52 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 38.

[0489] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 45 encoding the light chain variable region of SEQ ID NO: 37; the polynucleotide SEQ ID NO: 46 encoding the heavy chain variable region of SEQ ID NO: 38; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 47; SEQ ID NO: 48; and SEQ ID NO: 49) of the light chain variable region of SEQ ID NO: 37; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 50; SEQ ID NO: 51; and SEQ ID NO: 52) of the heavy chain variable region of SEQ ID NO: 38.

[0490] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 53:

[0491] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCATATGTGACCCTGTGCTGACCCAGACTCCATCTCCCGTATC TGCACCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTT ATGAGAACAACTATTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAG CTCCTGATCTATGGTGCATCCACTCTGGATTCTGGGGTCCCATCGCGGTTCAAA GGCAGTGGATCTGGGACACAGTTCACTCTCACCATTACAGACGTGCAGTGTGA CGATGCTGCCACTTACTATTGTGCAGGCGTTTATGATGATGATAGTGATGATGC CTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTG TCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG TGTGCCTGCTGAATAACTT (SEQ ID NO: 61)

[0492] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 54:

[0493] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTGGCTGTGCTCAAAGG TGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGAGGAGGCCTGGTAACGCCTG GAGGAACCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAATGCCTACT ACATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATTC ATTACTCTGAATAATAATGTAGCTTACGCGAACTGGGCGAAAGGCCGATTCAC CTTCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCCGACACCCG AGGACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTGCAATGGGT CGGTTGGATCTCTGGGGCCATGGCACCCTGGTCACCGTCTCGAGCGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGG CACAGCGGCCCTGGGCTGCCTGGTCAAGG (SEQ ID NO: 62).

[0494] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 53.

[0495] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 54.

[0496] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 61 encoding the light chain variable region of SEQ ID NO: 53; the polynucleotide SEQ ID NO: 62 encoding the heavy chain variable region of SEQ ID NO: 54; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 63; SEQ ID NO: 64; and SEQ ID NO: 65) of the light chain variable region of SEQ ID NO: 53; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 66; SEQ ID NO: 67; and SEQ ID NO: 68) of the heavy chain variable region of SEQ ID NO: 54.

[0497] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 69:

[0498] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTCCATCGCCTGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAACTGCCAGGCCAGTCAGAGTGTTG
ATGATAACAACTGGTTAGGCTGGTATCAGCAGAAACGAGGGCAGCCTCCCAAG
TACCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAA

GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGA
CGATGCTGCCACTTACTACTGTGCAGGCGGTTTTAGTGGTAATATCTTTGCTTTC
GGCGGAGGGACCGAGGTGGTGGTCAAACGTACGGTAGCGGCCCCATCTGTCTT
CATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTG
CCTGCTGAATAACTTCT (SEQ ID NO: 77)

[0499] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 70:

[0500] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGTCTCTGGCTTCTCCCTCAGTAGCTATGCAA
TGAGCTGGGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGATCGGAATCATT
GGTGGTTTTGGTACCACATACTACGCGACCTGGGCGAAAGGCCGATTCACCAT
CTCCAAAACCTCGACCACGGTGGATCTGAGAATCACCAGTCCGACAACCGAGG
ACACGGCCACCTATTTCTGTGCCAGAGGTGGTCCTGGTAATGGTGGTGACATCT
GGGGCCAAGGGACCCTGGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCG
GTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACT (SEQ ID NO: 78).

[0501] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 69.

[0502] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 70.

[0503] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 77 encoding the light chain variable region of SEQ ID NO: 69; the polynucleotide SEQ ID NO: 78 encoding the heavy chain variable region of SEQ ID NO: 70; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 79; SEQ ID NO: 80; and SEQ ID NO: 81) of the light chain variable region of SEQ ID NO: 69; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 82; SEQ ID NO: 83; and SEQ ID NO: 84) of the heavy chain variable region of SEQ ID NO: 70.

[0504] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 85:

[0505] ATGGACACGAGGGCCCCCACTCAGCTG
CTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCACATTTGCAGCCGTGCTGACC
CAGACACCATCGCCCGTGTCTGTACCTGTGGGAGGCACAGTCACCATCAAGTG
CCAGTCCAGTCAGAGTGTTTATAATAATTTCTTATCGTGGTATCAGCAGAAACC
AGGGCAGCCTCCCAAGCTCCTGATCTACCAGGCATCCAAACTGGCATCTGGGG
TCCCAGATAGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATC
AGCGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCGGTTATGAT
GATGATGCTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTAC
GGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTC (SEQ ID NO: 93)

[0506] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 86:

[0507] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACGCTCACCTGCACAGTCTCTGGAATCGACCTCAGTGACTATGCAA TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCATT TATGCTGGTAGTGGTAGCACATGGTACGCGAGCTGGGCGAAAGGCCGATTCAC CATCTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCG AGGACACGGCCACCTATTTCTGTGCCAGAGATGGATACGATGACTATGGTGAT TTCGATCGATTGGATCTCTGGGGCCCAGGCACCCTCGTCACCGTCTCGAGCGCC TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCT GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT (SEQ ID NO: 94).

[0508] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 85.

[0509] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 86.

[0510] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 93 encoding the light chain variable region of SEQ ID NO: 85; the polynucleotide SEQ ID NO: 94 encoding the heavy chain variable region of SEQ ID NO: 86; polynucleotides encoding the complementarity-determining regions (SEQ ID

NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97) of the light chain variable region of SEQ ID NO: 85; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100) of the heavy chain variable region of SEQ ID NO: 86.

[0511] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 101:

[0512] ATGGACACGAGGGCCCCCACTCAGCTG
CTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCCAGATGTGCCTATGATATGACC
CAGACTCCAGCCTCGGTGTCTGCAGCTGTGGGAGGCACAGTCACCATCAAATG
CCAGGCCAGTCAGAGCATTAACAATGAATTATCCTGGTATCAGCAGAAATCAG
GGCAGCGTCCCAAGCTCCTGATCTATAGGGCATCCACTCTGGCATCTGGGGTCT
CATCGCGGTTCAAAGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGC
GACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAACAGGGTTATAGTCTG
AGGAATATTGATAATGCTTTCGGCGGAGGGACCGAGGTGGTGGTCAAACGTAC
GGTAGCGGCCCCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTC (SEQ ID NO: 109)

[0513] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 102:

[0514] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCTCAGGT
GTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGAC
ACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAACTACTACAT
GACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATGATTT
ATGGTAGTGATGAAACAGCCTACGCGAACTGGGCGATAGGCCGATTCACCATC
TCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAGCCGCGGA
CACGGCCACCTATTTCTGTGCCAGAGATGATAGTAGTGACTGGGATGCAAAAT
TTAACTTGTGGGGCCAAGGGACCCTCGTCACCGTCTCGAGCGCCTCCACCAAG

GGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA GCGGCCCTGGGCTGCCTGGTCAAGG (SEQ ID NO: 110).

[0515] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 101.

[0516] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 102.

[0517] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 109 encoding the light chain variable region of SEQ ID NO: 101; the polynucleotide SEQ ID NO: 110 encoding the heavy chain variable region of SEQ ID NO: 102; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 111; SEQ ID NO: 112; and SEQ ID NO: 113) of the light chain variable region of SEQ ID NO: 101; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 114; SEQ ID NO: 115; and SEQ ID NO: 116) of the heavy chain variable region of SEQ ID NO: 102.

[0518] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 122:

[0519] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCACCCGTGTC TGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGTCAGAGTGTTG GTAATAACCAGGACTTATCCTGGTTTCAGCAGAGACCAGGGCAGCCTCCCAAG CTCCTGATCTACGAAATATCCAAACTGGAATCTGGGGTCCCATCGCGGTTCAGC GGCAGTGGATCTGGGACACACTTCACTCTCACCATCAGCGGCGTACAGTGTGA CGATGCTGCCACTTACTACTGTCTAGGCGGTTATGATGATGATGCTGATAATGC T (SEQ ID NO: 130)

[0520] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 123:

[0521] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCACTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTAGTCGTACAA TGTCCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATACATT TGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGATTGGGCGATACTGGTGGTCACGCTTATG CTACTCGCTTAAATCTC (SEQ ID NO: 131).

[0522] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 122.

[0523] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID

NO: 137 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 123.

[0524] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 130 encoding the light chain variable region of SEQ ID NO: 122; the polynucleotide SEQ ID NO: 131 encoding the heavy chain variable region of SEQ ID NO: 123; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 132; SEQ ID NO: 133; and SEQ ID NO: 134) of the light chain variable region of SEQ ID NO: 122; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137) of the heavy chain variable region of SEQ ID NO: 123.

[0525] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 138:

[0526] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCGTCCGTGTC
TGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTCAGAGTGTTT
ATAGTAATAAGTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAG
CTCCTGATCTACTGGACATCCAAACTGGCATCTGGGGCCCCATCACGGTTCAGC
GGCAGTGGATCTGGGACACAATTCACTCTCACCATCAGCGGCGTGCAGTGTGA
CGATGCTGCCACTTACTACTGTCTAGGCGCTTATGATGATGATGCTGATAATGC
T (SEQ ID NO: 146)

[0527] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 139:

[0528] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAAGAGTCCGGGGGTCGCCTGGTCAAGCCTGACG AAACCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTGGAGGGCGGCTAC ATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCA GTTATGATAGTGGTAGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACC ATCTCCAAGACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAAC CGAGGACACGGCCACCTATTTCTGCGTCAGATCACTAAAATATCCTACTGTTAC TTCTGATGACTTG (SEQ ID NO: 147).

[0529] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 138.

[0530] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 139.

[0531] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 146 encoding the light chain variable region of SEQ ID NO: 138; the polynucleotide SEQ ID NO: 147 encoding the heavy chain variable region of SEQ

ID NO: 139; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150) of the light chain variable region of SEQ ID NO: 138; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 151; SEQ ID NO: 152; and SEQ ID NO: 153) of the heavy chain variable region of SEQ ID NO: 139.

[0532] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 154:

[0533] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCACCCGTGTC TGCAGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGTCCAGTCAGAGTGTTT ATAATAATAACGACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCTAAA CTCCTGATCTATTATGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAA GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGGCGTGCAGTGTGA CGATGCTGCCGCTTACTACTGTCTAGGCGGTTATGATGATGATGCTGATAATGC T (SEQ ID NO: 162)

[0534] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 155:

[0535] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTATCTGGATTATCCCTCAGTAGCAATACAA TAAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATACATT TGGAGTGGTGGTAGTACATACTACGCGAGCTGGGTGAATGGTCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGAGGGGGTTACGCTAGTGGTGGTTATCCTT ATGCCACTCGGTTGGATCTC (SEQ ID NO: 163).

[0536] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 154.

[0537] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 155.

[0538] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 162 encoding the light chain variable region of SEQ ID NO: 154; the polynucleotide SEQ ID NO: 163 encoding the heavy chain variable region of SEQ ID NO: 155; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 164; SEQ ID NO: 165; and SEQ ID NO: 166) of the light chain variable region of SEQ ID NO: 154; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 167; SEQ ID NO: 168; and SEQ ID NO: 169) of the heavy chain variable region of SEQ ID NO: 155.

[0539] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 170:

[0540] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCAGCCGTGCTGACCCAGACACCATCCTCCGTGTC TGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCAGTCAGAGTGTTT ATAATAACGACTACTTATCCTGGTATCAACAGAGGCCAGGGCAACGTCCCAAG CTCCTAATCTATGGTGCTTCCAAACTGGCATCTGGGGTCCCGTCACGGTTCAAA GGCAGTGGATCTGGGAAACAGTTTACTCTCACCATCAGCGGCGTGCAGTGTGA CGATGCTGCCACTTACTACTGTCTGGGCGATTATGATGATGATGCTGATAATAC T (SEQ ID NO: 178)

[0541] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 171:

[0542] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACTTGCACAGTCTCTGGATTCACCCTCAGTACCAACTACT ACCTGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTAGAATGGATCGGAATC ATTTATCCTAGTGGTAACACATATTGCGCGAAGTGGGCGAAAGGCCGATTCAC CATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAA CCGAGGACACAGCCACGTATTTCTGTGCCAGAAATTATGGTGGTGATGAAAGT TTG (SEQ ID NO: 179).

[0543] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 180; SEQ ID NO: 181; and SEQ ID NO: 182 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 170.

[0544] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 171.

[0545] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 178 encoding the light chain variable region of SEQ ID NO: 170; the polynucleotide SEQ ID NO: 179 encoding the heavy chain variable region of SEQ ID NO: 171; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 180; SEQ ID NO: 181; and SEQ ID NO: 182) of the light chain variable region of SEQ ID NO: 170; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 183; SEQ ID NO: 184; and SEQ ID NO: 185) of the heavy chain variable region of SEQ ID NO: 171.

[0546] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 186:

[0547] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGG AGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTGAGACCATT GGCAATGCATTAGCCTGGTATCAGCAGAAATCAGGGCAGCCTCCCAAGCTCCT GATCTACAAGGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCA GTGGATCTGGGACAGAGTACACTCTCACCATCAGCGACCTGGAGTGTGCCGAT GCTGCCACTTACTACTGTCAATGGTGTTATTTTGGTGATAGTGTT (SEQ ID NO: 194)

[0548] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 187:

[0549] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCACTGTGCTCAAAGG TGTCCAGTGTCAGGAGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCCAGCCTG AGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCGGCT ACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCG TGTATTTTCACTATTACTACTAACACTTACTACGCGAGCTGGGCGAAAGGCCGA TTCACCATCTCCAAGACCTCGTCGACCACGGTGACTCTGCAAATGACCAGTCTG ACAGCCGCGGACACGGCCACCTATCTCTGTGCGAGAGGGATTTATTCTGATAA TAATTATTATGCCTTG (SEQ ID NO: 195).

[0550] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 196; SEQ ID NO: 197; and SEQ ID NO: 198 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 186.

[0551] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 187.

[0552] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 194 encoding the light chain variable region of SEQ ID NO: 186; the polynucleotide SEQ ID NO: 195 encoding the heavy chain variable region of SEQ ID NO: 187; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 196; SEQ ID NO: 197; and SEQ ID NO: 198) of the light chain variable region of SEQ ID NO: 186; and polynucleotides encoding the complementarity-determining regions

(SEQ ID NO: 199; SEQ ID NO: 200; and SEQ ID NO: 201) of the heavy chain variable region of SEQ ID NO: 187.

[0553] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 202:

[0554] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGG AGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTGAGAGCATT GGCAATGCATTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCT GATCTACAAGGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAGCGGCA GTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGGCGTGCAGTGTGCCGAT GCTGCCGCTTACTACTGTCAATGGTGTTATTTTGGTGATAGTGTT (SEQ ID NO: 210)

[0555] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 203:

[0556] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGCAGCAGCTGGTGGAGTCCGGGGGAGGCCTGGTCAAGCCGG GGGCATCCCTGACACTCACCTGCAAAGCCTCTGGATTCTCCTTCAGTAGCGGCT ACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTCGATCGCA TGCATTTTTACTATTACTGATAACACTTACTACGCGAACTGGGCGAAAGGCCGA TTCACCATCTCCAAGCCCTCGTCGCCCACGGTGACTCTGCAAATGACCAGTCTG ACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGGGGGATTTATTCTACTGAT AATTATTATGCCTTG (SEQ ID NO: 211).

[0557] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 202.

[0558] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 203.

[0559] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 210 encoding the light chain variable region of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain variable region of SEQ ID NO: 203; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 212; SEQ ID NO: 213; and SEQ ID NO: 214) of the light chain variable region of SEQ ID NO: 202; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217) of the heavy chain variable region of SEQ ID NO: 203.

[0560] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 218:

[0561] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGG
AGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTCAGAGCGTT
AGTAGCTACTTAAACTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCT
GATCTACAGGGCATCCACTCTGGAATCTGGGGTCCCATCGCGGTTCAAAGGCA

GTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGAT GCTGCCACTTACTACTGTCAATGTACTTATGGTACTAGTAGTAGTTATGGTGCT GCT (SEQ ID NO: 226)

[0562] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 219:

[0563] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACCGTCTCTGGTATCTCCCTCAGTAGCAATGCAA TAAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCATT AGTTATAGTGGTACCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCAT CTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATCACTAGTCCGACAACCG AGGACACGGCCACCTACTTCTGTGCCAGAGATGACCCTACGACAGTTATGGTT ATGTTGATACCTTTTGGAGCCGGCATGGACCTC (SEQ ID NO: 227).

[0564] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 218.

[0565] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 219.

[0566] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or

more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 226 encoding the light chain variable region of SEQ ID NO: 218; the polynucleotide SEQ ID NO: 227 encoding the heavy chain variable region of SEQ ID NO: 219; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230) of the light chain variable region of SEQ ID NO: 218; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 231; SEQ ID NO: 232; and SEQ ID NO: 233) of the heavy chain variable region of SEQ ID NO: 219.

[0567] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 234:

[0568] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTGCATCGCCCGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAACTGCCAGGCCAGTCAGAGTGTTT
ATAAGAACAACTACTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAA
GGCCTGATCTATTCTGCATCGACTCTAGATTCTGGGGTCCCATTGCGGTTCAGC
GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGA
CGATGCTGCCACTTACTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTG
TTATGCT (SEQ ID NO: 242)

[0569] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 235:

[0570] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGG
GATCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCTTCAGTAGCTACTGGA
TGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGCATT
GTTACTGGTAATGGTAACACTTACTACGCGAACTGGGCGAAAGGCCGATTCAC
CATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAAATGACCAGTCTGACAG

CCGCGGACACGGCCACCTATTTTTGTGCGAAAGCCTATGACTTG (SEQ ID NO: 243).

[0571] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 234.

[0572] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 235.

[0573] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 242 encoding the light chain variable region of SEQ ID NO: 234; the polynucleotide SEQ ID NO: 243 encoding the heavy chain variable region of SEQ ID NO: 235; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 244; SEQ ID NO: 245; and SEQ ID NO: 246) of the light chain variable region of SEQ ID NO: 234; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 247; SEQ ID NO: 248; and SEQ ID NO: 249) of the heavy chain variable region of SEQ ID NO: 235.

[0574] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 250:

[0575] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTTCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTC TGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTT ATGACAACAACTATTTATCCTGGTATCAGCAGAAACCAGGACAGCCTCCCAAG CTCCTGATCTATGGTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAA GGCACGGGATCTGGGACACAGTTCACTCTCACCATCACAGACGTGCAGTGTGA CGATGCTGCCACTTACTATTGTGCAGGCGTTTTTAATGATGATAGTGATGATGC C (SEQ ID NO: 258)

[0576] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 251:

[0577] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCCCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTGCATACTATA TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATTCATT ACTCTGAGTGATCATATATCTTACGCGAGGTGGGCGAAAGGCCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGGAGTCGTGGCTGGGGTGCAATGGGTCGG TTGGATCTC (SEQ ID NO: 259).

[0578] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 250.

[0579] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 263; SEQ ID NO: 264; and SEQ ID

NO: 265 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 251.

[0580] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 258 encoding the light chain variable region of SEQ ID NO: 250; the polynucleotide SEQ ID NO: 259 encoding the heavy chain variable region of SEQ ID NO: 251; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 260; SEQ ID NO: 261; and SEQ ID NO: 262) of the light chain variable region of SEQ ID NO: 250; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 263; SEQ ID NO: 264; and SEQ ID NO: 265) of the heavy chain variable region of SEQ ID NO: 251.

[0581] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 266:

[0582] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTCGCAGCCGTGCTGACCCAGACACCATCGCCCGTGT CTGCGGCTGTGGGAGGCACAGTCACCATCAGTTGCCAGGCCAGTCAGAGTGTT TATAACAACAAAAATTTAGCCTGGTATCAGCAGAAATCAGGGCAGCCTCCCAA GCTCCTGATCTACTGGGCATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAG CGGCAGTGGATCTGGGACACAGTTCACTCTCACCGTCAGCGGCGTGCAGTGTG ACGATGCTGCCACTTACTACTGTCTAGGCGTTTTTGATGATGATGCTGATAATG CT (SEQ ID NO: 274)

[0583] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 267:

[0584] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAATGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAGCTACTCCA TGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATATATCGGAGTCATT GGTACTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCCGATTCACCAT CTCCAGAACCTCGACCACGGTGGCTCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGTCAGGAGTCTTTCTTCTATTACTTTCTTG (SEQ ID NO: 275).

[0585] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 266.

[0586] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 279; SEQ ID NO: 280; and SEQ ID NO: 281 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 267.

[0587] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 274 encoding the light chain variable region of SEQ ID NO: 266; the polynucleotide SEQ ID NO: 275 encoding the heavy chain variable region of SEQ

ID NO: 267; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 276; SEQ ID NO: 277; and SEQ ID NO: 278) of the light chain variable region of SEQ ID NO: 266; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 279; SEQ ID NO: 280; and SEQ ID NO: 281) of the heavy chain variable region of SEQ ID NO: 267.

[0588] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 282:

[0589] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGCATTCGAATTGACCCAGACTCCAGCCTCCGTGG AGGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTCAGAACATT TATAGATACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGTTCCT GATCTATCTGGCATCTACTCTGGCATCTGGGGTCCCATCGCGGTTTAAAGGCAG TGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATG CTGCCACTTACTACTGTCAAAGTTATTATAGTAGTAATAGTGTCGCT (SEQ ID NO: 290)

[0590] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 283:

[0591] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGGAGCAGCTGGTGGAGTCCGGGGGAGACCTGGTCCAGCCTG AGGGATCCCTGACACTCACCTGCACAGCTTCTGAGTTAGACTTCAGTAGCGGCT ACTGGATATGCTGGGTCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGATCGGA TGCATTTATACTGGTAGTAGTGGTAGCACTTTTTACGCGAGTTGGGCGAAAGGC CGATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAAATGACCAG TCTGACAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGGTTATAGTGGCTT TGGTTACTTTAAGTTG (SEQ ID NO: 291).

[0592] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 282.

[0593] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 283.

[0594] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 290 encoding the light chain variable region of SEQ ID NO: 282; the polynucleotide SEQ ID NO: 291 encoding the heavy chain variable region of SEQ ID NO: 283; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 292; SEQ ID NO: 293; and SEQ ID NO: 294) of the light chain variable region of SEQ ID NO: 282; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 295; SEQ ID NO: 296; and SEQ ID NO: 297) of the heavy chain variable region of SEQ ID NO: 283.

[0595] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 298:

[0596] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGG AGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTGAGGACATT TATAGGTTATTGGCCTGGTATCAACAGAAACCAGGGCAGCCTCCCAAGCTCCT GATCTATGATTCATCCGATCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAG TGGATCTGGGACAGAGTTCACTCTCGCCATCAGCGGTGTGCAGTGTGACGATG CTGCCACTTACTACTGTCAACAGGCTTGGAGTTATAGTGATATTGATAATGCT (SEQ ID NO: 306)

[0597] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 299:

[0598] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCGGGGA CACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAGTAGCTACTACA TGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAATCATT ACTACTAGTGGTAATACATTTTACGCGAGCTGGGCGAAAGGCCGGCTCACCAT CTCCAGAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGAACTTCTGATATTTTTTATTATCGTAACTT G (SEQ ID NO: 307).

[0599] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 298.

[0600] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 311; SEQ ID NO: 312; and SEQ ID NO: 313 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 299.

[0601] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 306 encoding the light chain variable region of SEQ ID NO: 298; the polynucleotide SEQ ID NO: 307 encoding the heavy chain variable region of SEQ ID NO: 299; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 308; SEQ ID NO: 309; and SEQ ID NO: 310) of the light chain variable region of SEQ ID NO: 298; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 311; SEQ ID NO: 312; and SEQ ID NO: 313) of the heavy chain variable region of SEQ ID NO: 299.

[0602] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 314:

[0603] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACGTTTGCAGCCGTGCTGACCCAGACTGCATCACCCGTGTC TGCCGCTGTGGGAGCCACAGTCACCATCAACTGCCAGTCCAGTCAGAGTGTTT ATAATGACATGGACTTAGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAG CTCCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAGC GGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGGCGTGCAGTGTGA CGATGCTGCCACTTACTACTGTCTAGGCGCTTTTGATGATGATGCTGATAATAC T (SEQ ID NO: 322)

[0604] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 315:

[0605] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCACTAGGCATGCAA TAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATGCATT TGGAGTGGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTCAGAATCACCAGTCCGACAACCGAGG ACACGGCCACCTACTTCTGTGCCAGAGTCATTGGCGATACTGCTGGTTATGCTT ATTTTACGGGGCTTGACTTG (SEQ ID NO: 323).

[0606] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 314.

[0607] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 315.

[0608] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 322 encoding the light chain variable region of SEQ ID NO: 314; the polynucleotide SEQ ID NO: 323 encoding the heavy chain variable region of SEQ ID NO: 315; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 324; SEQ ID NO: 325; and SEQ ID NO: 326) of the light chain variable region of SEQ ID NO: 314; and polynucleotides encoding the complementarity-determining regions

(SEQ ID NO: 327; SEQ ID NO: 328; and SEQ ID NO: 329) of the heavy chain variable region of SEQ ID NO: 315.

[0609] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 330:

[0610] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGG AGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTCAGAGTGTT TATAATTGGTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCT GATCTATACTGCATCCAGTCTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCAG TGGATCTGGGACAGAGTTCACTCTCACCATCAGCGGCGTGGAGTGTGCCGATG CTGCCACTTACTACTGTCAACAGGGTTATACTAGTGATGTTGATAATGTT (SEQ ID NO: 338)

[0611] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 331:

[0612] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGGCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGAATCGACCTCAGTAGCTATGCAA TGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATACATCGGAATCATT AGTAGTAGTGGTAGCACATACTACGCGACCTGGGCGAAAGGCCGATTCACCAT CTCACAAGCCTCGTCGACCACGGTGGATCTGAAAATTACCAGTCCGACAACCG AGGACTCGGCCACATATTTCTGTGCCAGAGGGGGTGCTGGTAGTGGTGGTGTTT GGCTGCTTGATGGTTTTGATCCC (SEQ ID NO: 339).

[0613] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 330.

[0614] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 331.

[0615] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 338 encoding the light chain variable region of SEQ ID NO: 330; the polynucleotide SEQ ID NO: 339 encoding the heavy chain variable region of SEQ ID NO: 331; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 340; SEQ ID NO: 341; and SEQ ID NO: 342) of the light chain variable region of SEQ ID NO: 330; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 343; SEQ ID NO: 344; and SEQ ID NO: 345) of the heavy chain variable region of SEQ ID NO: 331.

[0616] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 346:

[0617] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAAATGTGCCGATGTTGTGATGACCCAGACTCCAGCCTCCGT
GTCTGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTGAGAACA
TTTATAATTGGTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTC
CTGATCTATACTGTAGGCGATCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGC

AGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGA
TGCTGCCACTTACTATTGTCAACAGGGTTATAGTAGTAGTTATGTTGATAATGT
T (SEQ ID NO: 354)

[0618] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 347:

[0619] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTG
GGACACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAATGACTATG
CAGTGGGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATAC
ATTCGTAGTAGTGGTACCACAGCCTACGCGACCTGGGCGAAAGGCCGATTCAC
CATCTCCGCTACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCG
AGGACACGGCCACCTATTTCTGTGCCAGAGGGGGTGCTGGTAGTAGTGGTGTG
TGGATCCTTGATGGTTTTGCTCCC (SEQ ID NO: 355).

[0620] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 346.

[0621] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 347.

[0622] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or

more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 354 encoding the light chain variable region of SEQ ID NO: 346; the polynucleotide SEQ ID NO: 355 encoding the heavy chain variable region of SEQ ID NO: 347; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 356; SEQ ID NO: 357; and SEQ ID NO: 358) of the light chain variable region of SEQ ID NO: 346; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 359; SEQ ID NO: 360; and SEQ ID NO: 361) of the heavy chain variable region of SEQ ID NO: 347.

[0623] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 362:

[0624] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCTCAAGTGCTGACCCAGACTCCATCCTCCGTGTC TGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTT ATCAGAACAACTACTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAG CTCCTGATCTATGGTGCGGCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAA GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGA CGATGCTGCCACTTACTACTGTGCAGGCGCTTATAGGGATGTGGATTCT (SEQ ID NO: 370)

[0625] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 363:

[0626] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGGGG CATCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCTTTACTAGTACCTACT ACATCTACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGT ATTGATGCTGGTAGTAGTGGTAGCACTTACTACGCGACCTGGGTGAATGGCCG ATTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAAATGACCAGTCT

GACAGCCGCGGACACGGCCACCTATTTCTGTGCGAAATGGGATTATGGTGGTA ATGTTGGTTGGGGTTATGACTTG (SEQ ID NO: 371).

[0627] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 362.

[0628] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 363.

[0629] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 370 encoding the light chain variable region of SEQ ID NO: 362; the polynucleotide SEQ ID NO: 371 encoding the heavy chain variable region of SEQ ID NO: 363; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 372; SEQ ID NO: 373; and SEQ ID NO: 374) of the light chain variable region of SEQ ID NO: 362; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 375; SEQ ID NO: 376; and SEQ ID NO: 377) of the heavy chain variable region of SEQ ID NO: 363.

[0630] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 378:

[0631] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGCATTCGAATTGACCCAGACTCCATCCTCCGTGGA GGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTCAGAGCATTA GTAGTTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGTTCCTG ATCTACAGGGCGTCCACTCTGGCATCTGGGGTCCCATCGCGATTCAAAGGCAG TGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATG CTGCCACTTACTACTGTCAAAGCTATTATGATAGTGTTTCAAATCCT (SEQ ID NO: 386)

[0632] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 379:

[0633] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGAGG GATCCCTGACACTCACCTGCAAAGCCTCTGGACTCGACCTCGGTACCTACTGGT TCATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCTTGT ATTTATACTGGTAGTAGTGGTTCCACTTTCTACGCGAGCTGGGTGAATGGCCGA TTCACCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAAATGACCAGTCTG ACAGCCGCGGACACGGCCACTTATTTTTGTGCGAGAGGTTATAGTGGTTATGGT TATTTTAAGTTG (SEQ ID NO: 387).

[0634] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 378.

[0635] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID

NO: 393 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 379.

[0636] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 386 encoding the light chain variable region of SEQ ID NO: 378; the polynucleotide SEQ ID NO: 387 encoding the heavy chain variable region of SEQ ID NO: 379; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 388; SEQ ID NO: 389; and SEQ ID NO: 390) of the light chain variable region of SEQ ID NO: 378; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 391; SEQ ID NO: 392; and SEQ ID NO: 393) of the heavy chain variable region of SEQ ID NO: 379.

[0637] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 394:

[0638] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGTCACATTTGCCATCGAAATGACCCAGAGTCCATTCTCCGTGTC
TGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGGCCAGTCAGAGTGTTT
ATAAGAACAACCAATTATCCTGGTATCAGCAGAAATCAGGGCAGCCTCCCAAG
CTCCTGATCTATGGTGCATCGGCTCTGGCATCTGGGGTCCCATCGCGGTTCAAA
GGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCGACGTGCAGTGTGA
CGATGCTGCCACTTACTACTGTGCAGGCGCTATTACTGGTAGTATTGATACGGA
TGGT (SEQ ID NO: 402)

[0639] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 395:

[0640] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGTTGGAGGAGTCCGGGGGAGACCTGGTCAAGCCTGGGG CATCCCTGACACTCACCTGCACAACTTCTGGATTCTCCTTCAGTAGCAGCTACT TCATTTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGCATGC ATTTATGGTGGTGATGGCAGCACATACTACGCGAGCTGGGCGAAAGGCCGATT CACCATCTCCAAAACCTCGTCGACCACGGTGACGCTGCAAATGACCAGTCTGA CAGCCGCGGACACGGCCACCTATTTCTGTGCGAGAGAATGGGCATATAGTCAA GGTTATTTTGGTGCTTTTGATCTC (SEQ ID NO: 403).

[0641] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 394.

[0642] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 395.

[0643] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 402 encoding the light chain variable region of SEQ ID NO: 394; the polynucleotide SEQ ID NO: 403 encoding the heavy chain variable region of SEQ

ID NO: 395; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 404; SEQ ID NO: 405; and SEQ ID NO: 406) of the light chain variable region of SEQ ID NO: 394; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 407; SEQ ID NO: 408; and SEQ ID NO: 409) of the heavy chain variable region of SEQ ID NO: 395.

[0644] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 410:

[0645] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGG
AGGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTGAGGATATT
AGTAGCTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCT
GATCTATGCTGCATCCAATCTGGAATCTGGGGTCTCATCGCGATTCAAAGGCA
GTGGATCTGGGACAGAGTACACTCTCACCATCAGCGACCTGGAGTGTGCCGAT
GCTGCCACCTATTACTGTCAATGTACTTATGGTACTATTTCTATTAGTGATGGTA
ATGCT (SEQ ID NO: 418)

[0646] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 411:

[0647] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAATGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTAGCTACTTCA
TGACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATACATCGGATTCATT
AATCCTGGTGGTAGCGCTTACTACGCGAGCTGGGTGAAAGGCCGATTCACCAT
CTCCAAGTCCTCGACCACGGTAGATCTGAAAATCACCAGTCCGACAACCGAGG
ACACGGCCACCTATTTCTGTGCCAGGGTTCTGATTGTTTCTTATGGAGCCTTTAC
CATC (SEQ ID NO: 419).

[0648] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 420; SEQ ID NO: 421; and SEQ ID NO: 422 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 410.

[0649] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 423; SEQ ID NO: 424; and SEQ ID NO: 425 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 411.

[0650] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 418 encoding the light chain variable region of SEQ ID NO: 410; the polynucleotide SEQ ID NO: 419 encoding the heavy chain variable region of SEQ ID NO: 411; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 420; SEQ ID NO: 421; and SEQ ID NO: 422) of the light chain variable region of SEQ ID NO: 410; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 423; SEQ ID NO: 424; and SEQ ID NO: 425) of the heavy chain variable region of SEQ ID NO: 411.

[0651] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 426:

[0652] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGATGTTGTGATGACCCAGACTCCAGCCTCCGTGTC TGCAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCAGTGAGGACATTG AAAGCTATCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTG ATCTATGGTGCATCCAATCTGGAATCTGGGGTCTCATCGCGGTTCAAAGGCAGT GGATCTGGGACAGAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGC TGCCACTTACTATTGTCAATGCACTTATGGTATTATTAGTATTAGTGATGGTAA TGCT (SEQ ID NO: 434)

[0653] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 427:

[0654] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTGTCTGGATTCTCCCTCAGTAGCTACTTCA TGACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATACATCGGATTCATG AATACTGGTGATAACGCATACTACGCGAGCTGGGCGAAAGGCCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGGGTTCTTGTTGTTGCTTATGGAGCCTTTA ACATC (SEQ ID NO: 435).

[0655] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 426.

[0656] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 427.

[0657] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 434 encoding the light chain variable region of SEQ ID NO: 426; the polynucleotide SEQ ID NO: 435 encoding the heavy chain variable region of SEQ ID NO: 427; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 436; SEQ ID NO: 437; and SEQ ID NO: 438) of the light chain variable region of SEQ ID NO: 426; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 439; SEQ ID NO: 440; and SEQ ID NO: 441) of the heavy chain variable region of SEQ ID NO: 427.

[0658] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 442:

[0659] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTC
TGAACCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTAAGAGTGTTA
TGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAG
CTCCTGATCTATGGTGCATCCAATCTGGCATCTGGGGTCCCATCACGGTTCAGC
GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGA
CGATGCTGCCACTTACTACTGTCAAGGCGGTTATACTGGTTATAGTGATCATGG
GACT (SEQ ID NO: 450)

[0660] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 443:

[0661] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCAAGCCTGACG AAACCCTGACACTCACCTGCACAGTCTCTGGAATCGACCTCAGTAGCTATCCA ATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGATTCAT TAATACTGGTGGTACCATAGTCTACGCGAGCTGGGCAAAAGGCCGATTCACCA TCTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAACCGAG GACACGGCCACCTATTTCTGTGCCAGAGGCAGTTATGTTTCATCTGGTTATGCC TACTATTTTAATGTC (SEQ ID NO: 451).

[0662] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 442.

[0663] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 443.

[0664] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 450 encoding the light chain variable region of SEQ ID NO: 442; the polynucleotide SEQ ID NO: 451 encoding the heavy chain variable region of SEQ ID NO: 443; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 452; SEQ ID NO: 453; and SEQ ID NO: 454) of the light chain variable region of SEQ ID NO: 442; and polynucleotides encoding the complementarity-determining regions

(SEQ ID NO: 455; SEQ ID NO: 456; and SEQ ID NO: 457) of the heavy chain variable region of SEQ ID NO: 443.

[0665] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 458:

[0666] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCCGTGTC TGCAGCTGTGGGAGGCACAGTCAGCATCAGTTGCCAGTCCAGTCAGAGTGTTT ATAATAACAACTGGTTATCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAG CTCCTGATCTACAAGGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAA GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGA CGATGTTGCCACTTACTACTGTGCGGGCGGTTATCTTGATAGTGTTATT (SEQ ID NO: 466)

[0667] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 459:

[0668] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTACCTATTCAA TAAACTGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAATGGATCGGAATCATT GCTAATAGTGGTACCACATTCTACGCGAACTGGGCGAAAGGCCGATTCACCGT CTCCAAAACCTCGACCACGGTGGATCTGAAAATCACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGAGAGAGTGGAATGTACAATGAATATGGT AAATTTAACATC (SEQ ID NO: 467).

[0669] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 458.

[0670] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 471; SEQ ID NO: 472; and SEQ ID NO: 473 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 459.

[0671] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 466 encoding the light chain variable region of SEQ ID NO: 458; the polynucleotide SEQ ID NO: 467 encoding the heavy chain variable region of SEQ ID NO: 459; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 468; SEQ ID NO: 469; and SEQ ID NO: 470) of the light chain variable region of SEQ ID NO: 458; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 471; SEQ ID NO: 472; and SEQ ID NO: 473) of the heavy chain variable region of SEQ ID NO: 459.

[0672] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 474:

[0673] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGCCTCTGATATGACCCAGACTCCATCCTCCGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTGAGAACATTT
ATAGCTTTTTGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTG
ATCTTCAAGGCTTCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGT

GGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGACGATGC
TGCCACTTACTACTGTCAACAGGGTGCTACTGTGTATGATATTGATAATAAT
(SEQ ID NO: 482)

[0674] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 475:

[0675] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGTTTCTGGAATCGACCTCAGTGCCTATGCAA
TGATCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCACAATCATT
TATCCTAATGGTATCACATACTACGCGAACTGGGCGAAAGGCCGATTCACCGT
CTCCAAAACCTCGACCGCGATGGATCTGAAAATCACCAGTCCGACAACCGAGG
ACACGGCCACCTATTTCTGTGCCAGAGATGCAGAAAGTAGTAAGAATGCTTAT
TGGGGCTACTTTAACGTC (SEQ ID NO: 483).

[0676] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 474.

[0677] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 475.

[0678] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or

more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 482 encoding the light chain variable region of SEQ ID NO: 474; the polynucleotide SEQ ID NO: 483 encoding the heavy chain variable region of SEQ ID NO: 475; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 484; SEQ ID NO: 485; and SEQ ID NO: 486) of the light chain variable region of SEQ ID NO: 474; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 487; SEQ ID NO: 488; and SEQ ID NO: 489) of the heavy chain variable region of SEQ ID NO: 475.

[0679] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 490:

[0680] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGCCTCTGATATGACCCAGACTCCATCCTCCGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTGAGAACATTT
ATAGCTTTTTGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTCCTG
ATCTTCAGGGCTTCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGT
GGATCTGGGACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGACGATGC
TGCCACTTACTACTGTCAACAGGGTGCTACTGTGTATGATATTGATAATAAT
(SEQ ID NO: 498)

[0681] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 491:

[0682] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGTTTCTGGAATCGACCTCAGTGCCTATGCAA
TGATCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCACAATCATT
TATCCTAATGGTATCACATACTACGCGAACTGGGCGAAAGGCCGATTCACCGT
CTCCAAAACCTCGACCGCGATGGATCTGAAAATCACCAGTCCGACAACCGAGG

ACACGGCCACCTATTTCTGTGCCAGAGATGCAGAAAGTAGTAAGAATGCTTAT TGGGGCTACTTTAACGTC (SEQ ID NO: 499).

[0683] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 490.

[0684] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 491.

[0685] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 498 encoding the light chain variable region of SEQ ID NO: 490; the polynucleotide SEQ ID NO: 499 encoding the heavy chain variable region of SEQ ID NO: 491; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 500; SEQ ID NO: 501; and SEQ ID NO: 502) of the light chain variable region of SEQ ID NO: 490; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 503; SEQ ID NO: 504; and SEQ ID NO: 505) of the heavy chain variable region of SEQ ID NO: 491.

[0686] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 506:

[0687] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCACATTTGCCATTGAAATGACCCAGACTCCATCCCCCGTGTC TGCCGCTGTGGGAGGCACAGTCACCATCAATTGCCAGGCCAGTGAGAGTGTTT TTAATAATATGTTATCCTGGTATCAGCAGAAACCAGGGCACTCTCCTAAGCTCC TGATCTATGATGCATCCGATCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCA GTGGATCTGGGACACAGTTCACTCTCACCATCAGTGGCGTGGAGTGTGACGAT GCTGCCACTTACTATTGTGCAGGGTATAAAAGTGATAGTAATGATGGCGATAA TGTT (SEQ ID NO: 514)

[0688] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 507:

[0689] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAACAGGAATTCAA TAACCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCGGAATCATT ACTGGTAGTGGTAGAACGTACTACGCGAACTGGGCAAAAGGCCGATTCACCAT CTCCAAAACCTCGACCACGGTGGATCTGAAAATGACCAGTCCGACAACCGAGG ACACGGCCACCTATTTCTGTGCCAGAGGCCATCCTGGTCTTGGTAGTGGTAACA TC (SEQ ID NO: 515).

[0690] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 506.

[0691] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID

NO: 521 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 507.

[0692] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 514 encoding the light chain variable region of SEQ ID NO: 506; the polynucleotide SEQ ID NO: 515 encoding the heavy chain variable region of SEQ ID NO: 507; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 516; SEQ ID NO: 517; and SEQ ID NO: 518) of the light chain variable region of SEQ ID NO: 506; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 519; SEQ ID NO: 520; and SEQ ID NO: 521) of the heavy chain variable region of SEQ ID NO: 507.

[0693] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 522:

[0694] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCGCAAGTGCTGACCCAGACTGCATCGTCCGTGTC
TGCAGCTGTGGGAGGCACAGTCACCATCAATTGCCAGTCCAGTCAGAGTGTTT
ATAATAACTACTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCTC
CTGATCTATACTGCATCCAGCCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGC
AGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGAAGTGCAGTGTGACGA
TGCTGCCACTTACTACTGTCAAGGCTATTATAGTGGTCCTATAATTACT (SEQ ID NO: 530)

[0695] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 523:

[0696] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACAGCCTCTGGATTCTCCCTCAATAACTACTACA TACAATGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATGGATCGGGATCATT TATGCTGGTGGTAGCGCATACTACGCGACCTGGGCAAACGGCCGATTCACCAT CGCCAAAACCTCGTCGACCACGGTGGATCTGAAGATGACCAGTCTGACAACCG AGGACACGGCCACCTATTTCTGTGCCAGAGGGACATTTGATGGTTATGAGTTG (SEQ ID NO: 531).

[0697] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 532; SEQ ID NO: 533; and SEQ ID NO: 534 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 522.

[0698] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 535; SEQ ID NO: 536; and SEQ ID NO: 537 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 523.

[0699] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 530 encoding the light chain variable region of SEQ ID NO: 522; the polynucleotide SEQ ID NO: 531 encoding the heavy chain variable region of SEQ

ID NO: 523; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 532; SEQ ID NO: 533; and SEQ ID NO: 534) of the light chain variable region of SEQ ID NO: 522; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 535; SEQ ID NO: 536; and SEQ ID NO: 537) of the heavy chain variable region of SEQ ID NO: 523.

[0700] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 538:

[0701] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTCCATCCCCTGTGTC
TGTCCCTGTGGGAGACACAGTCACCATCAGTTGCCAGTCCAGTGAGAGCGTTT
ATAGTAATAACCTCTTATCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAG
CTCCTGATCTACAGGGCATCCAATCTGGCATCTGGTGTCCCATCGCGGTTCAAA
GGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGGCGCACAGTGTGA
CGATGCTGCCACTTACTACTGTCAAGGCTATTATAGTGGTGTCATTAATAGT
(SEQ ID NO: 546)

[0702] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 539:

[0703] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CACCCCTGACACTCACCTGCACAGTGTCTGGATTCTCCCTCAGTAGCTACTTCA
TGAGCTGGGTCCGCCAGGCTCCAGGGGAGGGGCTGGAATACATCGGATTCATT
AATCCTGGTGGTAGCGCATACTACGCGAGCTGGGCGAGTGGCCGACTCACCAT
CTCCAAAACCTCGACCACGGTAGATCTGAAAATCACCAGTCCGACAACCGAGG
ACACGGCCACCTATTTCTGTGCCAGGATTCTTATTGTTTCTTATGGAGCCTTTAC
CATC (SEQ ID NO: 547).

[0704] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 538.

[0705] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 539.

[0706] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 546 encoding the light chain variable region of SEQ ID NO: 538; the polynucleotide SEQ ID NO: 547 encoding the heavy chain variable region of SEQ ID NO: 539; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 548; SEQ ID NO: 549; and SEQ ID NO: 550) of the light chain variable region of SEQ ID NO: 538; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 551; SEQ ID NO: 552; and SEQ ID NO: 553) of the heavy chain variable region of SEQ ID NO: 539.

[0707] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 554:

[0708] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGG AGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCACTGAGAGCATT GGCAATGAGTTATCCTGGTATCAGCAGAAACCAGGGCAGGCTCCCAAGCTCCT GATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAG TGGATCTGGGACACAGTTCACTCTCACCATCACCGGCGTGGAGTGTGATGATG CTGCCACTTACTACTGTCAACAGGGTTATAGTAGTGCTAATATTGATAATGCT (SEQ ID NO: 562)

[0709] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 555:

[0710] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA CACCCCTGACACTCACCTGCACCGTCTCTGGATTCTCCCTCAGTAAGTACTACA TGAGCTGGGTCCGCCAGGCTCCAGAGAAGGGGCTGAAATACATCGGATACATT GATAGTACTACTGTTAATACATACTACGCGACCTGGGCGAGAGGCCGATTCAC CATCTCCAAAACCTCGACCACGGTGGATCTGAAGATCACCAGTCCGACAAGTG AGGACACGGCCACCTATTTCTGTGCCAGAGGAAGTACTTATTTTACTGATGGAG GCCATCGGTTGGATCTC (SEQ ID NO: 563).

[0711] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 564; SEQ ID NO: 565; and SEQ ID NO: 566 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 554.

[0712] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 567; SEQ ID NO: 568; and SEQ ID NO: 569 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 555.

[0713] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 562 encoding the light chain variable region of SEQ ID NO: 554; the polynucleotide SEQ ID NO: 563 encoding the heavy chain variable region of SEQ ID NO: 555; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 564; SEQ ID NO: 565; and SEQ ID NO: 566) of the light chain variable region of SEQ ID NO: 554; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 567; SEQ ID NO: 568; and SEQ ID NO: 569) of the heavy chain variable region of SEQ ID NO: 555.

[0714] The invention is further directed to polynucleotides encoding polypeptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 570:

[0715] ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCAGATGTGCCTATGATATGACCCAGACTCCAGCCTCTGTGG
AGGTAGCTGTGGGAGGCACAGTCACCATCAAGTGCCAGGCCACTGAGAGCATT
GGCAATGAGTTATCCTGGTATCAGCAGAAACCAGGGCAGGCTCCCAAGCTCCT
GATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAG
TGGATCTGGGACACAGTTCACTCTCACCATCACCGGCGTGGAGTGTGATGATG
CTGCCACTTACTACTGTCAACAGGGTTATAGTAGTGCTAATATTGATAATGCT
(SEQ ID NO: 578)

[0716] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 571:

[0717] ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG TGTCCAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTAACGCCTGGGA CACCCCTGACACTCACCTGCACAGTCTCTGGATTCTCCCTCAGTACCTACAACA TGGGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAAGTATT ACTATTGATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCGT CTCCAAAAGCTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGGGG ACACGGCCACCTATTTCTGTGCCAGGATTCTTATTGTTTCTTATGGGGCCTTTAC CATC (SEQ ID NO: 579).

[0718] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 580; SEQ ID NO: 581; and SEQ ID NO: 582 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 570.

[0719] In a further embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 583; SEQ ID NO: 584; and SEQ ID NO: 585 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 571.

[0720] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 578 encoding the light chain variable region of SEQ ID NO: 570; the polynucleotide SEQ ID NO: 579 encoding the heavy chain variable region of SEQ ID NO: 571; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 580; SEQ ID NO: 581; and SEQ ID NO: 582) of the light chain variable region of SEQ ID NO: 570; and polynucleotides encoding the complementarity-determining regions

(SEQ ID NO: 583; SEQ ID NO: 584; and SEQ ID NO: 585) of the heavy chain variable region of SEQ ID NO: 571.

[0721] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the kappa constant light chain sequence of SEQ ID NO: 586:

[0722] GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAG
GCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGA
GAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC
CTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAG
TCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGT (SEQ ID NO: 587).

[0723] In another embodiment of the invention, polynucleotides of the invention further comprise, the following polynucleotide sequence encoding the gamma-1 constant heavy chain polypeptide sequence of SEQ ID NO: 588:

[0724] GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG
AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC
CGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACA
CCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGA
CCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACA
AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCA
GTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT
GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG
GAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCA
CCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCC
CTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT

GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCT GGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO: 589).

[0725] In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-IL-6 V_H antibody amino acid sequence selected from SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_H polypeptide or a conservative amino acid substitution.

[0726] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-IL-6 V_L antibody amino acid sequence of 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody V_L polypeptide or a conservative amino acid substitution.

[0727] In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO:101 and SEQ ID NO:118; SEQ ID NO:119 and SEQ ID NO:102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118;

SEQ ID NO:122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571.

[0728] In another embodiment, the invention is directed to an isolated isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said expressed polypeptide alone specifically binds IL-6 or specifically binds IL-6 when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said at least one CDR is selected from those contained in the V_L or V_H polypeptides contained in SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555; 571; 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570.

[0729] Host cells and vectors comprising said polynucleotides are also contemplated.

[0730] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity determining regions (CDRs, or hypervariable regions) set forth herein, as well as host cells comprising said sequences. In one embodiment of the

invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

Anti-IL-6 Activity

[0731] As stated previously, IL-6 is a member of a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 and the IL-6 receptor (IL-6R). The IL-6R may also be present in a soluble form (sIL-6R). IL-6 binds to IL-6R, which then dimerizes the signal-transducing receptor gp130.

[0732] It is believed that the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, are useful by exhibiting anti-IL-6 activity. In one non-limiting embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, exhibit anti-IL-6 activity by binding to IL-6 which may be soluble IL-6 or cell surface expressed IL-6 and/or may prevent or inhibit the binding of IL-6 to IL-6R and/or activation (dimerization) of the gp130 signal-transducing glycoprotein and the formation of IL-6/IL-6R/gp130 multimers and the biological effects of any of the foregoing. The subject IL-6 antibodies may possess different antagonistic activities based on where (i.e., epitope) the particular antibody binds IL-6 and/or how it affects the formation of the foregoing IL-6 complexes and/or multimers and the biological effects thereof. Consequently, different IL-6 antibodies according to the invention e.g., may be better suited for preventing or treating conditions involving the formation and accumulation of substantial soluble IL-6 such as rheumatoid arthritis whereas other antibodies may be favored in treatments wherein the prevention of IL-6/IL-6R/gp130 or IL-6/IL-6R/gp130 multimers is a desired therapeutic outcome. This can be determined in binding and other assays.

[0733] The anti-IL-6 activity of the anti-IL-6 antibody of the present invention, and fragments thereof having binding specificity to IL-6, may also be described by their strength of binding or their affinity for IL-6. This also may affect their therapeutic properties. In one embodiment of the invention, the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, bind to IL-6 with a

dissociation constant (K_D) of less than or equal to $5x10^{-7}$, 10^{-7}, $5x10^{-8}$, 10^{-8}, $5x10^{-9}$, 10^{-9}, $5x10^{-10}$, 10^{-10}, $5x10^{-11}$, 10^{-11}, $5x10^{-12}$, 10^{-12}, $5x10^{-13}$, 10^{-13}, $5x10^{-14}$, 10^{-14}, $5x10^{-15}$ or 10^{-15}. Preferably, the anti-IL-6 antibodies and fragments thereof bind IL-6 with a dissociation constant of less than or equal to $5x10^{-10}$.

[0734] In another embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, bind to IL-6 with an off-rate of less than or equal to 10^{-4} S^{-1}, $5x10^{-5}$ S^{-1}, 10^{-5} S^{-1}, $5x10^{-6}$ S^{-1}, 10^{-6} S^{-1}, $5x10^{-7}$ S^{-1}, or 10^{-7} S^{-1}. In one embodiment of the invention, the anti-IL-6 antibodies of the invention, and fragments thereof having binding specificity to IL-6, bind to a linear or conformational IL-6 epitope.

[0735] In a further embodiment of the invention, the anti-IL-6 activity of the anti-IL-6 antibodies of the present invention, and fragments thereof having binding specificity to IL-6, exhibit anti-IL-6 activity by ameliorating or reducing the symptoms of, or alternatively treating, or preventing, diseases and disorders associated with IL-6. Non-limiting examples of diseases and disorders associated with IL-6 are set forth *infra*. As noted cancer-related fatigue, cachexia and rheumatoid arthritis are preferred indications for the subject IL-6 antibodies.

[0736] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, do not have binding specificity for IL-6R or the gp-130 signal-transducing glycoprotein.

B-cell Screening and Isolation

[0737] In one embodiment, the present invention provides methods of isolating a clonal population of antigen-specific B cells that may be used for isolating at least one antigen-specific cell. As described and exemplified infra, these methods contain a series of culture and selection steps that can be used separately, in combination, sequentially, repetitively, or periodically. Preferably, these methods are used for isolating at least one antigen-specific cell, which can be used to produce a monoclonal antibody, which is specific to a desired antigen, or a nucleic acid sequence corresponding to such an antibody.

[0738] In one embodiment, the present invention provides a method comprising the steps of:

[0739] a. preparing a cell population comprising at least one antigen-specific B cell;

[0740] b. enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;

[0741] c. isolating a single B cell from the enriched B cell population; and

[0742] d. determining whether the single B cell produces an antibody specific to the antigen.

[0743] In another embodiment, the present invention provides an improvement to a method of isolating a single, antibody-producing B cell, the improvement comprising enriching a B cell population obtained from a host that has been immunized or naturally exposed to an antigen, wherein the enriching step precedes any selection steps, comprises at least one culturing step, and results in a clonal population of B cells that produces a single monoclonal antibody specific to said antigen.

[0744] Throughout this application, a "clonal population of B cells" refers to a population of B cells that only secrete a single antibody specific to a desired antigen. That is to say that these cells produce only one type of monoclonal antibody specific to the desired antigen.

[0745] In the present application, "enriching" a cell population cells means increasing the frequency of desired cells, typically antigen-specific cells, contained in a mixed cell population, e.g., a B cell-containing isolate derived from a host that is immunized against a desired antigen. Thus, an enriched cell population encompasses a cell population having a higher frequency of antigen-specific cells as a result of an enrichment step, but this population of cells may contain and produce different antibodies.

[0746] The general term "cell population" encompasses pre- and a post-enrichment cell populations, keeping in mind that when multiple enrichment steps are performed, a cell population can be both pre- and post-enrichment. For example, in one embodiment, the present invention provides a method:

[0747] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[0748] b. creating at least one single cell suspension from the harvested cell population;

[0749] c. enriching at least one single cell suspension to form a first enriched cell population;

[0750] d. enriching the first enriched cell population to form a second enriched cell population;

[0751] e. enriching the second enriched cell population to form a third enriched cell population; and

[0752] f. selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[0753] Each cell population may be used directly in the next step, or it can be partially or wholly frozen for long--or short- term storage or for later steps. Also, cells from a cell population can be individually suspended to yield single cell suspensions. The single cell suspension can be enriched, such that a single cell suspension serves as the pre-enrichment cell population. Then, one or more antigen-specific single cell suspensions together form the enriched cell population; the antigen-specific single cell suspensions can be grouped together, e.g., re-plated for further analysis and/or antibody production.

[0754] In one embodiment, the present invention provides a method of enriching a cell population to yield an enriched cell population having an antigen-specific cell frequency that is about 50% to about 100%, or increments therein. Preferably, the enriched cell population has an antigen-specific cell frequency greater than or equal to about 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or 100%.

[0755] In another embodiment, the present invention provides a method of enriching a cell population whereby the frequency of antigen-specific cells is increased by at least about 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or increments therein.

[0756] Throughout this application, the term "increment" is used to define a numerical value in varying degrees of precision, e.g., to the nearest 10, 1, 0.1, 0.01, etc. The increment can be rounded to any measurable degree of precision, and the increment need not be rounded to the same degree of precision on both sides of a range. For example, the range 1 to 100 or increments therein includes ranges such as 20 to 80, 5 to 50, and 0.4 to 98. When a range is open-ended, e.g., a range of less than 100, increments therein means

increments between 100 and the measurable limit. For example, less than 100 or increments therein means 0 to 100 or increments therein unless the feature, e.g., temperature, is not limited by 0.

[0757] Antigen-specificity can be measured with respect to any antigen. The antigen can be any substance to which an antibody can bind including, but not limited to, peptides, proteins or fragments thereof; carbohydrates; organic and inorganic molecules; receptors produced by animal cells, bacterial cells, and viruses; enzymes; agonists and antagonists of biological pathways; hormones; and cytokines. Exemplary antigens include, but are not limited to, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-α, IFN-γ, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF) and Hepcidin. Preferred antigens include IL-6, IL-13, TNF-α, VEGF-α, Hepatocyte Growth Factor (HGF) and Hepcidin. In a method utilizing more than one enrichment step, the antigen used in each enrichment step can be the same as or different from one another. Multiple enrichment steps with the same antigen may yield a large and/or diverse population of antigen-specific cells; multiple enrichment steps with different antigens may yield an enriched cell population with cross-specificity to the different antigens.

[0758] Enriching a cell population can be performed by any cell-selection means known in the art for isolating antigen-specific cells. For example, a cell population can be enriched by chromatographic techniques, e.g., Miltenyi bead or magnetic bead technology. The beads can be directly or indirectly attached to the antigen of interest. In a preferred embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step.

[0759] A cell population can also be enriched by performed by any antigen-specificity assay technique known in the art, e.g., an ELISA assay or a halo assay. ELISA assays include, but are not limited to, selective antigen immobilization (e.g., biotinylated antigen capture by streptavidin, avidin, or neutravidin coated plate), non-specific antigen plate coating, and through an antigen build-up strategy (e.g., selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). The antigen can be directly or indirectly attached to a solid matrix or support, e.g., a column. A halo assay comprises contacting the cells with antigen-loaded beads and labeled anti-host

antibody specific to the host used to harvest the B cells. The label can be, e.g., a fluorophore. In one embodiment, at least one assay enrichment step is performed on at least one single cell suspension. In another embodiment, the method of enriching a cell population includes at least one chromatographic enrichment step and at least one assay enrichment step.

[0760] Methods of "enriching" a cell population by size or density are known in the art. See, e.g., U.S. Patent 5,627,052. These steps can be used in the present method in addition to enriching the cell population by antigen-specificity.

[0761] The cell populations of the present invention contain at least one cell capable of recognizing an antigen. Antigen-recognizing cells include, but are not limited to, B cells, plasma cells, and progeny thereof. In one embodiment, the present invention provides a clonal cell population containing a single type of antigen-specific B-cell, i.e., the cell population produces a single monoclonal antibody specific to a desired antigen.

[0762] In such embodiment, it is believed that the clonal antigen-specific population of B cells consists predominantly of antigen-specific, antibody-secreting cells, which are obtained by the novel culture and selection protocol provided herein. Accordingly, the present invention also provides methods for obtaining an enriched cell population containing at least one antigen-specific, antibody-secreting cell. In one embodiment, the present invention provides an enriched cell population containing about 50% to about 100%, or increments therein, or greater than or equal to about 60%, 70%, 80%, 90%, or 100% of antigen-specific, antibody-secreting cells.

[0763] In one embodiment, the present invention provides a method of isolating a single B cell by enriching a cell population obtained from a host before any selection steps, e.g., selecting a particular B cell from a cell population and/or selecting an antibody produced by a particular cell. The enrichment step can be performed as one, two, three, or more steps. In one embodiment, a single B cell is isolated from an enriched cell population before confirming whether the single B cell secretes an antibody with antigen-specificity and/or a desired property.

[0764] In one embodiment, a method of enriching a cell population is used in a method for antibody production and/or selection. Thus, the present invention provides a method

comprising enriching a cell population before selecting an antibody. The method can include the steps of: preparing a cell population comprising at least one antigen-specific cell, enriching the cell population by isolating at least one antigen-specific cell to form an enriched cell population, and inducing antibody production from at least one antigen-specific cell. In a preferred embodiment, the enriched cell population contains more than one antigen-specific cell. In one embodiment, each antigen-specific cell of the enriched population is cultured under conditions that yield a clonal antigen-specific B cell population before isolating an antibody producing cell therefrom and/or producing an antibody using said B cell, or a nucleic acid sequence corresponding to such an antibody. In contrast to prior techniques where antibodies are produced from a cell population with a low frequency of antigen-specific cells, the present invention allows antibody selection from among a high frequency of antigen-specific cells. Because an enrichment step is used prior to antibody selection, the majority of the cells, preferably virtually all of the cells, used for antibody production are antigen-specific. By producing antibodies from a population of cells with an increased frequency of antigen specificity, the quantity and variety of antibodies are increased.

[0765] In the antibody selection methods of the present invention, an antibody is preferably selected after an enrichment step and a culture step that results in a clonal population of antigen-specific B cells. The methods can further comprise a step of sequencing a selected antibody or portions thereof from one or more isolated, antigen-specific cells. Any method known in the art for sequencing can be employed and can include sequencing the heavy chain, light chain, variable region(s), and/or complementarity determining region(s) (CDR).

[0766] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antigen recognition and/or antibody functionality. For example, the desired antibodies may have specific structural features, such as binding to a particular epitope or mimicry of a particular structure; antagonist or agonist activity; or neutralizing activity, e.g., inhibiting binding between the antigen and a ligand. In one embodiment, the antibody functionality screen is ligand-dependent. Screening for antibody functionality includes, but is not limited to, an in vitro

protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein; and a cell-based response that is ligand dependent and easily monitored (e.g., proliferation response). In one embodiment, the method for antibody selection includes a step of screening the cell population for antibody functionality by measuring the inhibitory concentration (IC50). In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody having an IC50 of less than about 100, 50, 30, 25, 10 μg/mL, or increments therein.

[0767] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antibody binding strength. Antibody binding strength can be measured by any method known in the art (e.g., Biacore). In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody having a high antigen affinity, e.g., a dissociation constant (Kd) of less than about $5x10^{-10}$ M-1, preferably about $1x10^{-13}$ to $5x10^{-10}$, $1x10^{-12}$ to $1x10^{-10}$, $1x10^{-12}$ to $7.5x10^{-11}$, $1x10^{-11}$ to $2x10^{-11}$, about $1.5x10^{-11}$ or less, or increments therein. In this embodiment, the antibodies are said to be affinity mature. In a preferred embodiment, the affinity of the antibodies is comparable to or higher than the affinity of any one of Panorex® (edrecolomab), Rituxan® (rituximab), Herceptin® (traztuzumab), Mylotarg® (gentuzumab), Campath® (alemtuzumab), Zevalin™ (ibritumomab), Erbitux™ (cetuximab), Avastin™ (bevicizumab), Raptiva™ (efalizumab), Remicade® (infliximab), Humira™ (adalimumab), and Xolair™ (omalizumab). Preferably, the affinity of the antibodies is comparable to or higher than the affinity of Humira™. The affinity of an antibody can also be increased by known affinity maturation techniques. In one embodiment, at least one cell population is screened for at least one of, preferably both, antibody functionality and antibody binding strength.

[0768] In addition to the enrichment step, the method for antibody selection can also include one or more steps of screening a cell population for antibody sequence homology, especially human homology. In one embodiment, at least one of the isolated, antigen-specific cells produces an antibody that has a homology to a human antibody of about 50% to about 100%, or increments therein, or greater than about 60%, 70%, 80%, 85%, 90%, or 95% homologous. The antibodies can be humanized to increase the homology to a human

sequence by techniques known in the art such as CDR grafting or selectivity determining residue grafting (SDR).

[0769] In another embodiment, the present invention also provides the antibodies themselves according to any of the embodiments described above in terms of IC50, Kd, and/or homology.

[0770] The B cell selection protocol disclosed herein has a number of intrinsic advantages versus other methods for obtaining antibody-secreting B cells and monoclonal antibodies specific to desired target antigens. These advantages include, but are not restricted to, the following:

[0771] First, it has been found that when these selection procedures are utilized with a desired antigen such as IL-6 or TNF-α, the methods reproducibly result in antigen-specific B cells capable of generating what appears to be a substantially comprehensive complement of antibodies, i.e., antibodies that bind to the various different epitopes of the antigen. Without being bound by theory, it is hypothesized that the comprehensive complement is attributable to the antigen enrichment step that is performed prior to initial B cell recovery. Moreover, this advantage allows for the isolation and selection of antibodies with different properties as these properties may vary depending on the epitopic specificity of the particular antibody.

[0772] Second, it has been found that the B cell selection protocol reproducibly yields a clonal B cell culture containing a single B cell, or its progeny, secreting a single monoclonal antibody that generally binds to the desired antigen with a relatively high binding affinity, i.e. picomolar or better antigen binding affinities. By contrast, prior antibody selection methods tend to yield relatively few high affinity antibodies and therefore require extensive screening procedures to isolate an antibody with therapeutic potential. Without being bound by theory, it is hypothesized that the protocol results in both in vivo B cell immunization of the host (primary immunization) followed by a second in vitro B cell stimulation (secondary antigen priming step) that may enhance the ability and propensity of the recovered clonal B cells to secrete a single high affinity monoclonal antibody specific to the antigen target.

[0773] Third, it has been observed (as shown herein with IL-6 specific B cells) that the B cell selection protocol reproducibly yields enriched B cells producing IgG's that are, on average, highly selective (antigen specific) to the desired target. Antigen-enriched B cells recovered by these methods are believed to contain B cells capable of yielding the desired full complement of epitopic specificities as discussed above.

[0774] Fourth, it has been observed that the B cell selection protocols, even when used with small antigens, i.e., peptides of 100 amino acids or less, e.g., 5-50 amino acids long, reproducibly give rise to a clonal B cell culture that secretes a single high affinity antibody to the small antigen, e.g., a peptide. This is highly surprising as it is generally quite difficult, labor intensive, and sometimes not even feasible to produce high affinity antibodies to small peptides. Accordingly, the invention can be used to produce therapeutic antibodies to desired peptide targets, e.g., viral, bacterial or autoantigen peptides, thereby allowing for the production of monoclonal antibodies with very discrete binding properties or even the production of a cocktail of monoclonal antibodies to different peptide targets, e.g., different viral strains. This advantage may especially be useful in the context of the production of a therapeutic or prophylactic vaccine having a desired valency, such as an HPV vaccine that induces protective immunity to different HPV strains.

[0775] Fifth, the B cell selection protocol, particularly when used with B cells derived from rabbits, tends to reproducibly yield antigen-specific antibody sequences that are very similar to endogenous human immunoglobulins (around 90% similar at the amino acid level) and that contain CDRs that possess a length very analogous to human immunoglobulins and therefore require little or no sequence modification (typically at most only a few CDR residues may be modified in the parent antibody sequence and no framework exogenous residues introduced) in order to eliminate potential immunogenicity concerns. In particular, preferably the recombinant antibody will contain only the host (rabbit) CDR1 and CDR2 residues required for antigen recognition and the entire CDR3. Thereby, the high antigen binding affinity of the recovered antibody sequences produced according to the B cell and antibody selection protocol remains intact or substantially intact even with humanization.

[0776] In sum, these method can be used to produce antibodies exhibiting higher binding affinities to more distinct epitopes by the use of a more efficient protocol than was previously known.

[0777] In a specific embodiment, the present invention provides a method for identifying a single B cell that secretes an antibody specific to a desired antigen and that optionally possesses at least one desired functional property such as affinity, avidity, cytolytic activity, and the like by a process including the following steps:

[0778] a. immunizing a host against an antigen;

[0779] b. harvesting B cells from the host;

[0780] c. enriching the harvested B cells to increase the frequency of antigen-specific cells;

[0781] d. creating at least one single cell suspension;

[0782] e. culturing a sub-population from the single cell suspension under conditions that favor the survival of a single antigen-specific B cell per culture well;

[0783] f. isolating B cells from the sub-population; and

[0784] g. determining whether the single B cell produces an antibody specific to the antigen.

[0785] Typically, these methods will further comprise an additional step of isolating and sequencing, in whole or in part, the polypeptide and nucleic acid sequences encoding the desired antibody. These sequences or modified versions or portions thereof can be expressed in desired host cells in order to produce recombinant antibodies to a desired antigen.

[0786] As noted previously, it is believed that the clonal population of B cells predominantly comprises antibody-secreting B cells producing antibody against the desired antigen. It is also believed based on experimental results obtained with several antigens and with different B cell populations that the clonally produced B cells and the isolated antigen-specific B cells derived therefrom produced according to the invention secrete a monoclonal antibody that is typically of relatively high affinity and moreover is capable of efficiently and reproducibly producing a selection of monoclonal antibodies of greater epitopic variability as compared to other methods of deriving monoclonal antibodies from

cultured antigen-specific B cells. In an exemplary embodiment the population of immune cells used in such B cell selection methods will be derived from a rabbit. However, other hosts that produce antibodies, including non-human and human hosts, can alternatively be used as a source of immune B cells. It is believed that the use of rabbits as a source of B cells may enhance the diversity of monoclonal antibodies that may be derived by the methods. Also, the antibody sequences derived from rabbits according to the invention typically possess sequences having a high degree of sequence identity to human antibody sequences making them favored for use in humans since they should possess little antigenicity. In the course of humanization, the final humanized antibody contains a much lower foreign/host residue content, usually restricted to a subset of the host CDR residues that differ dramatically due to their nature versus the human target sequence used in the grafting. This enhances the probability of complete activity recovery in the humanized antibody protein.

[0787] The methods of antibody selection using an enrichment step disclosed herein include a step of obtaining a immune cell-containing cell population from an immunized host. Methods of obtaining an immune cell-containing cell population from an immunized host are known in the art and generally include inducing an immune response in a host and harvesting cells from the host to obtain one or more cell populations. The response can be elicited by immunizing the host against a desired antigen. Alternatively, the host used as a source of such immune cells can be naturally exposed to the desired antigen such as an individual who has been infected with a particular pathogen such as a bacterium or virus or alternatively has mounted a specific antibody response to a cancer that the individual is afflicted with.

[0788] Host animals are well-known in the art and include, but are not limited to, guinea pig, rabbit, mouse, rat, non-human primate, human, as well as other mammals and rodents, chicken, cow, pig, goat, and sheep. Preferably the host is a mammal, more preferably, rabbit, mouse, rat, or human. When exposed to an antigen, the host produces antibodies as part of the native immune response to the antigen. As mentioned, the immune response can occur naturally, as a result of disease, or it can be induced by immunization with the antigen. Immunization can be performed by any method known in the art, such as, by one

or more injections of the antigen with or without an agent to enhance immune response, such as complete or incomplete Freund's adjuvant. In another embodiment, the invention also contemplates intrasplenic immunization. As an alternative to immunizing a host animal in vivo, the method can comprise immunizing a host cell culture in vitro.

[0789] After allowing time for the immune response (e.g., as measured by serum antibody detection), host animal cells are harvested to obtain one or more cell populations. In a preferred embodiment, a harvested cell population is screened for antibody binding strength and/or antibody functionality. A harvested cell population is preferably from at least one of the spleen, lymph nodes, bone marrow, and/or peripheral blood mononuclear cells (PBMCs). The cells can be harvested from more than one source and pooled. Certain sources may be preferred for certain antigens. For example, the spleen, lymph nodes, and PBMCs are preferred for IL-6; and the lymph nodes are preferred for TNF. The cell population is harvested about 20 to about 90 days or increments therein after immunization, preferably about 50 to about 60 days. A harvested cell population and/or a single cell suspension therefrom can be enriched, screened, and/or cultured for antibody selection. The frequency of antigen-specific cells within a harvested cell population is usually about 1% to about 5%, or increments therein.

[0790] In one embodiment, a single cell suspension from a harvested cell population is enriched, preferably by using Miltenyi beads. From the harvested cell population having a frequency of antigen-specific cells of about 1% to about 5%, an enriched cell population is thus derived having a frequency of antigen-specific cells approaching 100%.

[0791] The method of antibody selection using an enrichment step includes a step of producing antibodies from at least one antigen-specific cell from an enriched cell population. Methods of producing antibodies in vitro are well known in the art, and any suitable method can be employed. In one embodiment, an enriched cell population, such as an antigen-specific single cell suspension from a harvested cell population, is plated at various cell densities, such as 50, 100, 250, 500, or other increments between 1 and 1000 cells per well. Preferably, the sub-population comprises no more than about 10,000 antigen-specific, antibody-secreting cells, more preferably about 50-10,000, about 50-5,000, about 50-1,000, about 50-500, about 50-250 antigen-specific, antibody-secreting

cells, or increments therein. Then, these sub-populations are cultured with suitable medium (e.g., an activated T cell conditioned medium, particularly 1-5% activated rabbit T cell conditioned medium) on a feeder layer, preferably under conditions that favor the survival of a single proliferating antibody-secreting cell per culture well. The feeder layer, generally comprised of irradiated cell matter, e.g., EL4B cells, does not constitute part of the cell population. The cells are cultured in a suitable media for a time sufficient for antibody production, for example about 1 day to about 2 weeks, about 1 day to about 10 days, at least about 3 days, about 3 to about 5 days, about 5 days to about 7 days, at least about 7 days, or other increments therein. In one embodiment, more than one sub-population is cultured simultaneously. Preferably, a single antibody-producing cell and progeny thereof survives in each well, thereby providing a clonal population of antigen-specific B cells in each well. At this stage, the immunoglobulin G (IgG) produced by the clonal population is highly correlative with antigen specificity. In a preferred embodiment, the IgGs exhibit a correlation with antigen specificity that is greater than about 50%, more preferably greater than 70%, 85%, 90%, 95%, 99%, or increments therein. See Fig. 3, which demonstrates an exemplary correlation for IL-6. The correlations were demonstrated by setting up B cell cultures under limiting conditions to establish single antigen-specific antibody products per well. Antigen-specific versus general IgG synthesis was compared. Three populations were observed: IgG that recognized a single format of antigen (biotinylated and direct coating), detectable IgG and antigen recognition irrespective of immobilization, and IgG production alone. IgG production was highly correlated with antigen-specificity.

[0792] A supernatant containing the antibodies is optionally collected, which can be can be enriched, screened, and/or cultured for antibody selection according to the steps described above. In one embodiment, the supernatant is enriched (preferably by an antigen-specificity assay, especially an ELISA assay) and/or screened for antibody functionality.

[0793] In another embodiment, the enriched, preferably clonal, antigen-specific B cell population from which a supernatant described above is optionally screened in order to detect the presence of the desired secreted monoclonal antibody is used for the isolation of

a few B cells, preferably a single B cell, which is then tested in an appropriate assay in order to confirm the presence of a single antibody-producing B cell in the clonal B cell population. In one embodiment about 1 to about 20 cells are isolated from the clonal B cell population, preferably less than about 15, 12, 10, 5, or 3 cells, or increments therein, most preferably a single cell. The screen is preferably effected by an antigen-specificity assay, especially a halo assay. The halo assay can be performed with the full length protein, or a fragment thereof. The antibody-containing supernatant can also be screened for at least one of: antigen binding affinity; agonism or antagonism of antigen-ligand binding, induction or inhibition of the proliferation of a specific target cell type; induction or inhibition of lysis of a target cell, and induction or inhibition of a biological pathway involving the antigen.

[0794] The identified antigen-specific cell can be used to derive the corresponding nucleic acid sequences encoding the desired monoclonal antibody. (An AluI digest can confirm that only a single monoclonal antibody type is produced per well.) As mentioned above, these sequences can be mutated, such as by humanization, in order to render them suitable for use in human medicaments.

[0795] As mentioned, the enriched B cell population used in the process can also be further enriched, screened, and/or cultured for antibody selection according to the steps described above which can be repeated or performed in a different order. In a preferred embodiment, at least one cell of an enriched, preferably clonal, antigen-specific cell population is isolated, cultured, and used for antibody selection.

[0796] Thus, in one embodiment, the present invention provides a method comprising:

[0797] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[0798] b. creating at least one single cell suspension from a harvested cell population;

[0799] c. enriching at least one single cell suspension, preferably by chromatography, to form a first enriched cell population;

[0800] d. enriching the first enriched cell population, preferably by ELISA assay, to form a second enriched cell population which preferably is clonal, i.e., it contains only a single type of antigen-specific B cell;

[0801] e. enriching the second enriched cell population, preferably by halo assay, to form a third enriched cell population containing a single or a few number of B cells that produce an antibody specific to a desired antigen; and

[0802] f. selecting an antibody produced by an antigen-specific cell isolated from the third enriched cell population.

[0803] The method can further include one or more steps of screening the harvested cell population for antibody binding strength (affinity, avidity) and/or antibody functionality. Suitable screening steps include, but are not limited to, assay methods that detect: whether the antibody produced by the identified antigen-specific B cell produces an antibody possessing a minimal antigen binding affinity, whether the antibody agonizes or antagonizes the binding of a desired antigen to a ligand; whether the antibody induces or inhibits the proliferation of a specific cell type; whether the antibody induces or elicits a cytolytic reaction against target cells; whether the antibody binds to a specific epitope; and whether the antibody modulates (inhibits or agonizes) a specific biological pathway or pathways involving the antigen.

[0804] Similarly, the method can include one or more steps of screening the second enriched cell population for antibody binding strength and/or antibody functionality.

[0805] The method can further include a step of sequencing the polypeptide sequence or the corresponding nucleic acid sequence of the selected antibody. The method can also include a step of producing a recombinant antibody using the sequence, a fragment thereof, or a genetically modified version of the selected antibody. Methods for mutating antibody sequences in order to retain desired properties are well known to those skilled in the art and include humanization, chimerisation, production of single chain antibodies; these mutation methods can yield recombinant antibodies possessing desired effector function, immunogenicity, stability, removal or addition of glycosylation, and the like. The recombinant antibody can be produced by any suitable recombinant cell, including, but not limited to mammalian cells such as CHO, COS, BHK, HEK-293, bacterial cells, yeast cells, plant cells, insect cells, and amphibian cells. In one embodiment, the antibodies are expressed in polyploidal yeast cells, i.e., diploid yeast cells, particularly Pichia.

[0806] In one embodiment, the method comprises:

[0807] a. immunizing a host against an antigen to yield host antibodies;

[0808] b. screening the host antibodies for antigen specificity and neutralization;

[0809] c. harvesting B cells from the host;

[0810] d. enriching the harvested B cells to create an enriched cell population having an increased frequency of antigen-specific cells;

[0811] e. culturing one or more sub-populations from the enriched cell population under conditions that favor the survival of a single B cell to produce a clonal population in at least one culture well;

[0812] f. determining whether the clonal population produces an antibody specific to the antigen;

[0813] g. isolating a single B cell; and

[0814] h. sequencing the nucleic acid sequence of the antibody produced by the single B cell.

Methods of Humanizing Antibodies

[0815] In another embodiment of the invention, there is provided a method for humanizing antibody heavy and light chains. In this embodiment, the following method is followed for the humanization of the heavy and light chains:

[0816] Light Chain

[0817] 1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically, but not necessarily 22 amino acids in length for rabbit light chain protein sequences. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm. This is also the start of Framework 1 as classically defined by those in the field.

[0818] Example: RbtVL Amino acid residue 1 in Figure 2, starting 'AYDM...'

[0819] 2. Identify the end of Framework 3. This is typically 86-90 amino acids following the start of Framework 1 and is typically a cysteine residue preceded by two tyrosine residues. This is the end of the Framework 3 as classically defined by those in the field.

[0820] Example: RbtVL amino acid residue 88 in Figure 2, ending as 'TYYC'

[0821] 3. Use the rabbit light chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be a search against human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be found from various sources such as NCBI (National Center for Biotechnology Information).

[0822] Example: RbtVL amino acid sequence from residues numbered 1 through 88 in Figure 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Figure 2 as L12A, V1 and Vx02.

[0823] 4. Generally the most homologous human germline variable light chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn't the highest homology as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

[0824] Example: In Figure 2, L12A was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbtVL.

[0825] 5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the light chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable light chain sequence with the human homolog, while maintaining the layout of the framework and CDR regions.

[0826] Example: In Figure 2, the RbtVL sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

[0827] 6. Replace the human homologous light chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. It is possible that the specificity, affinity and/or

immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted.

[0828] Example: In Figure 2, the CDR1 and CDR2 amino acid residues of the human homologous variable light chain L12A are replaced with the CDR1 and CDR2 amino acid sequences from the RbtVL rabbit antibody light chain sequence. The human L12A frameworks 1, 2 and 3 are unaltered. The resulting humanized sequence is shown below as VLh from residues numbered 1 through 88. Note that the only residues that are different from the L12A human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 8 of the 88 residues are different than the human sequence.

[0829] 7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit light chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 9 to 15 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and identifiable by those skilled in the art. Typically the beginning of Framework 4, and thus after the end of CDR3 consists of the sequence 'FGGG...', however some variation may exist in these residues.

[0830] Example: In Figure 2, the CDR3 of RbtVL (amino acid residues numbered 89-100) is added after the end of framework 3 in the humanized sequence indicated as VLh.

[0831] 8. The rabbit light chain framework 4, which is typically the final 11 amino acid residues of the variable light chain and begins as indicated in Step 7 above and typically ends with the amino acid sequence '...VVKR' is replaced with the nearest human light chain framework 4 homolog, usually from germline sequence. Frequently this human light chain framework 4 is of the sequence 'FGGGTKVEIKR'. It is possible that other human light chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human light chain framework 4 sequence is added to the end of the variable light chain humanized sequence immediately following the CDR3

sequence from Step 7 above. This is now the end of the variable light chain humanized amino acid sequence.

[0832] Example: In Figure 2, Framework 4 (FR4) of the RbtVL rabbit light chain sequence is shown above a homologous human FR4 sequence. The human FR4 sequence is added to the humanized variable light chain sequence (VLh) right after the end of the CD3 region added in Step 7 above.

[0833] Heavy Chain

[0834] 1. Identify the amino acid that is the first one following the signal peptide sequence. This is the start of Framework 1. The signal peptide starts at the first initiation methionine and is typically 19 amino acids in length for rabbit heavy chain protein sequences. Typically, but not necessarily always, the final 3 amino acid residues of a rabbit heavy chain signal peptide are '...VQC', followed by the start of Framework 1. The start of the mature polypeptide can also be determined experimentally by N-terminal protein sequencing, or can be predicted using a prediction algorithm. This is also the start of Framework 1 as classically defined by those in the field.

[0835] Example: RbtVH Amino acid residue 1 in Figure 2, starting 'QEQL...'

[0836] 2. Identify the end of Framework 3. This is typically 95-100 amino acids following the start of Framework 1 and typically has the final sequence of '...CAR' (although the alanine can also be a valine). This is the end of the Framework 3 as classically defined by those in the field.

[0837] Example: RbtVH amino acid residue 98 in Figure 2, ending as '...FCVR'.

[0838] 3. Use the rabbit heavy chain sequence of the polypeptide starting from the beginning of Framework 1 to the end of Framework 3 as defined above and perform a sequence homology search for the most similar human antibody protein sequences. This will typically be against a database of human germline sequences prior to antibody maturation in order to reduce the possibility of immunogenicity, however any human sequences can be used. Typically a program like BLAST can be used to search a database of sequences for the most homologous. Databases of human antibody sequences can be

found from various sources such as NCBI (National Center for Biotechnology Information).

[0839] Example: RbtVH amino acid sequence from residues numbered 1 through 98 in Figure 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in Figure 2 as 3-64-04, 3-66-04, and 3-53-02.

[0840] 4. Generally the most homologous human germline variable heavy chain sequence is then used as the basis for humanization. However those skilled in the art may decide to use another sequence that wasn't the most homologous as determined by the homology algorithm, based on other factors including sequence gaps and framework similarities.

[0841] Example: 3-64-04 in Figure 2 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RbtVH.

[0842] 5. Determine the framework and CDR arrangement (FR1, FR2, FR3, CDR1 & CDR2) for the human homolog being used for the heavy chain humanization. This is using the traditional layout as described in the field. Align the rabbit variable heavy chain sequence with the human homolog, while maintaining the layout of the framework and CDR regions.

[0843] Example: In Figure 2, the RbtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

[0844] 6. Replace the human homologous heavy chain sequence CDR1 and CDR2 regions with the CDR1 and CDR2 sequences from the rabbit sequence. If there are differences in length between the rabbit and human CDR sequences then use the entire rabbit CDR sequences and their lengths. In addition, it may be necessary to replace the final three amino acids of the human heavy chain Framework 1 region with the final three amino acids of the rabbit heavy chain Framework 1. Typically but not always, in rabbit heavy chain Framework 1 these three residues follow a Glycine residue preceded by a Serine residue. In addition, it may be necessary replace the final amino acid of the human heavy chain Framework 2 region with the final amino acid of the rabbit heavy chain Framework 2. Typically, but not necessarily always, this is a Glycine residue preceded by an Isoleucine residue in the rabbit heavy chain Framework 2. It is possible that the

specificity, affinity and/or immunogenicity of the resulting humanized antibody may be unaltered if smaller or larger sequence exchanges are performed, or if specific residue(s) are altered, however the exchanges as described have been used successfully, but do not exclude the possibility that other changes may be permitted. For example, a tryptophan amino acid residue typically occurs four residues prior to the end of the rabbit heavy chain CDR2 region, whereas in human heavy chain CDR2 this residue is typically a Serine residue. Changing this rabbit tryptophan residue to a the human Serine residue at this position has been demonstrated to have minimal to no effect on the humanized antibody's specificity or affinity, and thus further minimizes the content of rabbit sequence-derived amino acid residues in the humanized sequence.

[0845] Example: In Figure 2, The CDR1 and CDR2 amino acid residues of the human homologous variable heavy chain are replaced with the CDR1 and CDR2 amino acid sequences from the RbtVH rabbit antibody light chain sequence, except for the boxed residue, which is tryptophan in the rabbit sequence (position number 63) and Serine at the same position in the human sequence, and is kept as the human Serine residue. In addition to the CDR1 and CDR2 changes, the final three amino acids of Framework 1 (positions 28-30) as well as the final residue of Framework 2 (position 49) are retained as rabbit amino acid residues instead of human. The resulting humanized sequence is shown below as VHh from residues numbered 1 through 98. Note that the only residues that are different from the 3-64-04 human sequence are underlined, and are thus rabbit-derived amino acid residues. In this example only 15 of the 98 residues are different than the human sequence.

[0846] 7. After framework 3 of the new hybrid sequence created in Step 6, attach the entire CDR3 of the rabbit heavy chain antibody sequence. The CDR3 sequence can be of various lengths, but is typically 5 to 19 amino acid residues in length. The CDR3 region and the beginning of the following framework 4 region are defined classically and are identifiable by those skilled in the art. Typically the beginning of framework 4, and thus after the end of CDR3 consists of the sequence WGXG...(where X is usually Q or P), however some variation may exist in these residues.

[0847] Example: The CDR3 of RbtVH (amino acid residues numbered 99-110) is added after the end of framework 3 in the humanized sequence indicated as VHh.

[0848] 8. The rabbit heavy chain framework 4, which is typically the final 11 amino acid residues of the variable heavy chain and begins as indicated in Step 7 above and typically ends with the amino acid sequence '...TVSS' is replaced with the nearest human heavy chain framework 4 homolog, usually from germline sequence. Frequently this human heavy chain framework 4 is of the sequence 'WGQGTLVTVSS'. It is possible that other human heavy chain framework 4 sequences that are not the most homologous or otherwise different may be used without affecting the specificity, affinity and/or immunogenicity of the resulting humanized antibody. This human heavy chain framework 4 sequence is added to the end of the variable heavy chain humanized sequence immediately following the CDR3 sequence from Step 7 above. This is now the end of the variable heavy chain humanized amino acid sequence.

[0849] Example: In Figure 2, framework 4 (FR4) of the RbtVH rabbit heavy chain sequence is shown above a homologous human heavy FR4 sequence. The human FR4 sequence is added to the humanized variable heavy chain sequence (VHh) right after the end of the CD3 region added in Step 7 above.

Methods of Producing Antibodies and Fragments thereof

[0850] The invention is also directed to the production of the antibodies described herein or fragments thereof. Recombinant polypeptides corresponding to the antibodies described herein or fragments thereof are secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast. In an exemplary embodiment, the invention is directed to methods for producing these recombinant polypeptides in secreted form for prolonged periods using cultures comprising polyploid yeast, i.e., at least several days to a week, more preferably at least a month or several months, and even more preferably at least 6 months to a year or longer. These polyploid yeast cultures will express at least 10-25 mg/liter of the polypeptide, more preferably at least 50-250 mg/liter, still more preferably at least 500-1000 mg/liter, and most preferably a gram per liter or more of the recombinant polypeptide(s).

[0851] In one embodiment of the invention a pair of genetically marked yeast haploid cells are transformed with expression vectors comprising subunits of a desired

heteromultimeric protein. One haploid cell comprises a first expression vector, and a second haploid cell comprises a second expression vector. In another embodiment diploid yeast cells will be transformed with one or more expression vectors that provide for the expression and secretion of one or more of the recombinant polypeptides. In still another embodiment a single haploid cell may be transformed with one or more vectors and used to produce a polyploidal yeast by fusion or mating strategies. In yet another embodiment a diploid yeast culture may be transformed with one or more vectors providing for the expression and secretion of a desired polypeptide or polypeptides. These vectors may comprise vectors e.g., linearized plasmids or other linear DNA products that integrate into the yeast cell's genome randomly, through homologous recombination, or using a recombinase such as Cre/Lox or Flp/Frt. Optionally, additional expression vectors may be introduced into the haploid or diploid cells; or the first or second expression vectors may comprise additional coding sequences; for the synthesis of heterotrimers; heterotetramers; *etc.* The expression levels of the non-identical polypeptides may be individually calibrated, and adjusted through appropriate selection, vector copy number, promoter strength and/or induction and the like. The transformed haploid cells are genetically crossed or fused. The resulting diploid or tetraploid strains are utilized to produce and secrete fully assembled and biologically functional proteins, humanized antibodies described herein or fragments thereof.

[0852] The use of diploid or tetraploid cells for protein production provides for unexpected benefits. The cells can be grown for production purposes, *i.e.* scaled up, and for extended periods of time, in conditions that can be deleterious to the growth of haploid cells, which conditions may include high cell density; growth in minimal media; growth at low temperatures; stable growth in the absence of selective pressure; and which may provide for maintenance of heterologous gene sequence integrity and maintenance of high level expression over time. Without wishing to be bound thereby, the inventors theorize that these benefits may arise, at least in part, from the creation of diploid strains from two distinct parental haploid strains. Such haploid strains can comprise numerous minor autotrophic mutations, which mutations are complemented in the diploid or tetraploid, enabling growth and enhanced production under highly selective conditions.

[0853] Transformed mating competent haploid yeast cells provide a genetic method that enables subunit pairing of a desired protein. Haploid yeast strains are transformed with each of two expression vectors, a first vector to direct the synthesis of one polypeptide chain and a second vector to direct the synthesis of a second, non-identical polypeptide chain. The two haploid strains are mated to provide a diploid host where optimized target protein production can be obtained.

[0854] Optionally, additional non-identical coding sequence(s) are provided. Such sequences may be present on additional expression vectors or in the first or the second expression vectors. As is known in the art, multiple coding sequences may be independently expressed from individual promoters; or may be coordinately expressed through the inclusion of an "internal ribosome entry site" or "IRES", which is an element that promotes direct internal ribosome entry to the initiation codon, such as ATG, of a cistron (a protein encoding region), thereby leading to the cap-independent translation of the gene. IRES elements functional in yeast are described by Thompson *et al.* (2001) P.N.A.S. 98:12866-12868.

[0855] In one embodiment of the invention, antibody sequences are produced in combination with a secretory J chain, which provides for enhanced stability of IgA (see U.S. Patent Nos. 5,959,177; and 5,202,422).

[0856] In a preferred embodiment the two haploid yeast strains are each auxotrophic, and require supplementation of media for growth of the haploid cells. The pair of auxotrophs are complementary, such that the diploid product will grow in the absence of the supplements required for the haploid cells. Many such genetic markers are known in yeast, including requirements for amino acids (*e.g. met, lys, his, arg, etc.*), nucleosides (*e.g. ura3, ade1, etc.*); and the like. Amino acid markers may be preferred for the methods of the invention. Alternatively diploid cells which contain the desired vectors can be selected by other means, e.g., by use of other markers, such as green fluorescent protein, antibiotic resistance genes, various dominant selectable markers, and the like.

[0857] Two transformed haploid cells may be genetically crossed and diploid strains arising from this mating event selected by their hybrid nutritional requirements and/or antibiotic resistance spectra. Alternatively, populations of the two transformed haploid

strains are spheroplasted and fused, and diploid progeny regenerated and selected. By either method, diploid strains can be identified and selectively grown based on their ability to grow in different media than their parents. For example, the diploid cells may be grown in minimal medium that may include antibiotics. The diploid synthesis strategy has certain advantages. Diploid strains have the potential to produce enhanced levels of heterologous protein through broader complementation to underlying mutations, which may impact the production and/or secretion of recombinant protein. Furthermore, once stable strains have been obtained, any antibiotics used to select those strains do not necessarily need to be continuously present in the growth media.

[0858] As noted above, in some embodiments a haploid yeast may be transformed with a single or multiple vectors and mated or fused with a non-transformed cell to produce a diploid cell containing the vector or vectors. In other embodiments, a diploid yeast cell may be transformed with one or more vectors that provide for the expression and secretion of a desired heterologous polypeptide by the diploid yeast cell.

[0859] In one embodiment of the invention, two haploid strains are transformed with a library of polypeptides, *e.g.* a library of antibody heavy or light chains. Transformed haploid cells that synthesize the polypeptides are mated with the complementary haploid cells. The resulting diploid cells are screened for functional protein. The diploid cells provide a means of rapidly, conveniently and inexpensively bringing together a large number of combinations of polypeptides for functional testing. This technology is especially applicable for the generation of heterodimeric protein products, where optimized subunit synthesis levels are critical for functional protein expression and secretion.

[0860] In another embodiment of the invention, the expression level ratio of the two subunits is regulated in order to maximize product generation. Heterodimer subunit protein levels have been shown previously to impact the final product generation (Simmons LC, J Immunol Methods. 2002 May 1;263(1-2):133-47). Regulation can be achieved prior to the mating step by selection for a marker present on the expression vector. By stably increasing the copy number of the vector, the expression level can be increased. In some cases, it may be desirable to increase the level of one chain relative to the other, so as to reach a balanced proportion between the subunits of the polypeptide. Antibiotic resistance

markers are useful for this purpose, *e.g.* Zeocin resistance marker, G418 resistance, *etc.* and provide a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin or G418. The proper ratio, *e.g.* 1:1; 1:2; *etc.* of the subunit genes may be important for efficient protein production. Even when the same promoter is used to transcribe both subunits, many other factors contribute to the final level of protein expressed and therefore, it can be useful to increase the number of copies of one encoded gene relative to the other. Alternatively, diploid strains that produce higher levels of a polypeptide, relative to single copy vector strains, are created by mating two haploid strains, both of which have multiple copies of the expression vectors.

[0861] Host cells are transformed with the above-described expression vectors, mated to form diploid strains, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants or amplifying the genes encoding the desired sequences. A number of minimal media suitable for the growth of yeast are known in the art. Any of these media may be supplemented as necessary with salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as phosphate, HEPES), nucleosides (such as adenosine and thymidine), antibiotics, trace elements, and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[0862] Secreted proteins are recovered from the culture medium. A protease inhibitor, such as phenyl methyl sulfonyl fluoride (PMSF) may be useful to inhibit proteolytic degradation during purification, and antibiotics may be included to prevent the growth of adventitious contaminants. The composition may be concentrated, filtered, dialyzed, etc., using methods known in the art.

[0863] The diploid cells of the invention are grown for production purposes. Such production purposes desirably include growth in minimal media, which media lacks pre-formed amino acids and other complex biomolecules, e.g., media comprising ammonia as a nitrogen source, and glucose as an energy and carbon source, and salts as a source of

phosphate, calcium and the like. Preferably such production media lacks selective agents such as antibiotics, amino acids, purines, pyrimidines, *etc.* The diploid cells can be grown to high cell density, for example at least about 50 g/L; more usually at least about 100 g/L; and may be at least about 300, about 400, about 500 g/L or more.

[0864] In one embodiment of the invention, the growth of the subject cells for production purposes is performed at low temperatures, which temperatures may be lowered during log phase, during stationary phase, or both. The term "low temperature" refers to temperatures of at least about 15°C, more usually at least about 17°C, and may be about 20°C, and is usually not more than about 25°C, more usually not more than about 22°C. In another embodiment of the invention, the low temperature is usually not more than about 28°C. Growth temperature can impact the production of full-length secreted proteins in production cultures, and decreasing the culture growth temperature can strongly enhance the intact product yield. The decreased temperature appears to assist intracellular trafficking through the folding and post-translational processing pathways used by the host to generate the target product, along with reduction of cellular protease degradation.

[0865] The methods of the invention provide for expression of secreted, active protein, preferably a mammalian protein. In one embodiment, secreted, "active antibodies", as used herein, refers to a correctly folded multimer of at least two properly paired chains, which accurately binds to its cognate antigen. Expression levels of active protein are usually at least about 10-50 mg/liter culture, more usually at least about 100 mg/liter, preferably at least about 500 mg/liter, and may be 1000 mg/liter or more.

[0866] The methods of the invention can provide for increased stability of the host and heterologous coding sequences during production. The stability is evidenced, for example, by maintenance of high levels of expression of time, where the starting level of expression is decreased by not more than about 20%, usually not more than 10%, and may be decreased by not more than about 5% over about 20 doublings, 50 doublings, 100 doublings, or more.

[0867] The strain stability also provides for maintenance of heterologous gene sequence integrity over time, where the sequence of the active coding sequence and requisite transcriptional regulatory elements are maintained in at least about 99% of the diploid cells,

usually in at least about 99.9% of the diploid cells, and preferably in at least about 99.99% of the diploid cells over about 20 doublings, 50 doublings, 100 doublings, or more. Preferably, substantially all of the diploid cells maintain the sequence of the active coding sequence and requisite transcriptional regulatory elements.

[0868] Other methods of producing antibodies are well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (*See*, for example, U.S. Patent No. 4,816,567 to Cabilly *et al.*; Morrison et al., P.N.A.S. USA, 81:8651-55 (1984); Neuberger, M.S. et al., Nature, 314:268-270 (1985); Boulianne, G.L. et al., Nature, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[0869] Likewise, other methods of producing humanized antibodies are now well known in the art (*See*, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen *et al*; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter *et al*; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. *et al*, Nature, 321:522-525 (1986); Reichmann, L., *et al*, Nature, 332:323-327 (1988); Verhoeyen, M, *et al*, Science, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[0870] Antibody polypeptides of the invention having IL-6 binding specificity may also be produced by constructing, using conventional techniques well known to those of ordinary skill in the art, an expression vector containing an operon and a DNA sequence encoding an antibody heavy chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[0871] A second expression vector is produced using the same conventional means well known to those of ordinary skill in the art, said expression vector containing an operon and a DNA sequence encoding an antibody light chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[0872] The expression vectors are transfected into a host cell by convention techniques well known to those of ordinary skill in the art to produce a transfected host cell, said transfected host cell cultured by conventional techniques well known to those of ordinary skill in the art to produce said antibody polypeptides.

[0873] The host cell may be co-transfected with the two expression vectors described above, the first expression vector containing DNA encoding an operon and a light chain-derived polypeptide and the second vector containing DNA encoding an operon and a heavy chain-derived polypeptide. The two vectors contain different selectable markers, but preferably achieve substantially equal expression of the heavy and light chain polypeptides. Alternatively, a single vector may be used, the vector including DNA encoding both the heavy and light chain polypeptides. The coding sequences for the heavy and light chains may comprise cDNA.

[0874] The host cells used to express the antibody polypeptides may be either a bacterial cell such as *E. coli*, or a eukaryotic cell. In a particularly preferred embodiment of the invention, a mammalian cell of a well-defined type for this purpose, such as a myeloma cell or a Chinese hamster ovary (CHO) cell line may be used.

[0875] The general methods by which the vectors may be constructed, transfection methods required to produce the host cell and culturing methods required to produce the antibody polypeptides from said host cells all include conventional techniques. Although preferably the cell line used to produce the antibody is a mammalian cell line, any other suitable cell line, such as a bacterial cell line such as an *E. coli*-derived bacterial strain, or a yeast cell line, may alternatively be used.

[0876] Similarly, once produced the antibody polypeptides may be purified according to standard procedures in the art, such as for example cross-flow filtration, ammonium sulphate precipitation, affinity column chromatography and the like.

[0877] The antibody polypeptides described herein may also be used for the design and synthesis of either peptide or non-peptide mimetics that would be useful for the same therapeutic applications as the antibody polypeptides of the invention. *See*, for example, Saragobi *et al*, Science, 253:792-795 (1991), the contents of which is herein incorporated by reference in its entirety.

Screening Assays

[0878] The invention also includes screening assays designed to assist in the identification of diseases and disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder.

[0879] In one embodiment of the invention, the anti-IL-6 antibodies of the invention, or IL-6 binding fragments thereof, are used to detect the presence of IL-6 in a biological sample obtained from a patient exhibiting symptoms of a disease or disorder associated with IL-6. The presence of IL-6, or elevated levels thereof when compared to pre-disease levels of IL-6 in a comparable biological sample, may be beneficial in diagnosing a disease or disorder associated with IL-6.

[0880] Another embodiment of the invention provides a diagnostic or screening assay to assist in diagnosis of diseases or disorders associated with IL-6 in patients exhibiting symptoms of an IL-6 associated disease or disorder identified herein, comprising assaying the level of IL-6 expression in a biological sample from said patient using a post-translationally modified anti-IL-6 antibody or binding fragment thereof. The anti-IL-6 antibody or binding fragment thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

[0881] The IL-6 level in the biological sample is determined using a modified anti-IL-6 antibody or binding fragment thereof as set forth herein, and comparing the level of IL-6 in the biological sample against a standard level of IL-6 (e.g., the level in normal biological samples). The skilled clinician would understand that some variability may exist between normal biological samples, and would take that into consideration when evaluating results.

[0882] The above-recited assay may also be useful in monitoring a disease or disorder, where the level of IL-6 obtained in a biological sample from a patient believed to have an IL-6 associated disease or disorder is compared with the level of IL-6 in prior biological samples from the same patient, in order to ascertain whether the IL-6 level in said patient has changed with, for example, a treatment regimen.

[0883] The invention is also directed to a method of *in vivo* imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective

amount of a diagnostic composition. Said in vivo imaging is useful for the detection and imaging of IL-6 expressing tumors or metastases and IL-6 expressing inflammatory sites, for example, and can be used as part of a planning regimen for design of an effective cancer or arthritis treatment protocol. The treatment protocol may include, for example, one or more of radiation, chemotherapy, cytokine therapy, gene therapy, and antibody therapy, as well as an anti-IL-6 antibody or fragment thereof.

[0884] A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucous, pleural fluid, synovial fluid and spinal fluid.

Methods of Ameliorating or Reducing Symptoms of, or Treating, or Preventing, Diseases and Disorders Associated with, IL-6

[0885] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with IL-6. Anti-IL-6 antibodies described herein, or fragments thereof, can also be administered in a therapeutically effective amount to patients in need of treatment of diseases and disorders associated with IL-6 in the form of a pharmaceutical composition as described in greater detail below.

[0886] In one embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with fatigue. Diseases and disorders associated with fatigue include, but are not limited to, general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue and chronic fatigue syndrome. *See*, for example, Esper DH, *et al*, The cancer cachexia syndrome: a review of metabolic and clinical manifestations, Nutr Clin Pract., 2005 Aug;20 (4):369-76; Vgontzas AN, *et al*, IL-6 and its circadian secretion in humans, Neuroimmunomodulation, 2005;12(3):131-40; Robson-Ansley, PJ, *et al*, Acute interleukin-6 administration impairs athletic performance in healthy, trained male runners, Can J Appl Physiol., 2004 Aug;29(4):411-8; Shephard RJ., Cytokine responses to physical activity, with particular reference to IL-6: sources, actions, and clinical implications, Crit Rev Immunol., 2002;22(3):165-82; Arnold, MC, *et al*, Using an interleukin-6 challenge to evaluate

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[0887] In a preferred embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, cachexia. Diseases and disorders associated with cachexia include, but are not limited to, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia and age-related cachexia. *See*, for example, Barton, BE., Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative diseases and paraneoplastic syndromes, Expert Opin Ther Targets, 2005 Aug;9(4):737-52; Zaki MH, *et al*, CNTO 328, a monoclonal antibody to IL-6, inhibits human tumor-induced cachexia in nude mice, Int J Cancer, 2004 Sep 10;111(4):592-5; Trikha M, *et al*, Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence, Clin Cancer Res., 2003 Oct 15;9(13):4653-65; Lelli G, *et al*, Treatment of the cancer anorexia-cachexia syndrome: a critical reappraisal, J Chemother., 2003 Jun;15(3):220-5; Argiles JM, *et al*, Cytokines in the pathogenesis of cancer cachexia, Curr Opin Clin Nutr Metab Care, 2003 Jul;6(4):401-6; Barton BE., IL-6-like cytokines and cancer cachexia: consequences of chronic inflammation, Immunol Res., 2001;23(1):41-58; Yamashita JI, *et al*, Medroxyprogesterone acetate and cancer cachexia: interleukin-6 involvement, Breast Cancer, 2000;7(2):130-5; Yeh SS, *et al*, Geriatric cachexia: the role of cytokines, Am J Clin Nutr., 1999 Aug;70(2):183-97; Strassmann G, *et al*, Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy, Cytokines Mol Ther., 1995 Jun;1(2):107-13; Fujita J, *et al*, Anti-interleukin-6 receptor antibody prevents muscle atrophy in colon-26 adenocarcinoma-bearing mice with

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[0888] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, autoimmune diseases and disorders. Diseases and disorders associated with autoimmunity include, but are not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease. In a preferred embodiment of the invention, humanized anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, rheumatoid arthritis and systemic juvenile idiopathic arthritis. *See*, for example, Nishimoto N., Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan, Clin Rev Allergy Immunol., 2005 Jun;28(3):221-30; Nishimoto N, *et al*, Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial, Arthritis Rheum., 2004 Jun;50(6):1761-9; Choy E., Interleukin 6 receptor as a target for the treatment of rheumatoid arthritis, Ann Rheum Dis., 2003 Nov;62 Suppl 2:ii68-9; Nishimoto N, *et al*, Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study, J Rheumatol., 2003 Jul;30(7):1426-35; Mihara M, *et al*, Humanized antibody to human interleukin-6 receptor inhibits the development of collagen arthritis in cynomolgus monkeys, Clin Immunol.,

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Immunol Ther Exp., 2002 50(6):371-8; Zeiser, R, *et al*, Immunopathogenesis of acute graft-versus-host disease: implications for novel preventive and therapeutic strategies, Ann Hematol., 2004 83(9):551-65; Dickinson, AM, *et al*, Genetic polymorphisms predicting the outcome of bone marrow transplants, Br. J Haematol., 2004 127(5):479-90; and Scheinberg MA, *et al*, Interleukin 6: a possible marker of disease activity in adult onset Still's disease, Clin Exp Rheumatol., 1996 Nov-Dec;14 (6):653-5, the disclosures of each of which are herein incorporated by reference in their entireties.

[0889] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with the skeletal system. Diseases and disorders associated with the skeletal system include, but are not limited to, osteoarthritis, osteoporosis and Paget's disease of bone. In a preferred embodiment of the invention, humanized anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, osteoarthritis. *See*, for example, Malemud CJ., Cytokines as therapeutic targets for osteoarthritis, BioDrugs, 2004;18(1):23-35; Westacott CI, *et al*, Cytokines in osteoarthritis: mediators or markers of joint destruction?, Semin Arthritis Rheum., 1996 Feb;25(4):254-72; Sugiyama T., Involvement of interleukin-6 and prostaglandin E2 in particular osteoporosis of postmenopausal women with rheumatoid arthritis, J Bone Miner Metab., 2001;19(2):89-96; Abrahamsen B, *et al*, Cytokines and bone loss in a 5-year longitudinal study - hormone replacement therapy suppresses serum soluble interleukin-6 receptor and increases interleukin-1-receptor antagonist: the Danish Osteoporosis Prevention Study, J Bone Miner Res., 2000 Aug;15(8):1545-54; Straub RH, *et al*, Hormone replacement therapy and interrelation between serum interleukin-6 and body mass index in postmenopausal women: a population-based study, J Clin Endocrinol Metab., 2000 Mar;85(3):1340-4; Manolagas SC, The role of IL-6 type cytokines and their receptors in bone, Ann N Y Acad Sci., 1998 May 1;840:194-204; Ershler WB, *et al*, Immunologic aspects of osteoporosis, Dev Comp Immunol., 1997 Nov-Dec;21(6):487-99; Jilka RL, *et al*, Increased osteoclast development after estrogen loss: mediation by interleukin-6, Science, 1992 Jul 3;257(5066):88-91; Kallen KJ, *et al*, New developments in IL-6 dependent biology and therapy: where do we

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[0890] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with cancer. Diseases and disorders associated with cancer include, but are not limited to, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy and cancer chemotherapy toxicity. *See*, for example, Hirata T, *et al*, Humanized anti-interleukin-6 receptor monoclonal antibody induced apoptosis of fresh and cloned human myeloma cells in vitro, Leuk Res., 2003 Apr;27(4):343-9, Bataille R, *et al*, Biologic effects of anti-interleukin-6 murine monoclonal antibody in advanced multiple myeloma, Blood, 1995 Jul 15;86 (2):685-91; Goto H, *et al*, Mouse anti-human interleukin-6 receptor monoclonal antibody inhibits proliferation of fresh human myeloma cells in vitro, Jpn J Cancer Res., 1994 Sep;85(9):958-65; Klein B, *et al*, Murine anti-interleukin-6 monoclonal antibody therapy for a patient with plasma cell leukemia, Blood, 1991 Sep 1;78(5):1198-204; Mauray S, *et al*, Epstein-Barr virus-dependent lymphoproliferative disease: critical role of IL-6, Eur J Immunol., 2000 Jul;30(7):2065-73; Tsunenari T, *et al*, New xenograft model of multiple myeloma and efficacy of a humanized antibody against human interleukin-6 receptor, Blood, 1997 Sep 15;90(6):2437-44; Emilie D, *et al*, Interleukin-6 production in high-grade B lymphomas: correlation with the presence of malignant immunoblasts in acquired immunodeficiency syndrome and in human immunodeficiency virus-seronegative patients, Blood, 1992 Jul 15;80(2):498-504; Emilie D, *et al*,

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[0891] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating,

or preventing, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, and transplant rejection. *See*, for example, Tzoulaki I, *et al*, C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study, Circulation, 2005 Aug 16;112(7):976-83, Epub 2005 Aug 8; Rattazzi M, *et al*, C-reactive protein and interleukin-6 in vascular disease: culprits or passive bystanders?, J Hypertens., 2003 Oct;21(10):1787-803; Ito T, *et al*, HMG-CoA reductase inhibitors reduce interleukin-6 synthesis in human vascular smooth muscle cells, Cardiovasc Drugs Ther., 2002 Mar;16(2):121-6; Stenvinkel P, *et al*, Mortality, malnutrition, and atherosclerosis in ESRD: what is the role of interleukin-6?, Kidney Int Suppl., 2002 May;(80):103-8; Yudkin JS, *et al*, Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?, Atherosclerosis, 2000 Feb;148(2):209-14; Huber SA, *et al*, Interleukin-6 exacerbates early atherosclerosis in mice, Arterioscler Thromb Vasc Biol., 1999 Oct;19(10):2364-7; Kado S, *et al*, Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus, Acta Diabetol.,1999 Jun;36(1-2):67-72; Sukovich DA, *et al*, Expression of interleukin-6 in atherosclerotic lesions of male ApoE-knockout mice: inhibition by 17beta-estradiol, Arterioscler Thromb Vasc Biol.,1998 Sept;8(9):1498-505; Klover PJ, *et al*, Interleukin-6 depletion selectively improves hepatic insulin action in obesity, Endocrinology, 2005 Aug;146(8):3417-27, Epub 2005 Apr 21; Lee YH, *et al*, The evolving role of inflammation in obesity and the metabolic syndrome, Curr Diab Rep., 2005 Feb;5(1):70-5; Diamant M, *et al*, The association between abdominal visceral fat and carotid stiffness is mediated by circulating inflammatory markers in uncomplicated type 2 diabetes, J Clin Endocrinol Metab., 2005 Mar;90(3):1495-501, Epub 2004 Dec 21; Bray GA, Medical consequences of obesity, J Clin Endocrinol Metab., 2004 Jun;89(6):2583 9; Klover PJ, *et al*, Chronic exposure to interleukin-6 causes hepatic insulin resistance in

mice, Diabetes, 2003 Nov;52 (11):2784-9; Yudkin JS, *et al*, Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link?, Atherosclerosis, 2000 Feb;148(2):209-14; Doganci A, *et al*, Pathological role of IL-6 in the experimental allergic bronchial asthma in mice, Clin Rev Allergy Immunol., 2005 Jun;28(3):257-70; Doganci A, *et al*, The IL-6R alpha chain controls lung CD4+CD25+ Treg development and function during allergic airway inflammation *in vivo*, J Clin Invest., 2005 Feb;l15(2):313 25, (Erratum in: J Clin Invest., 2005 May;l15(5):1388, Lehr, Hans A [added]); Stelmasiak Z, *et al*, IL 6 and sIL-6R concentration in the cerebrospinal fluid and serum of MS patients, Med Sci Monit., 2001 Sep-Oct;7(5):914-8; Tilgner J, *et al*, Continuous interleukin-6 application *in vivo* via macroencapsulation of interleukin-6-expressing COS-7 cells induces massive gliosis, Glia, 2001 Sep;35(3):234-45, Brunello AG, *et al*, Astrocytic alterations in interleukin-6 Soluble interleukin-6 receptor alpha double-transgenic mice, Am J Pathol., 2000 Nov;157(5):1485-93; Hampel H, *et al*, Pattern of interleukin-6 receptor complex immunoreactivity between cortical regions of rapid autopsy normal and Alzheimer's disease brain, Eur Arch Psychiatry Clin Neurosci., 2005 Aug;255(4):269-78, Epub 2004 Nov 26; Cacquevel M, *et al*, Cytokines in neuroinflammation and Alzheimer's disease, Curr Drug Targets, 2004 Aug;5(6):529-34; Quintanilla RA, *et al*, Interleukin 6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway, Exp Cell Res., 2004 Apr 15; 295 (1):245-57; Gadient RA, *et al*, Interleukin-6 (IL-6)--a molecule with both beneficial and destructive potentials, Prog Neurobiol., 1997 Aug;52(5):379-90; Hull M, *et al*, Occurrence of interleukin-6 in cortical plaques of Alzheimer's disease patients may precede transformation of diffuse into neuritic plaques, Ann N Y Acad Sci., 1996 Jan 17;777:205-12; Rallidis LS, *et al*, Inflammatory markers and in-hospital mortality in acute ischaemic stroke, Atherosclerosis, 2005 Dec 30; Emsley HC, *et al*, Interleukin-6 and acute ischaemic stroke, Acta Neurol Scand., 2005 Oct;112(4):273-4; Smith CJ, *et al*, Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome, BMC Neurol., 2004 Jan 15;4:2; Vila N, *et al*, Proinflammatory cytokines and early neurological worsening in ischemic stroke, Stroke, 2000 Oct;31(10):2325-9; and Tarkowski E, *et al*, Early intrathecal production of interleukin-6

predicts the size of brain lesion in stroke, Stroke, 1995 Aug;26(8):1393-8; the disclosures of each of which are herein incorporated by reference in their entireties.

[0892] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with cytokine storm. Diseases and disorders associated with cytokine storm include, but are not limited to, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS). *See*, for example, Cecil, R. L., Goldman, L., & Bennett, J. C. (2000). Cecil textbook of medicine. Philadelphia: W.B. Saunders; Ferrara JL, *et al.*, Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1, Transplant Proc. 1993 Feb;25(1 Pt 2):1216-7; Osterholm MT, Preparing for the Next Pandemic, N Engl J Med. 2005 May 5;352(18):1839-42; Huang KJ, *et al.*, An interferon-gamma-related cytokine storm in SARS patients, J Med Virol. 2005 Feb;75(2):185-94; and Cheung CY, *et al.*, Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? Lancet. 2002 Dec 7;360(9348):1831-7.

[0893] In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful as a wakefulness aid.

Administration

[0894] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a concentration of between about 0.1 and 20 mg/kg, such as about 0.4 mg/kg, about 0.8 mg/kg, about 1.6 mg/kg, or about 4 mg/kg, of body weight of recipient subject. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of

said antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or less, such as once every sixteen weeks or less, once every eight weeks or less, or once every four weeks, or less.

[0895] It is understood that the effective dosage may depend on recipient subject attributes, such as, for example, age, gender, pregnancy status, body mass index, lean body mass, condition or conditions for which the composition is given, other health conditions of the recipient subject that may affect metabolism or tolerance of the composition, levels of IL-6 in the recipient subject, and resistance to the composition (for example, arising from the patient developing antibodies against the composition). A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[0896] In another embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, are administered to a subject in a pharmaceutical formulation.

[0897] A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration *via* one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally *via* an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

[0898] In one embodiment of the invention, the anti-IL-6 antibodies described herein, or IL-6 binding fragments thereof, as well as combinations of said antibody fragments, may be optionally administered in combination with one or more active agents. Such active agents include analgesic, antipyretic, anti-inflammatory, antibiotic, antiviral, and anti-cytokine agents. Active agents include agonists, antagonists, and modulators of TNF-α, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-α, IFN-γ, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampyrone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofezone, COX-2 inhibitors, Dexibuprofen, Dexketoprofen, Diclofenac, Diflunisal, Droxicam, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indometacin, Indoprofen, Kebuzone, Ketoprofen, Ketorolac, Lornoxicam, Loxoprofen, Lumiracoxib, Magnesium salicylate, Meclofenamic acid, Mefenamic acid, Meloxicam, Metamizole, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylanthranilic acids, Oxametacin, Oxaprozin, Oxicams, Oxyphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Sulfinpyrazone, Sulindac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolfenamic acid, Tolmetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arsphenamine, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbenicillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefalotin, Cefamandole, Cefazolin, Cefdinir, Cefditoren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftobiprole, Ceftriaxone, Cefuroxime, Cephalosporins, Chloramphenicol, Cilastatin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Colistin, Co-trimoxazole, Dalfopristin, Demeclocycline, Dicloxacillin, Dirithromycin, Doripenem, Doxycycline, Enoxacin,

Ertapenem, Erythromycin, Ethambutol, Flucloxacillin, Fosfomycin, Furazolidone, Fusidic acid, Gatifloxacin, Geldanamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Isoniazid, Kanamycin, Levofloxacin, Lincomycin, Linezolid, Lomefloxacin, Loracarbef, Macrolides, Mafenide, Meropenem, Meticillin, Metronidazole, Mezlocillin, Minocycline, Monobactams, Moxifloxacin, Mupirocin, Nafcillin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxacin, Ofloxacin, Oxacillin, Oxytetracycline, Paromomycin, Penicillin, Penicillins, Piperacillin, Platensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulfacetamide, Sulfamethizole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Sulfonamides, Teicoplanin, Telithromycin, Tetracycline, Tetracyclines, Ticarcillin, Tinidazole, Tobramycin, Trimethoprim, Trimethoprim-Sulfamethoxazole, Troleandomycin, Trovafloxacin, and Vancomycin. Active agents also include Aldosterone, Beclometasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, Deoxycorticosterone acetate, Dexamethasone, Fludrocortisone acetate, Glucocorticoids, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Steroids, and Triamcinolone. Antiviral agents include abacavir, aciclovir, acyclovir, adefovir, amantadine, amprenavir, an antiretroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, atazanavir, atripla, brivudine, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, entry inhibitors, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, fusion inhibitor, ganciclovir, gardasil, ibacitabine, idoxuridine, imiquimod, imunovir, indinavir, inosine, integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine, lopinavir, loviride, maraviroc, MK-0518, moroxydine, nelfinavir, nevirapine, nexavir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxin, protease inhibitor, reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, and zidovudine. Any suitable combination of these active agents is also contemplated.

[0899] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[0900] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0901] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition.

[0902] 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.

Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0903] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[0904] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[0905] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[0906] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[0907] Certain teachings related to methods for obtaining a clonal population of antigen-specific B cells were disclosed in U.S. Provisional patent application no. 60/801,412, filed May 19, 2006, the disclosure of which is herein incorporated by reference in its entirety.

[0908] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in International Application No. _____, corresponding to Attorney Docket No. 67858.701802, entitled "Novel Rabbit Antibody Humanization Method and Humanized Rabbit Antibodies", filed May 21, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[0909] Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. Patent application no. 11/429,053, filed May 8, 2006, (U.S. Patent Application Publication No. US2006/0270045), the disclosure of which is herein incorporated by reference in its entirety.

[0910] Certain teachings related to IL-6 antibodies, methods of producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. provisional patent application no. 60/924,550, filed May 21, 2007, the disclosure of which is herein incorporated by reference in its entirety.

[0911] Certain anti-IL-6 antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[0912] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

[0913] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.* amounts, temperature, concentrations, *etc.*) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLES

Example 1 Production of Enriched Antigen-Specific B Cell Antibody Culture

[0914] Panels of antibodies are derived by immunizing traditional antibody host animals to exploit the native immune response to a target antigen of interest. Typically, the host used for immunization is a rabbit or other host that produces antibodies using a similar maturation process and provides for a population of antigen-specific B cells producing antibodies of comparable diversity, e.g., epitopic diversity. The initial antigen immunization can be conducted using complete Freund's adjuvant (CFA), and the subsequent boosts effected with incomplete adjuvant. At about 50-60 days after immunization, preferably at day 55, antibody titers are tested, and the Antibody Selection (ABS) process is initiated if appropriate titers are established. The two key criteria for ABS initiation are potent antigen recognition and function-modifying activity in the polyclonal sera.

[0915] At the time positive antibody titers are established, animals are sacrificed and B cell sources isolated. These sources include: the spleen, lymph nodes, bone marrow, and peripheral blood mononuclear cells (PBMCs). Single cell suspensions are generated, and the cell suspensions are washed to make them compatible for low temperature long term storage. The cells are then typically frozen.

[0916] To initiate the antibody identification process, a small fraction of the frozen cell suspensions are thawed, washed, and placed in tissue culture media. These suspensions are then mixed with a biotinylated form of the antigen that was used to generate the animal immune response, and antigen-specific cells are recovered using the Miltenyi magnetic bead cell selection methodology. Specific enrichment is conducted using streptavidin beads. The enriched population is recovered and progressed in the next phase of specific B cell isolation.

Example 2 Production of Clonal, Antigen-Specific B Cell-Containing Culture

[0917] Enriched B cells produced according to Example 1 are then plated at varying cell densities per well in a 96 well microtiter plate. Generally, this is at 50, 100, 250, or 500

cells per well with 10 plates per group. The media is supplemented with 4% activated rabbit T cell conditioned media along with 50K frozen irradiated EL4B feeder cells. These cultures are left undisturbed for 5-7 days at which time supernatant-containing secreted antibody is collected and evaluated for target properties in a separate assay setting. The remaining supernatant is left intact, and the plate is frozen at -70°C. Under these conditions, the culture process typically results in wells containing a mixed cell population that comprises a clonal population of antigen-specific B cells, i.e., a single well will only contain a single monoclonal antibody specific to the desired antigen.

Example 3 **Screening of Antibody Supernatants for Monoclonal Antibody of Desired Specificity and/or Functional Properties**

[0918] Antibody-containing supernatants derived from the well containing a clonal antigen-specific B cell population produced according to Example 2 are initially screened for antigen recognition using ELISA methods. This includes selective antigen immobilization (e.g., biotinylated antigen capture by streptavidin coated plate), non-specific antigen plate coating, or alternatively, through an antigen build-up strategy (e.g., selective antigen capture followed by binding partner addition to generate a heteromeric protein-antigen complex). Antigen-positive well supernatants are then optionally tested in a function-modifying assay that is strictly dependant on the ligand. One such example is an in vitro protein-protein interaction assay that recreates the natural interaction of the antigen ligand with recombinant receptor protein. Alternatively, a cell-based response that is ligand dependent and easily monitored (e.g., proliferation response) is utilized. Supernatant that displays significant antigen recognition and potency is deemed a positive well. Cells derived from the original positive well are then transitioned to the antibody recovery phase.

Example 4 **Recovery of Single, Antibody-Producing B Cell of Desired Antigen Specificity**

[0919] Cells are isolated from a well that contains a clonal population of antigen-specific B cells (produced according to Example 2 or 3), which secrete a single antibody

sequence. The isolated cells are then assayed to isolate a single, antibody-secreting cell. Dynal streptavidin beads are coated with biotinylated target antigen under buffered medium to prepare antigen-containing microbeads compatible with cell viability. Next antigen-loaded beads, antibody-producing cells from the positive well, and a fluorescein isothiocyanate (FITC)-labeled anti-host H&L IgG antibody (as noted, the host can be any mammalian host, e.g., rabbit, mouse, rat, etc.) are incubated together at 37°C. This mixture is then re-pipetted in aliquots onto a glass slide such that each aliquot has on average a single, antibody-producing B-cell. The antigen-specific, antibody-secreting cells are then detected through fluorescence microscopy. Secreted antibody is locally concentrated onto the adjacent beads due to the bound antigen and provides localization information based on the strong fluorescent signal. Antibody-secreting cells are identified via FITC detection of antibody-antigen complexes formed adjacent to the secreting cell. The single cell found in the center of this complex is then recovered using a micromanipulator. The cell is snap-frozen in an eppendorf PCR tube for storage at -80°C until antibody sequence recovery is initiated.

Example 5 **Isolation of Antibody Sequences From Antigen-Specific B Cell**

[0920] Antibody sequences are recovered using a combined RT-PCR based method from a single isolated B-cell produced according to Example 4 or an antigenic specific B cell isolated from the clonal B cell population obtained according to Example 2. Primers are designed to anneal in conserved and constant regions of the target immunoglobulin genes (heavy and light), such as rabbit immunoglobulin sequences, and a two-step nested PCR recovery step is used to obtain the antibody sequence. Amplicons from each well are analyzed for recovery and size integrity. The resulting fragments are then digested with AluI to fingerprint the sequence clonality. Identical sequences display a common fragmentation pattern in their electrophoretic analysis. Significantly, this common fragmentation pattern which proves cell clonality is generally observed even in the wells originally plated up to 1000 cells/well. The original heavy and light chain amplicon fragments are then restriction enzyme digested with HindIII and XhoI or HindIII and BsiWI to prepare the respective pieces of DNA for cloning. The resulting digestions are

then ligated into an expression vector and transformed into bacteria for plasmid propagation and production. Colonies are selected for sequence characterization.

Example 6 **Recombinant Production of Monoclonal Antibody of Desired Antigen Specificity and/or Functional Properties**

[0921] Correct full-length antibody sequences for each well containing a single monoclonal antibody is established and miniprep DNA is prepared using Qiagen solid-phase methodology. This DNA is then used to transfect mammalian cells to produce recombinant full-length antibody. Crude antibody product is tested for antigen recognition and functional properties to confirm the original characteristics are found in the recombinant antibody protein. Where appropriate, large-scale transient mammalian transfections are completed, and antibody is purified through Protein A affinity chromatography. Kd is assessed using standard methods (e.g., Biacore) as well as IC50 in a potency assay.

Example 7 **Preparation of Antibodies that Bind Human IL-6**

[0922] By using the antibody selection protocol described herein, one can generate an extensive panel of antibodies. The antibodies have high affinity towards IL-6 (single to double digit pM Kd) and demonstrate potent antagonism of IL-6 in multiple cell-based screening systems (T1165 and HepG2). Furthermore, the collection of antibodies display distinct modes of antagonism toward IL-6-driven processes.

[0923] Immunization Strategy

[0924] Rabbits were immunized with huIL-6 (R&R). Immunization consisted of a first subcutaneous (sc) injection of 100 μg in complete Freund's adjuvant (CFA) (Sigma) followed by two boosts, two weeks apart, of 50 μg each in incomplete Freund's adjuvant (IFA) (Sigma). Animals were bled on day 55, and serum titers were determined by ELISA (antigen recognition) and by non-radioactive proliferation assay (Promega) using the T1165 cell line.

[0925] Antibody Selection Titer Assessment

[0926] Antigen recognition was determined by coating Immulon 4 plates (Thermo) with 1 μg/ml of huIL-6 (50 μl/well) in phosphate buffered saline (PBS, Hyclone) overnight at 4°C. On the day of the assay, plates were washed 3 times with PBS /Tween 20 (PBST tablets, Calbiochem). Plates were then blocked with 200 μl/well of 0.5% fish skin gelatin (FSG, Sigma) in PBS for 30 minutes at 37°C. Blocking solution was removed, and plates were blotted. Serum samples were made (bleeds and pre-bleeds) at a starting dilution of 1:100 (all dilutions were made in FSG 50 μl/well) followed by 1:10 dilutions across the plate (column 12 was left blank for background control). Plates were incubated for 30 minutes at 37°C. Plates were washed 3 times with PBS/Tween 20. Goat anti-rabbit FC-HRP (Pierce) diluted 1:5000 was added to all wells (50 μl/well), and plates were incubated for 30 minutes at 37°C. Plates were washed as described above. 50 μl/well of TMB-Stable stop (Fitzgerald Industries) was added to plates, and color was allowed to develop, generally for 3 to 5 minutes. The development reaction was stopped with 50 μl/well 0.5 M HCl. Plates were read at 450 nm. Optical density (OD) versus dilution was plotted using Graph Pad Prizm software, and titers were determined.

[0927] Functional Titer Assessment

[0928] The functional activity of the samples was determined by a T1165 proliferation assay. T1165 cells were routinely maintained in modified RPMI medium (Hyclone) supplemented with Hepes, sodium pyruvate, sodium bicarbonate, L-glutamine, high glucose, penicillin/streptomycin, 10% heat inactivated fetal bovine serum (FBS) (all supplements from Hyclone), 2-mercaptoethanol (Sigma), and 10 ng/ml of huIL-6 (R&D). On the day of the assay, cell viability was determined by trypan blue (Invitrogen), and cells were seeded at a fixed density of 20,000 cells/well. Prior to seeding, cells were washed twice in the medium described above without human-IL-6 (by centrifuging at 13000 rpm for 5 minutes and discarding the supernatant). After the last wash, cells were resuspended in the same medium used for washing in a volume equivalent to 50 μl/well. Cells were set aside at room temperature.

[0929] In a round-bottom, 96-well plate (Costar), serum samples were added starting at 1:100, followed by a 1:10 dilution across the plate (columns 2 to 10) at 30 µl/well in replicates of 5 (rows B to F: dilution made in the medium described above with no huIL-6). Column 11 was medium only for IL-6 control. 30 µl/well of huIL-6 at 4x concentration of the final EC50 (concentration previously determined) were added to all wells (huIL-6 was diluted in the medium described above). Wells were incubated for 1 hour at 37°C to allow antibody binding to occur. After 1 hour, 50 µl/well of antibody-antigen (Ab-Ag) complex were transferred to a flat-bottom, 96-well plate (Costar) following the plate map format laid out in the round-bottom plate. On Row G, 50 µl/well of medium were added to all wells (columns 2 to 11) for background control. 50 µl/well of the cell suspension set aside were added to all wells (columns 2 to 11, rows B to G). On Columns 1 and 12 and on rows A and H, 200 µl/well of medium was added to prevent evaporation of test wells and to minimize edge effect. Plates were incubated for 72 h at 37°C in 4% CO2. At 72 h, 20 µl/well of CellTiter96 (Promega) reagents was added to all test wells per manufacturer protocol, and plates were incubated for 2 h at 37°C. At 2 h, plates were gently mixed on an orbital shaker to disperse cells and to allow homogeneity in the test wells. Plates were read at 490 nm wavelength. Optical density (OD) versus dilution was plotted using Graph Pad Prizm software, and functional titer was determined. A positive assay control plate was conducted as described above using MAB2061 (R&D Systems) at a starting concentration of 1 µg/ml (final concentration) followed by 1:3 dilutions across the plate.

[0930] Tissue Harvesting

[0931] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[0932] Spleen and lymph nodes were processed into a single cell suspension by disassociating the tissue and pushing through sterile wire mesh at 70 µm (Fisher) with a plunger of a 20 cc syringe. Cells were collected in the modified RPMI medium described above without huIL-6, but with low glucose. Cells were washed twice by centrifugation. After the last wash, cell density was determined by trypan blue. Cells were centrifuged at 1500 rpm for 10 minutes; the supernatant was discarded. Cells were resuspended in the

appropriate volume of 10% dimethyl sulfoxide (DMSO, Sigma) in FBS (Hyclone) and dispensed at 1 ml/vial. Vials were then stored at -70°C for 24 h prior to being placed in a liquid nitrogen (LN2) tank for long-term storage.

[0933] Peripheral blood mononuclear cells (PBMCs) were isolated by mixing whole blood with equal parts of the low glucose medium described above without FBS. 35 ml of the whole blood mixture was carefully layered onto 8 ml of Lympholyte Rabbit (Cedarlane) into a 45 ml conical tube (Corning) and centrifuged 30 minutes at 2500 rpm at room temperature without brakes. After centrifugation, the PBMC layers were carefully removed using a glass Pasteur pipette (VWR), combined, and placed into a clean 50 ml vial. Cells were washed twice with the modified medium described above by centrifugation at 1500 rpm for 10 minutes at room temperature, and cell density was determined by trypan blue staining. After the last wash, cells were resuspended in an appropriate volume of 10% DMSO/FBS medium and frozen as described above.

[0934] B cell culture

[0935] On the day of setting up B cell culture, PBMC, splenocyte, or lymph node vials were thawed for use. Vials were removed from LN2 tank and placed in a 37°C water bath until thawed. Contents of vials were transferred into 15 ml conical centrifuge tube (Corning) and 10 ml of modified RPMI described above was slowly added to the tube. Cells were centrifuged for 5 minutes at 1.5K rpm, and the supernatant was discarded. Cells were resuspended in 10 ml of fresh media. Cell density and viability was determined by trypan blue. Cells were washed again and resuspended at 1E07 cells/80 ul medium. Biotinylated huIL-6 (B huIL-6) was added to the cell suspension at the final concentration of 3 ug/mL and incubated for 30 minutes at 4oC. Unbound B huIL-6 was removed with two 10 ml washes of phosphate-buffered (PBF):Ca/Mg free PBS (Hyclone), 2 mM ethylenediamine tetraacetic acid (EDTA), 0.5% bovine serum albumin (BSA) (Sigma-biotin free). After the second wash, cells were resuspended at 1E07 cells/80 µl PBF. 20 µl of MACS® streptavidin beads (Milteni)/10E7 cells were added to the cell suspension. Cells were incubated at 4°C for 15 minutes. Cells were washed once with 2 ml of PBF/10E7 cells. After washing, the cells were resuspended at 1E08 cells/500 µl of PBF

and set aside. A MACS® MS column (Milteni) was pre-rinsed with 500 ml of PBF on a magnetic stand (Milteni). Cell suspension was applied to the column through a pre-filter, and unbound fraction was collected. The column was washed with 1.5 ml of PBF buffer. The column was removed from the magnet stand and placed onto a clean, sterile 5 ml Polypropylene Falcon tube. 1 ml of PBF buffer was added to the top of the column, and positive selected cells were collected. The yield and viability of positive and negative cell fraction was determined by trypan blue staining. Positive selection yielded an average of 1% of the starting cell concentration.

[0936] A pilot cell screen was established to provide information on seeding levels for the culture. Three 10-plate groups (a total of 30 plates) were seeded at 50, 100, and 200 enriched B cells/well. In addition, each well contained 50K cells/well of irradiated EL-4.B5 cells (5,000 Rads) and an appropriate level of T cell supernatant (ranging from 1-5% depending on preparation) in high glucose modified RPMI medium at a final volume of 250 µl/well. Cultures were incubated for 5 to 7 days at 37°C in 4% CO2 .

[0937] Identification of Selective Antibody Secreting B Cells

[0938] Cultures were tested for antigen recognition and functional activity between days 5 and 7.

[0939] Antigen Recognition Screening

[0940] The ELISA format used is as described above except 50 µl of supernatant from the B cell cultures (BCC) wells (all 30 plates) was used as the source of the antibody. The conditioned medium was transferred to antigen-coated plates. After positive wells were identified, the supernatant was removed and transferred to a 96-well master plate(s). The original culture plates were then frozen by removing all the supernatant except 40 µl/well and adding 60 µl/well of 16% DMSO in FBS. Plates were wrapped in paper towels to slow freezing and placed at -70°C.

[0941] Functional Activity Screening

[0942] Master plates were then screened for functional activity in the T1165 proliferation assay as described before, except row B was media only for background control, row C was media + IL-6 for positive proliferation control, and rows D-G and columns 2-11 were the wells from the BCC (50 µl/well, single points). 40 µl of IL-6 was added to all wells except the media row at 2.5 times the EC50 concentration determined for the assay. After 1 h incubation, the Ab/Ag complex was transferred to a tissue culture (TC) treated, 96-well, flat-bottom plate. 20 µl of cell suspension in modified RPMI medium without huIL-6 (T1165 at 20,000 cells/well) was added to all wells (100 µl final volume per well). Background was subtracted, and observed OD values were transformed into % of inhibition.

[0943] B cell recovery

[0944] Plates containing wells of interest were removed from -70°C, and the cells from each well were recovered with 5-200 µl washes of medium/well. The washes were pooled in a 1.5 ml sterile centrifuge tube, and cells were pelleted for 2 minutes at 1500 rpm.

[0945] The tube was inverted, the spin repeated, and the supernatant carefully removed. Cells were resuspended in 100 µl/tube of medium. 100 µl biotinylated IL-6 coated streptavidin M280 dynabeads (Invitrogen) and 16 µl of goat anti-rabbit H&L IgG-FITC diluted 1:100 in medium was added to the cell suspension.

[0946] 20 µl of cell/beads/FITC suspension was removed, and 5 µl droplets were prepared on a glass slide (Corning) previously treated with Sigmacote (Sigma), 35 to 40 droplets/slide. An impermeable barrier of parafin oil (JT Baker) was added to submerge the droplets, and the slide was incubated for 90 minutes at 37°C, 4% CO2 in the dark.

[0947] Specific B cells that produce antibody can be identified by the fluorescent ring around them due to antibody secretion, recognition of the bead-associated biotinylated antigen, and subsequent detection by the fluorescent-IgG detection reagent. Once a cell of interest was identified, the cell in the center of the fluorescent ring was recovered via a micromanipulator (Eppendorf). The single cell synthesizing and exporting the antibody was transferred into a 250 µl microcentrifuge tube and placed in dry ice. After recovering all cells of interest, these were transferred to -70°C for long-term storage.

Example 8 **Yeast Cell Expression**

[0948] *Antibody genes:* Genes were cloned and constructed that directed the synthesis of a chimeric humanized rabbit monoclonal antibody.

[0949] *Expression vector:* The vector contains the following functional components: 1) a mutant ColE1 origin of replication, which facilitates the replication of the plasmid vector in cells of the bacterium *Escherichia coli*; 2) a bacterial *Sh ble* gene, which confers resistance to the antibiotic Zeocin and serves as the selectable marker for transformations of both *E. coli* and *P. pastoris*; 3) an expression cassette composed of the glyceraldehyde dehydrogenase gene (*GAP* gene) promoter, fused to sequences encoding the *Saccharomyces cerevisiae* alpha mating factor pre pro secretion leader sequence, foilowed by sequences encoding a *P. pastoris* transcriptional termination signal from the *P. pastoris* alcohol oxidase I gene (*AOX1*). The Zeocin resistance marker gene provides a means of enrichment for strains that contain multiple integrated copies of an expression vector in a strain by selecting for transformants that are resistant to higher levels of Zeocin.

[0950] *P. pastoris* strains: *P. pastoris* strains *met1*, *lys3*, *ura3* and *ade1* may be used. Although any two complementing sets of auxotrophic strains could be used for the construction and maintenance of diploid strains, these two strains are especially suited for this method for two reasons. First, they grow more slowly than diploid strains that are the result of their mating or fusion. Thus, if a small number of haploid *ade1* or *ura3* cells remain present in a culture or arise through meiosis or other mechanism, the diploid strain should outgrow them in culture.

[0951] The second is that it is easy to monitor the sexual state of these strains since diploid Ade+ colonies arising from their mating are a normal white or cream color, whereas cells of any strains that are haploid *ade1* mutants will form a colony with a distinct pink color. In addition, any strains that are haploid *ura3* mutants are resistant to the drug 5-fluoro-orotic acid (FOA) and can be sensitively identified by plating samples of a culture on minimal medium + uracil plates with FOA. On these plates, only uracil-requiring *ura3* mutant (presumably haploid) strains can grow and form colonies. Thus, with haploid

parent strains marked with *ade1* and *ura3*, one can readily monitor the sexual state of the resulting antibody-producing diploid strains (haploid versus diploid).

[0952] Methods

[0953] *Construction of pGAPZ-alpha expression vectors for transcription of light and heavy chain antibody genes.* The humanized light and heavy chain fragments were cloned into the pGAPZ expression vectors through a PCR directed process. The recovered humanized constructs were subjected to amplification under standard KOD polymerase (Novagen) kit conditions ((1) 94° C, 2 minutes; (2) 94° C, 30 seconds (3) 55° C, 30 seconds; (4) 72° C, 30 seconds-cycling through steps 2-4 for 35 times; (5) 72° C 2 minutes) employing the following primers (1) light chain forward AGCGCTTATTCCGCTATCCAGATGACCCAGTC-the AfeI site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable light chain (not underlined); the reverse CGTACGTTTGATTTCCACCTTG.

[0954] Variable light chain reverse primer. BsiWI site is underlined, followed by the reverse complement for the 3' end of the variable light chain. Upon restriction enzyme digest with AfeI and BsiWI this enable insertion in-frame with the pGAPZ vector using the human HAS leader sequence in frame with the human kapp light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGCGCTTATTCCGAGGTGCAGCTGGTGGAGTC. The AfeI site is single underlined. The end of the HSA signal sequence is double underlined, followed by the sequence for the mature variable heavy chain (not underlined). The reverse heavy chain primer is CTCGAGACGGTGACGAGGGT. The XhoI site is underlined, followed by the reverse complement for the 3' end of the variable heavy chain. This enables cloning of the heavy chain in-frame with IgG-γ1 CH1-CH2-CH3 region previous inserted within pGAPZ using a comparable directional cloning strategy.

[0955] *Transformation of expression vectors into haploid ade1 ura3, met1 and lys3 host strains of P. pastoris.* All methods used for transformation of haploid *P. pastoris* strains and genetic manipulation of the *P. pastoris* sexual cycle are as described in Higgins, D. R.,

and Cregg, J. M., Eds. 1998. Pichia *Protocols. Methods in Molecular Biology.* Humana Press, Totowa, NJ.

[0956] Prior to transformation, each expression vector is linearized within the *GAP* promoter sequences with AvrII to direct the integration of the vectors into the *GAP* promoter locus of the *P. pastoris* genome. Samples of each vector are then individually transformed into electrocompetent cultures of the *ade1*, *ura3, met1* and *lys3* strains by electroporation and successful transformants are selected on YPD Zeocin plates by their resistance to this antibiotic. Resulting colonies are selected, streaked for single colonies on YPD Zeocin plates and then examined for the presence of the antibody gene insert by a PCR assay on genomic DNA extracted from each strain for the proper antibody gene insert and/or by the ability of each strain to synthesize an antibody chain by a colony lift/immunoblot method (Wung *et al.* Biotechniques 21 808-812 (1996). Haploid *ade1, met1* and *lys3* strains expressing one of the three heavy chain constructs are collected for diploid constructions along with haploid *ura3* strain expressing light chain gene. The haploid expressing heavy chain genes are mated with the appropriate light chain haploid *ura3* to generate diploid secreting protein.

[0957] Mating of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. To mate P. pastoris haploid strains, each ade1 (or met1 or lys3) heavy chain producing strain to be crossed is streaked across a rich YPD plate and the ura3 light chain producing strain is streaked across a second YPD plate (~10 streaks per plate). After one or two days incubation at 30°C, cells from one plate containing heavy chain strains and one plate containing ura3 light chain strains are transferred to a sterile velvet cloth on a replica-plating block in a cross hatched pattern so that each heavy chain strain contain a patch of cells mixed with each light chain strain. The cross-streaked replica plated cells are then transferred to a mating plate and incubated at 25°C to stimulate the initiation of mating between strains. After two days, the cells on the mating plates are transferred again to a sterile velvet on a replica-plating block and then transferred to minimal medium plates. These plates are incubated at 30°C for three days to allow for the selective growth of colonies of prototrophic diploid strains. Colonies that arose are picked and streaked onto a second

minimal medium plate to single colony isolate and purify each diploid strain. The resulting diploid cell lines are then examined for antibody production.

[0958] Putative diploid strains are tested to demonstrate that they are diploid and contain both expression vectors for antibody production. For diploidy, samples of a strain are spread on mating plates to stimulate them to go through meiosis and form spores. Haploid spore products are collected and tested for phenotype. If a significant percentage of the resulting spore products are single or double auxotrophs it may be concluded that the original strain must have been diploid. Diploid strains are examined for the presence of both antibody genes by extracting genomic DNA from each and utilizing this DNA in PCR reactions specific for each gene.

[0959] Fusion of haploid strains synthesizing a single antibody chain and selection of diploid derivatives synthesizing tetrameric functional antibodies. As an alternative to the mating procedure described above, individual cultures of single-chain antibody producing haploid ade1 and ura3 strains are spheroplasted and their resulting spheroplasts fused using polyethylene glycol/$CaCl_2$. The fused haploid strains are then embedded in agar containing 1 M sorbitol and minimal medium to allow diploid strains to regenerate their cell wall and grow into visible colonies. Resulting colonies are picked from the agar, streaked onto a minimal medium plate, and the plates are incubated for two days at 30°C to generate colonies from single cells of diploid cell lines. The resulting putative diploid cell lines are then examined for diploidy and antibody production as described above.

[0960] Purification and analysis of antibodies. A diploid strain for the production of full length antibody is derived through the mating of met1 light chain and lys3 heavy chain using the methods described above. Culture media from shake-flask or fermenter cultures of diploid P. pastoris expression strains are collected and examined for the presence of antibody protein via SDS-PAGE and immunoblotting using antibodies directed against heavy and light chains of human IgG, or specifically against the heavy chain of IgG.

[0961] To purify the yeast secreted antibodies, clarified media from antibody producing cultures are passed through a protein A column and after washing with 20 mM sodium phosphate, pH 7.0, binding buffer, protein A bound protein is eluted using 0.1 M glycine HCl buffer, pH 3.0. Fractions containing the most total protein are examined by Coomasie

blue strained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.

[0962] *Assay for antibody activity.* The recombinant yeast-derived humanized antibody is evaluated for functional activity through the IL-6 driven T1165 cell proliferation assay and IL-6 stimulated HepG2 haptoglobin assay described above.

Example 9 **Acute Phase Response Neutralization by Intravenous Administration of Anti-IL-6 Antibody Ab1.**

[0963] Human IL-6 can provoke an acute phase response in rats, and one of the major acute phase proteins that is stimulated in the rat is α-2 macroglobulin (A2M). A study was designed to assess the dose of antibody Ab1 required to ablate the A2M response to a single s.c. injection of 100 μg of human IL-6 given one hour after different doses (0.03, 0.1, 0.3, 1, and 3 mg/kg) of antibody Ab1 administered intravenously (n=10 rats/dose level) or polyclonal human IgG1 as the control (n=10 rats). Plasma was recovered and the A2M was quantitated via a commercial sandwich ELISA kit (ICL Inc., Newberg OR; cat. no.- E-25A2M). The endpoint was the difference in the plasma concentration of A2M at the 24 hour time point (post-Ab1). The results are presented in Figure 4.

[0964] The ID50 for antibody Ab1 was 0.1 mg/kg with complete suppression of the A2M response at the 0.3 mg/kg. This firmly establishes *in vivo* neutralization of human IL-6 can be accomplished by antibody Ab1.

Example 10 **RXF393 Cachexia Model Study 1.**

[0965] Introduction

[0966] The human renal cell cancer cell line, RXF393 produces profound weight loss when transplanted into athymic nude mice. Weight loss begins around day 15 after transplantation with 80% of all animals losing at least 30% of their total body weight by day 18 - 20 after transplantation. RXF393 secretes human IL-6 and the plasma concentration of human IL-6 in these animals is very high at around 10ng/ml. Human IL-6

can bind murine soluble IL-6 receptor and activate IL-6 responses in the mouse. Human IL-6 is approximately 10 times less potent than murine IL-6 at activating IL-6 responses in the mouse. The objectives of this study were to determine the effect of antibody Ab1, on survival, body weight, serum amyloid A protein, and hematology parameters in athymic nude mice transplanted with the human renal cell cancer cell line, RXF393.

[0967] Methods

[0968] Eighty, 6 week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40mg) subcutaneously in the right flank. Animals were then divided into eight groups of ten mice. Three groups were given either antibody Ab1 at 3mg/kg, 10mg/kg, or 30mg/kg intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation (progression groups). Another three groups were given either antibody Ab1 at 3mg/kg, or 10mg/kg, or 30mg/kg intravenously weekly on day 8, day 15 and day 22 after transplantation (regression groups). Finally, one control group was given polyclonal human IgG 30mg/kg and a second control group was given phosphate buffered saline intravenously weekly on day 1, day 8, day 15 and day 22 after transplantation.

[0969] Animals were euthanized at either day 28, when the tumor reached 4,000 mm^3 or if they became debilitated (>30% loss of body weight). Animals were weighed on days 1, 6 and then daily from days 9 to 28 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: (Body Weight – Tumor Weight)/Baseline Body Weight x 100. Tumor weight was measured on days 1, 6, 9, 12, 15, 18, 22, 25 and 28 after transplantation. Blood was taken under anesthesia from five mice in each group on days 5 and 13 and all ten mice in each group when euthanized (day 28 in most cases). Blood was analyzed for hematology and serum amyloid A protein (SAA) concentration. An additional group of 10 non-tumor bearing 6 week old, athymic nude male mice had blood samples taken for hematology and SAA concentration estimation to act as a baseline set of values.

[0970] Results - Survival

[0971] No animals were euthanized or died in any of the antibody Ab1 groups prior to the study termination date of day 28. In the two control groups, 15 animals (7/9 in the polyclonal human IgG group and 8/10 in the phosphate buffered saline group) were found dead or were euthanized because they were very debilitated (>30% loss of body weight). Median survival time in both control groups was 20 days.

[0972] The survival curves for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) groups are presented in Figure 5.

[0973] The survival curves for the two control groups and the anibody Ab1 regression (dosed from day 8 of the study) groups are presented in Figure 6.

[0974] There was a statistically significant difference between the survival curves for the polyclonal human IgG (p=0.0038) and phosphate buffered saline (p=0.0003) control groups and the survival curve for the six antibody Ab1 groups. There was no statistically significant difference between the two control groups (p=0.97).

[0975] Results – Plasma Serum Amyloid A

[0976] The mean (± SEM) plasma serum amyloid A concentration versus time for the two control groups and the antibody Ab1 progression (dosed from day 1 of the study) and regression (dosed from day 8 of the study) groups are presented in Table 1.

Table 1: Mean Plasma SAA - antibody Ab1, all groups versus control groups

	Mean Plasma SAA±SEM Day 5 (µg/ml)	Mean Plasma SAA±SEM Day 13 (µg/ml)	Mean Plasma SAA±SEM Terminal Bleed (µg/ml)
Polyclonal IgG iv weekly from day 1	675 ± 240 (n=5)	3198 ± 628 (n=4)	13371 ± 2413 (n=4)
PBS iv weekly from day 1	355 ± 207 (n=5)	4844 ± 1126 (n=5)	15826 ± 802 (n=3)
Ab1 30mg/kg iv weekly from day 1	246 ± 100 (n=5)	2979 ± 170 (n=5)	841 ± 469 (n=10)
Ab1 10mg/kg iv weekly from day 1	3629 ± 624 (n=5)	3096 ± 690 (n=5)	996 ± 348 (n=10)
Ab1 3mg/kg iv weekly from day 1	106 ± 9 (n=5)	1623 ± 595 (n=4)	435 ± 70 (n=9)

Ab1 30mg/kg iv weekly from day 8	375 ± 177 (n=5)	1492 ± 418 (n=4)	498 ± 83 (n=9)
Ab1 10mg/kg iv weekly from day 8	487 ± 170 (n=5)	1403 ± 187 (n=5)	396 ± 58 (n=10)
Ab1 3mg/kg iv weekly from day 8	1255 ± 516 (n=5)	466 ± 157 (n=5)	685 ± 350 (n=5)

[0977] SAA is up-regulated via the stimulation of hIL-6 and this response is directly correlated with circulating levels of hIL-6 derived from the implanted tumor. The surrogate marker provides an indirect readout for active hIL-6. Thus in the two treatment groups described above there are significantly decreased levels of SAA due to the neutralization of tumor-derived hIL-6. This further supports the contention that antibody Ab1 displays *in vivo* efficacy.

Example 11 **RXF393 Cachexia Model Study 2.**

[0978] Introduction

[0979] A second study was performed in the RXF-393 cachexia model where treatment with antibody Ab1 was started at a later stage (days 10 and 13 post-transplantation) and with a more prolonged treatment phase (out to 49 days post transplantation). The dosing interval with antibody Ab1 was shortened to 3 days from 7 and also daily food consumption was measured. There was also an attempt to standardize the tumor sizes at the time of initiating dosing with antibody Ab1.

[0980] Methods

[0981] Eighty, 6 week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40mg) subcutaneously in the right flank. 20 mice were selected whose tumors had reached between 270 – 320mg in size and divided into two groups. One group received antibody Ab1 at 10mg/kg i.v. every three days and the other group received polyclonal human IgG 10mg/kg every 3 days from that time-point (day 10 after transplantation). Another 20 mice were selected when their tumor size had reached 400 – 527mg in size and divided into two groups. One group received antibody Ab1 at 10mg/kg

i.v. every three days and the other group received polyclonal human IgG 10mg/kg every 3 days from that time-point (day 13 after transplantation). The remaining 40 mice took no further part in the study and were euthanized at either day 49, when the tumor reached 4,000 mm^3 or if they became very debilitated (>30% loss of body weight).

[0982] Animals were weighed every 3-4 days from day 1 to day 49 after transplantation. Mean Percent Body Weight (MPBW) was used as the primary parameter to monitor weight loss during the study. It was calculated as follows: ((Body Weight – Tumor Weight)/Baseline Body Weight) x 100. Tumor weight was measured every 3-4 days from day 5 to day 49 after transplantation. Food consumption was measured (amount consumed in 24 hours by weight (g) by each treatment group) every day from day 10 for the 270-320mg tumor groups and day 13 for the 400-527mg tumor groups.

[0983] Results -survival

[0984] The survival curves for antibody Ab1 at 10mg/kg i.v. every three days (270-320mg tumor size) and for the polyclonal human IgG 10mg/kg i.v. every three days (270-320mg tumor size) are presented in Figure 7.

[0985] Median survival for the antibody Ab1 at 10mg/kg i.v. every three days (270-320mg tumor size) was 46 days and for the polyclonal human IgG at 10mg/kg i.v. every three days (270-320mg tumor size) was 32.5 days (p=0.0071).

[0986] The survival curves for the antibody Ab1 at 10mg/kg i.v. every three days (400-527mg tumor size) and for the polyclonal human IgG at 10mg/kg i.v. every three days (400-527mg tumor size) are presented in Figure 8. Median survival for the antibody Ab1 at 10mg/kg i.v. every three days (400-527mg tumor size) was 46.5 days and for the polyclonal human IgG at 10mg/kg i.v. every three days (400-527mg tumor size) was 27 days (p=0.0481).

Example 12 **Multi-dose Pharmacokinetic Evaluation of Antibody Ab1 in Non-human Primates.**

[0987] Antibody Ab1 was dosed in a single bolus infusion to a single male and single female cynomologus monkey in phosphate buffered saline. Plasma samples were removed at fixed time intervals and the level of antibody Ab1 was quantitated through of the use of an antigen capture ELISA assay. Biotinylated IL-6 (50 µl of 3 µg/mL) was captured on Streptavidin coated 96 well microtiter plates. The plates were washed and blocked with 0.5% Fish skin gelatin. Appropriately diluted plasma samples were added and incubated for 1 hour at room temperature. The supernatants removed and an anti-hFc-HRP conjugated secondary antibody applied and left at room temperature.

[0988] The plates were then aspirated and TMB added to visualize the amount of antibody. The specific levels were then determined through the use of a standard curve. A second dose of antibody Ab1 was administered at day 35 to the same two cynomologus monkeys and the experiment replicated using an identical sampling plan. The resulting concentrations are then plot vs. time as show in Figure 9.

[0989] This humanized full length aglycosylated antibody expressed and purified *Pichia pastoris* displays comparable characteristics to mammalian expressed protein. In addition, multiple doses of this product display reproducible half-lives inferring that this production platform does not generate products that display enhanced immunogenicity.

Example 13 Octet Mechanistic Characterization of Antibody Proteins.

[0990] IL-6 signaling is dependent upon interactions between IL-6 and two receptors, IL-6R1 (CD126) and GP130 (IL-6 signal transducer). To determine the antibody mechanism of action, mechanistic studies were performed using bio-layer interferometry with an Octet QK instrument (ForteBio; Menlo Park, CA). Studies were performed in two different configurations. In the first orientation, biotinylated IL-6 (R&D systems part number 206-IL-001MG/CF, biotinylated using Pierce EZ-link sulfo-NHS-LC-LC-biotin product number 21338 according to manufacturer's protocols) was initially bound to a streptavidin coated biosensor (ForteBio part number 18-5006). Binding is monitored as an increase in signal.

[0991] The IL-6 bound to the sensor was then incubated either with the antibody in question or diluent solution alone. The sensor was then incubated with soluble IL-6R1 (R&D systems product number 227-SR-025/CF) molecule. If the IL-6R1 molecule failed to bind, the antibody was deemed to block IL-6/IL-6R1 interactions. These complexes were incubated with GP130 (R&D systems 228-GP-010/CF) in the presence of IL-6R1 for stability purposes. If GP130 did not bind, it was concluded that the antibody blocked GP130 interactions with IL-6.

[0992] In the second orientation, the antibody was bound to a biosensor coated with an anti-human IgG1 Fc-specific reagent (ForteBio part number 18-5001). The IL-6 was bound to the immobilized antibody and the sensor was incubated with IL-6R1. If the IL-6R1 did not interact with the IL-6, then it was concluded that the IL-6 binding antibody blocked IL-6/IL-6R1 interactions. In those situations where antibody/IL-6/IL-6R1 was observed, the complex was incubated with GP130 in the presence of IL-6R1. If GP130 did not interact, then it was concluded that the antibody blocked IL-6/GP130 interactions. All studies were performed in a 200 μL final volume, at 30C and 1000 rpms. For these studies, all proteins were diluted using ForteBio's sample diluent buffer (part number 18-5028).

[0993] Results are presented in Figures 10A-E and 11.

Example 14 **Peptide Mapping.**

[0994] In order to determine the epitope recognized by Ab1 on human IL-6, the antibody was employed in a western-blot based assay. The form of human IL-6 utilized in this example had a sequence of 183 amino acids in length (shown below). A 57-member library of overlapping 15 amino acid peptides encompassing this sequence was commercially synthesized and covalently bound to a PepSpots nitrocellulose membrane (JPT Peptide technologies, Berlin, Germany). The sequences of the overlapping 15 amino acid peptides is shown in Figure 12. Blots were prepared and probed according to the manufacturer's recommendations.

[0995] Briefly, blots were pre-wet in methanol, rinsed in PBS, and blocked for over 2 hours in 10% non-fat milk in PBS/0.05% Tween (Blocking Solution). The Ab1 antibody

was used at 1 mg/ml final dilution, and the HRP-conjugated Mouse Anti-Human-Kappa secondary antibody (Southern BioTech #9220-05) was used at a 1:5000 dilution. Antibody dilutions/incubations were performed in blocking solution. Blots were developed using Amersham ECL advance reagents (GE# RPN2135) and chemiluminescent signal documented using a CCD camera (AlphaInnotec). The results of the blots is shown in Figures 13 and 14.

The sequence of the form of human IL-6 utilized to generate peptide library is set forth: VPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMCESSKEALA ENNLNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARA VQMSTKVLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSF KEFLQSSLRALRQM (SEQ ID NO: 1).

CLAIMS

1.) An anti-human IL-6 antibody or antibody fragment which specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571, with the proviso that said antibody does not comprise VL CDRs that are identical variable light CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:4, 5 and 6 respectively, or VH CDRs that are identical to the variable heavy CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:7, 8 or 120 and 9 respectively.

2.) The anti-human IL-6 antibody or fragment of claim 1 which specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as as an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3.

3.) The anti-human IL-6 antibody or fragment of claim 1 which specifically binds to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or fragment thereof as an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122

and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571, with the proviso that said antibody does not comprise the variable light CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:4, 5 and 6 respectively, or the variable heavy chain CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:7, 8 or 120 and 9 respectively.

4.) The anti-human IL-6 antibody or fragment of claim 3 which specifically binds to the same linear or conformational epitope(s) on an intact human IL-6 polypeptide or a fragment thereof as an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3.

5.) The anti-human IL-6 antibody of claim 4 wherein the epitope on an intact IL-6 polypeptide or fragment specifically bound by said antibody when ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human IL-6 polypeptide includes one or more residues comprised in IL-6 fragments selected from those respectively encompassing amino acid residues 37-51, amino acid residues 70-84, amino acid residues 169-183, amino acid residues 31-45 and/or amino acid residues 58-72.

6.) The anti-human IL-6 antibody of claim 1 which comprises at least 2 complementarity determining regions (CDRs) which are identical to those contained in an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442

and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571, with the proviso that said antibody does not comprise the variable light CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:4, 5 and 6 respectively, or the variable heavy chain CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:7, 8 or 120 and 9 respectively.

7.) The anti-human IL-6 antibody of claim 6 which comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3.

8.) The anti-human IL-6 antibody of claim 6 wherein all of the CDRs are identical to the CDRs contained in an anti-human IL-6 antibody selected from the group consisting of anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571, with the proviso that said antibody does not comprise the variable light CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:4, 5 and 6 respectively, or the variable heavy chain CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:7, 8 or 120 and 9 respectively.

9.) The anti-human IL-6 antibody or fragment of claim 1 which is aglycosylated.

10.) The anti-human IL-6 antibody of claim 1 which contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

11.) The anti-human Il-6 antibody or fragment of claim 1 which is a human, humanized, single chain or chimeric antibody.

12.) The anti-human IL-6 antibody of claim 10 or 11 which is a humanized antibody derived from a rabbit (parent) anti-human IL-6 antibody.

13.) The anti-human IL-6 antibody or fragment of claim 1 which specifically binds to IL-6 expressing human cells and/or to circulating soluble IL-6 molecules in vivo.

14.) The anti-human IL-6 antibody or fragment of claim 15 which specifically binds to IL-6 expressed on or by human cells in a patient with a disease associated with cells that express IL-6.

15.) The anti-human IL-6 antibody or fragment of claim 14 wherein the disease is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS).

16.) The anti-human IL-6 antibody or fragment of claim 14 wherein the disease is selected from a cancer, inflammatory disorder, viral disorder, or autoimmune disorder.

17.) The anti-human IL-6 antibody or fragment of claim 16 wherein the disease is selected from arthritis, cachexia, and wasting syndrome.

18.) The anti-human IL-6 antibody or fragment of claim 1 which is directly or indirectly attached to a detectable label or therapeutic agent.

19.) A nucleic acid sequence or nucleic acid sequences which result in the expression of an anti-human IL-6 antibody or antibody fragment comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID

NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or one containing the same CDRs as any of the foregoing antibodies.

20.) The nucleic acid sequence or sequences of claim 19 which are comprised of yeast or human preferred codons.

21.) A vector comprising a nucleic acid sequence or sequences according to claim 19.

22.) The vector of claim 21 which is a plasmid or recombinant viral vector.

23.) A recombinant cell which expresses an antibody or antibody fragment comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or one containing the same CDRs as any of the foregoing antibodies.

24.) The cell of claim 23 which is selected from a mammalian, yeast, bacterial, and insect cell.

25.) The cell of claim 24 which is a yeast cell.

26.) The cell of claim 25 which is a diploidal yeast cell.

27.) The yeast cell of claim 28 which is a Pichia yeast.

28.) A method of treatment comprising administering to a patient with a disease or condition associated with IL-6 expressing cells a therapeutically effective amount of at least one anti-human IL-6 antibody or fragment comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or an antibody containing the same CDRs as any of the foregoing antibodies.

29.) The method of claim 28 wherein the disease is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic

illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS).

30.) The method of claim 28 wherein the disease or condition is a cancer, autoimmune disease, or inflammatory condition.

31.) The method of claim 28 wherein the treatment further includes the administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy.

32.) The method of claim 28 which is used to treat a side effect of cancer or viral infection.

33.) The method of claim 32 wherein the side effect is fatigue or weight loss (wasting syndrome).

34.) A method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of at least one anti-human IL-6 antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or one compriising the same CDRs as any of the foregoing antibodies.

35.) The method of claim 34 wherein said administration further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at IL-6 expressing disease sites.

36.) The method of claim 34 which is used to detect IL-6 expressing tumors or metastases.

37.) The method of claim 34 which is used to detect the presence of sites of inflammation associated with IL-6 expressing cells.

38.) The method of claim 36 wherein the results are used to facilitate design of an appropriate therapeutic regimen.

39.) The method of claim 38 wherein said therapeutic regimen includes radiotherapy, chemotherapy or a combination thereof.

40.) An isolated anti-IL-6 antibody comprising a VH polypeptide sequence selected from the group consisting of 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571; and further comprising a VL polypeptide sequence selected from the group consisting of: 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570 or a variant thereof wherein one or more of the framework residues (FR residues) in said VH or VL polypeptide has been substituted with another amino acid residue resulting in an anti-IL-6 antibody that specifically binds IL-6.

41) The isolated antibody of claim 40 wherein one or more of said FR residues are substituted with an amino acid present at the corresponding site in a parent rabbit anti-IL-6 antibody from which the complementarity determining regions (CDRs) contained in said VH or VL polypeptides have been derived or by a conservative amino acid substitution.

42.) The antibody of claim 40, wherein said antibody is humanized.

43.) The antibody of claim 40, wherein said antibody is chimeric.

44.) The antibody of claim 42 or 43, wherein said chimeric antibody comprises a human Fc.

45.) The antibody of claim 46, wherein said human Fc is derived from IgG1, IgG2, IgG3, or IgG4.

46.) The antibody of any one of claims 40-45 wherein said antibody binds at least one of soluble Il-6, cell-surface expressed IL-6, IL-6/IL-6R, IL-6/IL-6R/gp130 complexes and or multimers thereof and/or antagonizes the biological effects of one or more of the foregoing.

47.) An isolated anti-IL-6 antibody comprising a polypeptide sequence having at least 90% or greater homology to any one of the polypeptide sequences of claim 40.

48.) The antibody of claim 46, wherein said antibody binds to IL-6 with a dissociation constant (K_D) of less than or equal to $5x10^{-7}$, 10^{-7}, $5x10^{-8}$, 10^{-8}, $5x10^{9}$, 10^{-9}, $5x10^{-10}$, 10^{-10}, 5x 10-^{11}, 10-^{11}, 5x 10^{-12}, 10^{-12}, $5x10^{-13}$, or 10^{-13}.

49.) The antibody of claim 48, wherein said antibody binds to IL-6 with a dissociation constant (K_D) of less than or equal to $5X\ 10^{-10}$.

50.) The antibody of claim 46, wherein said antibody binds to IL-6 with an off-rate (K_{off}) of less than or equal to $10^{-4}S^{-1}$, $5x\ 10^{-5}\ S^{-1}$, $5x\ 10^{-5}\ S^{-1}$, $5\ X\ 10^{-6}\ S^{-1}$, $10^{-6}\ S^{-1}$, $5x10^{-7}\ S^{-1}$, or $10^{-7}\ S^{-1}$.

51.) The antibody of claim 40, wherein the VH or VL polypeptides contained in said antibody originated from one or more rabbit B cell populations.

52.) The antibody of any one of claims 40-51, wherein the antibody has binding specificity for primate homologs of human IL-6.

53.) The antibody of claim 52, wherein the primate is Macaca fascicularis.

54.) The antibody of any one of claims 40-53, wherein said antibody does not have binding specificity for IL-6R or gp130.

55.) The antibody of any one of claims 40-53, wherein said antibody inhibits the association of Il-6 with IL-6R, and/or the production of IL-6/IL-6R/gp130 complexes and/or the production of IL-6/IL-6R/gp130 multimers.

56.) The antibody of claim 54, wherein the IL-6R is soluble IL-6R (sIL-6R).

57.) The antibody of claim 55, wherein the IL-6R is soluble IL-6R (sIL-6R).

58.) A fragment of the antibody of any one of claims 40-57, wherein said fragment is selected from an Fab fragment, an Fab' fragment, or an F(ab')2 fragment.

59.) The antibody of any one of claims 40-57, wherein said antibody further comprises an effector moiety.

60.) The antibody of claim 59, wherein the effector moiety is a detectable moiety or a functional moiety.

61.) The antibody of claim 60, wherein said detectable moiety is a fluorescent dye, an enzyme, a substrate, a bioluminescent material, a radioactive material, or a chemiluminescent material.

62.) The antibody of claim 60, wherein said functional moiety is streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, or a radioactive material.

63.) A method of ameliorating or reducing symptoms of a disease or disorder associated with IL-6, comprising administering to a patient exhibiting symptoms of a disease or disorder associated with IL-6 a therapeutically effective amount of the antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID

NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: 122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or one containing the identical CDRs to any of the foregoing antibodies.

64.) The method of claim 63, wherein said disease or disorder associated with IL-6 is cancer associated fatigue or cachexia or arthritis.

65.) The method of claim 63, wherein said disease or disorder associated with IL-6 is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS).

66.) A method of making an antibody comprising the variable light and heavy chain polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ

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67.) The method of claim 66, wherein said yeast is selected from the following genera: Arxiozyma; Ascobotryozyma; Citeromyces; Debaryomyces; Dekkera; Eremothecium; Issatchenkia; Kazachstania; Kluyveromyces; Kodamaea; Lodderomyces; Pachysolen; Pichia; Saccharomyces; Saturnispora; Tetrapisispora; Torulaspora; Williopsis; and Zygosaccharomyces.

68.) The method of claim 67, wherein said yeast genera is Pichia.

69.) The method of claim 68, wherein the species of Pichia is selected from Pichia pastoris, Pichia methanolica and Hansenula polymorpha (Pichia angusta).

70.) An isolated polynucleotide comprising a polynucleotide encoding an anti-IL-6 VH antibody amino acid sequence selected from SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody VH polypeptide or a conservative amino acid substitution.

71.) A vector comprising the polynucleotide sequence of claim 70.

72.) A host cell comprising the vector of claim 71.

73.) The host cell of claim 72, wherein said host cell is a yeast cell belonging to the genus Pichia.

74.) The method of claim 70, wherein said heterologous polynucleotide further comprises a polynucleotide sequence encoding a VL amino acid sequence selected from 2, 20, 21, 37, 53, 69, 85, I01, 119, 122, I38, 154, 170, I86, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody VL polypeptide or a conservative amino acid substitution.

75.) An isolated polynucleotide comprising the polynucleotide sequence encoding an anti-IL-6 VL antibody amino acid sequence of 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-IL-6 antibody VL polypeptide or a conservative amino acid substitution.

76.) A vector comprising the polynucleotide sequence of claim 75.

77.) A host cell comprising the vector of claim 76.

78.) The host cell of claim 79, wherein said host cell is a yeast cell belonging to the genus Pichia.

79.) The method of claim 66, wherein said method expresses polynucleotide sequence or sequences encoding an antibody or fragment comprising the polypeptides contained in SEQ ID NO:2 and SEQ ID NO:3; SEQ ID NO:2 and SEQ ID NO:18; SEQ ID NO:2 and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:3; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:37 and SEQ ID NO:38; SEQ ID NO:53 and SEQ ID NO:54; SEQ ID NO:69 and SEQ ID NO:70; SEQ ID NO:85 and SEQ ID NO:86; SEQ ID NO:101 and SEQ ID NO:102; SEQ ID NO:101 and SEQ ID NO:117; SEQ ID NO: 101 and SEQ ID NO: 118; SEQ ID NO: 119 and SEQ ID NO: 102; SEQ ID NO:119 and SEQ ID NO:117; SEQ ID NO:119 and SEQ ID NO:118; SEQ ID NO: I22 and SEQ ID NO:123; SEQ ID NO:I38 and SEQ ID NO:139; SEQ ID NO:154 and SEQ ID NO:155; SEQ ID NO:170 and SEQ ID NO:171; SEQ ID NO:186 and SEQ ID NO:187; SEQ ID NO:202 and SEQ ID NO:203; SEQ ID NO:218 and SEQ ID NO:219; SEQ ID NO:234 and SEQ ID NO:235; SEQ ID NO:250 and SEQ ID NO:251; SEQ ID NO:266 and SEQ ID NO:267; SEQ ID NO:282 and SEQ ID NO:283; SEQ ID NO:298 and SEQ ID NO:299; SEQ ID NO:314 and SEQ ID NO:315; SEQ ID NO:330 and SEQ ID NO:331; SEQ ID NO:346 and SEQ ID NO:347; SEQ ID NO:362 and SEQ ID NO:363; SEQ ID NO:378 and SEQ ID NO:379; SEQ ID NO:394 and SEQ ID NO:395; SEQ ID NO:410 and SEQ ID NO:411; SEQ ID NO:426 and SEQ ID NO:427; SEQ ID NO:442 and SEQ ID NO:443; SEQ ID NO:458 and SEQ ID NO:459; SEQ ID NO:474 and SEQ ID NO:475; SEQ ID NO:490 and SEQ ID NO:491; SEQ ID NO:506 and SEQ ID NO:507; SEQ ID NO:522 and SEQ ID NO:523; SEQ ID NO:538 and SEQ ID NO:539; SEQ ID NO:554 and SEQ ID NO:555; or SEQ ID NO:570 and SEQ ID NO:571 or one containing the same CDRs as any of the foregoing antibodies.

80.) An isolated anti-IL-6 antibody or antibody fragment according to claim 1, comprising one or more of the CDRs contained in the VH polypeptide sequences selected from the group consisting of: SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, I71, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555 and SEQ ID NO: 571 and/or one or more of the CDRs contained in the VL polypeptide sequence consisting of: 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, I70, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570, with the proviso that said antibody does not comprise VL CDRs that are identical variable light CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:4, 5 and 6 respectively, or VH CDRs that are identical to the variable heavy CDR1, CDR2 and CDR3 complementarity regions having the sequences in SEQ ID NO:7, 8 or 120 and 9 respectively.

81.) The antibody of claim 80, wherein said antibody is humanized.

82.) The antibody of claim 80, wherein said antibody is chimeric.

83.) The antibody of claim 81 or 82, wherein said chimeric antibody comprises a human Fc.

84.) The antibody of claim 81 or 82 which comprises a single chain antibody.

85.) The antibody of claim 87 wherein said human Fc is derived from human IgG1, IgG2, IgG3, or IgG4.

86.) The antibody of any one of claims 80-85, wherein said antibody binds to at least one of soluble IL-6, cell surface expressed Il-6, IL-6/IL-6R, IL-6/IL-6R/gp130 complexes and/or IL-6/IL-6R/gp130 complex multimers.

87.) An isolated anti-IL-6 antibody comprising a VL or VH polypeptide sequence having at least 90% or greater homology to any one of the polypeptide sequences recited in claim 80.

88.) The antibody of claim 80, wherein said antibody binds to IL-6 with a dissociation constant (K_D) of less than or equal to $5x10^{-7}$, 10^{-7}, $5x10^{-8}$, $10^{"8}$, $5x10^{9}$, $10^{"9}$, $5x10^{-10}$, 10^{-10}, 5x 10-^{11}, 10-^{11}, 5x 10^{-12}, 10^{-12}, $5x10^{-13}$, or 10^{-13}.

89.) The antibody of claim 80, wherein said antibody binds to IL-6 with a dissociation constant (K_D) of less than or equal to $5X\ 10^{-10}$.

90.) The antibody of claim 80, wherein said antibody binds to IL-6 with an off-rate (K_{off}) of less than or equal to $10^{-4}S^{-1}$, 5x 10^{-5} S^{-1}, 5x 10^{-5} S^{-1} , 5 X 10^{-6} S^{-1} , 10^{-6} S^{-1}, $5x10^{-7}$ S^{-1}, or 10^{-7} S^{-1}.

91.) The antibody of any one of claims 80-90, wherein the antibody originated from one or more rabbit B cell populations.

92.) The antibody of any one of claims 80-90, wherein the antibody has binding specificity for

primate homologs of human IL-6.

93.) The antibody of claim 92, wherein the primate is Macaca fascicularis.

94.) The antibody of any one of claims 82-89, wherein said antibody does not have binding specificity for IL-6R or gp130.

95.) The antibody of any one of claims 80-94, wherein said antibody inhibits the association of Il-6 with IL-6R; and/or the association of IL-6/IL-6R with gp130 and/or the formation of IL-6/IL-6R/gp130 multimers and/or inhibits a biological effect of any of the foregoing.

96.) The antibody of claim 95, wherein the IL-6R is soluble IL-6R (sIL-6R).

97.) A fragment of the antibody of any one of claims 80-96, wherein said fragment is selected from an Fab fragment, an Fab' fragment, or an F(ab')2 fragment.

98.) The antibody of any one of claims 80-97, wherein said antibody further comprises an effector moiety.

99.) The antibody of claim 98, wherein the effector moiety is a detectable moiety or a functional moiety.

100.) The antibody of claim 99, wherein said detectable moiety is a fluorescent dye, an enzyme, a substrate, a bioluminescent material, a radioactive material, or a chemiluminescent material.

101.) The antibody of claim 99, wherein said functional moiety is streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, or a radioactive material.

102.) A method of ameliorating or reducing symptoms of a disease or disorder associated with IL-6, comprising administering to a patient exhibiting symptoms of a disease or disorder associated with IL-6 a therapeutically effective amount of the antibody containing VL CDRs identical to those in SEQ ID NO:4, 4 and 6; and VH CDRs identical to those in SEQ ID NO:7, 8 or 120 and 9.

103.) The method of claim 102, wherein the antibody or fragment comprises a VL having the sequence in SEQ ID NO:20 and a VH having the sequence in SEQ ID NO:18.

104.) The method of claim 102, wherein the antibody or fragment comprises a VL having the sequence in SEQ ID NO:20 and a VH having the sequence in SEQ ID NO:19.

105.) The method of claim 102, wherein said disease or disorder associated with IL-6 is cancer-associated fatigue, cachexia or arthritis.

106.) The method of claim 102, 103 or 104, wherein said disease or disorder associated with IL-6 is selected from general fatigue, exercise-induced fatigue, cancer-related fatigue, inflammatory

disease-related fatigue, chronic fatigue syndrome, cancer-related cachexia, cardiac-related cachexia, respiratory-related cachexia, renal-related cachexia, age-related cachexia, rheumatoid arthritis, systemic lupus erythematosis (SLE), systemic juvenile idiopathic arthritis, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), Sjogren's syndrome, adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, osteoarthritis, osteoporosis, Paget's disease of bone, osteoarthritis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, prostate cancer, leukemia, renal cell cancer, multicentric Castleman's disease, ovarian cancer, drug resistance in cancer chemotherapy, cancer chemotherapy toxicity, ischemic heart disease, atherosclerosis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, anemia, anemia of inflammation (anemia of chronic disease), hypertension, depression, depression associated with a chronic illness, thrombosis, thrombocytosis, acute heart failure, metabolic syndrome, miscarriage, obesity, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, transplant rejection, graft versus host disease (GVHD), avian influenza, smallpox, pandemic influenza, adult respiratory distress syndrome (ARDS), severe acute respiratory syndrome (SARS), sepsis, and systemic inflammatory response syndrome (SIRS).

107) The method of claim 105 or 106, wherein said antibody comprises a VL polypeptide at least 90% identical to the VL polypeptide in SEQ ID NO:2 or 20, and a VH polypeptide at least 90% identical to the VH polypeptide in SEQ ID NO:3, 19 or 19.

108) The method of any of claim 105 or 106, wherein said antibody comprises a VL polypeptide at least 95% identical to the VL polypeptide in SEQ ID NO:2 or 20, and a VH polypeptide at least 95% identical to the VH polypeptide in SEQ ID NO:3, 19 or 19.

109) The method of claim 102 105 or 106, wherein said antibody comprises a VL polypeptide at least 98% identical to the VL polypeptide in SEQ ID NO:2 or 20, and a VH polypeptide at least 98% identical to the VH polypeptide in SEQ ID NO:3, 18 or 19.

110) The method of claim 102, 105 or 106, wherein said antibody comprises a VL polypeptide identical to the VL polypeptide in SEQ ID NO:2 or 20, and a VH polypeptide identical to the VH polypeptide in SEQ ID NO:3, 19 or 19.

111) The method claim 110, wherein said antibody comprises a VL polypeptide identical to the VL polypeptide in SEQ ID NO:20, and a VH polypeptide identical to the VH polypeptide in SEQ ID NO:19.

112) The method of claim 110, wherein said antibody comprises a VL polypeptide identical to the VL polypeptide in SEQ ID NO:20, and a VH polypeptide identical to the VH polypeptide in SEQ ID NO:18..

113.) A method of making the antibody used in a methods of according to any one of claims

102-112 in a polyploid yeast culture that stably expresses and secretes into the culture medium at least 10-25 mg/liter of said antibody, comprising: (i) introducing at least one expression vector containing one or more heterologous polynucleotides encoding said antibody operably linked to a promoter and a signal sequence into a haploid yeast cell; (ii) producing by mating or spheroplast fusion a polyploidal yeast from said first and/or second haploid yeast cell; (iii) selecting polyploidal yeast cells that stably express said antibody; and (iv) producing stable polyploidal yeast cultures from said polyploidal yeast cells that stably express at least 10-25 mg/liter of said antibody into the culture medium.

114.) The method of claim 113, wherein said yeast is selected from the following genera: Arxiozyma; Ascobotryozyma; Citeromyces; Debaryomyces; Dekkera; Eremothecium; Issatchenkia; Kazachstania; Kluyveromyces; Kodamaea; Lodderomyces; Pachysolen; Pichia; Saccharomyces; Saturnispora; Tetrapisispora; Torulaspora; Williopsis; and Zygosaccharomyces.

115.) The method of claim 113, wherein said yeast genera is Pichia.

116.) The method of claim 115, wherein the species of Pichia is selected from Pichia pastoris, Pichia methanolica and Hansenula polymorpha (Pichia angusta).

117.) An isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said expressed polypeptide alone specifically binds IL-6 or specifically binds IL-6 when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-IL-6 antibody wherein said at least one CDR is selected from those contained in the VL or VH polypeptides contained in SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555; 571; 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570.

118.) A vector comprising at least one of the polynucleotide sequences of claim 117.

119.) A host cell comprising the vector of claim 118.

120.) The host cell of claim 119, wherein said host cell is a yeast cell belonging to the genus Pichia.

121.) The method of claim 113, wherein said heterologous polynucleotide comprises one or more of the polynucleotide sequences encoding at least one CDR contained in a VL or VH polypeptide selected from the group consisting of SEQ ID NO: 3, 18, 19, 22, 38, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555; 571; 2, 20, 21, 37, 53, 69, 85, 101, 119, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554 and SEQ ID NO: 570.

122.) A pharmaceutical or diagnostic composition containing at least one IL-6 antibody or

fragment according to one of claims 1 or 80-101 and a pharmaceutically acceptable carrier.

123.) The pharmaceutical or diagnostic composition of claim 122 which further comprises at least one stabilizer.

124.) The pharmaceutical or diagnostic composition of claim 122 which is lyophilized.

125.) A method of treating an IL-6 associated disease comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim 122.

126.) The method of claim 125, wherein the disease is selected from a cancerous condition, autoimmune condition and an inflammatory disease.

127.) The method of claim 125, wherein the disease is cancer-associated fatigue, cachexia or arthritis.

128.) A method of in vivo imaging which detects the presence of cells which express IL-6 comprising administering a diagnostically effective amount of a diagnostic composition containing the VL CDRS in SEQ ID NO:4, 5 and 6, and the VH CDRS in SEQ ID NO:7, 8 or 120 and 9..

129.) The method of claim 128 which is used to detect or image IL-6 expressing tumors or metastases.

130.) The method of claim 128 which is used to detect or image IL-6 expressing inflammatory sites.

131.) The method of claim 128, 129 or 130 which is used as part of a planning regimen for design of an effective cancer or arthritis treatment protocol.

132.) The method of claim 131 wherein the treatment protocol includes one or more of radiation, chemotherapy, cytokine therapy, gene therapy, and antibody therapy.

133.) The method of claim 128, wherein the antibody is a single chain antibody selected from a scFv, camelbody, nanobody, IgNAR, SMIP, and combinations thereof.

SEQUENCE LISTING

<110> Garcia, Leon
Jensen, Anne E.C.
Olson, Katie
Dutzar, Ben
Ojala, Ethan
Kovacevich, Brian
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aaaccagggc agcgtcccaa gctcctgatc tatagggcat ccactctggc atctggggtc 240

tcatcgcggt tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

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aatgct 366

<210> 11
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acagcctctg gattctccct cagtaactac tacgtgacct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatcatttat ggtagtgatg aaacggccta cgcgacctgg 240

gcgataggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ctgacagccg cggacacggc cacctatttc tgtgccagag atgatagtag tgactgggat 360

gcaaaattta acttg 375

<210> 12
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<210> 13
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<400> 13
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<210> 15
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<212> DNA
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<400> 15
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<210> 16
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 16
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<210> 17
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<212> DNA
<213> Oryctolagus cuniculus

<400> 17
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<210> 18
<211> 109
<212> PRT
<213> Oryctolagus cuniculus

<400> 18

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

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

Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp Ala Ile
50 55 60

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

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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
100 105

<210> 19
<211> 109
<212> PRT
<213> Oryctolagus cuniculus

<400> 19

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

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

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

Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile
50 55 60

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

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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
100 105

<210> 20
<211> 99
<212> PRT
<213> Oryctolagus cuniculus

<400> 20

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

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

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

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

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

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn Ile
                85                  90                  95

Asp Asn Ala
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<210> 21
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 21

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1               5                   10                  15

Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
            20                  25                  30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
        35                  40                  45

Glu Thr Ile Tyr Ser Trp Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
    50                  55                  60

Pro Pro Lys Leu Leu Ile Tyr Gln Ala Ser Asp Leu Ala Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ala Gly Thr Glu Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Gly Tyr Ser Gly Ser Asn Val Asp Asn Val
        115                 120
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<210> 22
<211> 126
<212> PRT
<213> Oryctolagus cuniculus

<400> 22

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1               5                   10                  15

Val Gln Cys Gln Glu Gln Leu Lys Glu Ser Gly Gly Arg Leu Val Thr
            20                  25                  30
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Pro Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu
35 40 45

Asn Asp His Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Tyr Ile Gly Phe Ile Asn Ser Gly Gly Ser Ala Arg Tyr Ala Ser
65 70 75 80

Trp Ala Glu Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp
85 90 95

Leu Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Val Arg Gly Gly Ala Val Trp Ser Ile His Ser Phe Asp Pro
115 120 125

<210> 23
<211> 11
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<213> Oryctolagus cuniculus

<400> 23

Gln Ala Ser Glu Thr Ile Tyr Ser Trp Leu Ser
1 5 10

<210> 24
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 24

Gln Ala Ser Asp Leu Ala Ser
1 5

<210> 25
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 25

Gln Gln Gly Tyr Ser Gly Ser Asn Val Asp Asn Val
1 5 10

<210> 26
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 26

Asp His Ala Met Gly
1 5

<210> 27
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 27

Phe Ile Asn Ser Gly Gly Ser Ala Arg Tyr Ala Ser Trp Ala Glu Gly
1 5 10 15

<210> 28
<211> 12
<212> PRT
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<400> 28

Gly Gly Ala Val Trp Ser Ile His Ser Phe Asp Pro
1 5 10

<210> 29
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

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aagccagggc agcctcccaa gctcctgatc taccaggcat ccgatctggc atctggggtc 240

ccatcgcgat tcagcggcag tggggctggg acagagtaca ctctcaccat cagcggcgtg 300

cagtgtgacg atgctgccac ttactactgt caacagggtt atagtggtag taatgttgat 360

aatgtt 366

<210> 30
<211> 378
<212> DNA
<213> Oryctolagus cuniculus

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gagcagctga aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacacttacc 120

tgcacagcct ctggattctc cctcaatgac catgcaatgg gctgggtccg ccaggctcca 180

gggaaggggc tggaatacat cggattcatt aatagtggtg gtagcgcacg ctacgcgagc 240

tgggcagaag gccgattcac catctccaga acctcgacca cggtggatct gaaaatgacc 300

agtctgacaa ccgaggacac ggccacctat ttctgtgtca gaggggggtgc tgtttggagt 360

attcatagtt ttgatccc 378

<210> 31
<211> 33
<212> DNA
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<400> 31
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<210> 32
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<212> DNA
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<400> 32
caggcatccg atctggcatc t 21

<210> 33
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<212> DNA
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<400> 33
caacagggtt atagtggtag taatgttgat aatgtt 36

<210> 34
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<212> DNA
<213> Oryctolagus cuniculus

<400> 34
gaccatgcaa tgggc 15

<210> 35
<211> 48
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<400> 35
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<210> 36
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<212> DNA
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<400> 36
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<210> 37
<211> 123
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<213> Oryctolagus cuniculus

<400> 37

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
35 40 45

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Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro
    50                  55                  60

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

Gly Val Pro Ser Arg Phe Val Gly Ser Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95

Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Ala Gly Val Tyr Asp Asp Asp Ser Asp Asn Ala
        115                 120
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<210> 38
<211> 125
<212> PRT
<213> Oryctolagus cuniculus

<400> 38

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1               5                   10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
        35                  40                  45

Val Tyr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Phe Ile Thr Met Ser Asp Asn Ile Asn Tyr Ala Ser Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Ser Arg Gly Trp Gly Thr Met Gly Arg Leu Asp Leu
        115                 120                 125
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<210> 39
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 39

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1 5 10

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<213> Oryctolagus cuniculus

<400> 40

Gly Ala Ser Thr Leu Ala Ser
1 5

<210> 41
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 41

Ala Gly Val Tyr Asp Asp Asp Ser Asp Asn Ala
1 5 10

<210> 42
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 42

Val Tyr Tyr Met Asn
1 5

<210> 43
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 43

Phe Ile Thr Met Ser Asp Asn Ile Asn Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 44
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 44

Ser Arg Gly Trp Gly Thr Met Gly Arg Leu Asp Leu
1 5 10

<210> 45
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 45
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acatttgccg ccgtgctgac ccagactcca tctcccgtgt ctgcagctgt gggaggcaca 120

gtcagcatca gttgccaggc cagtcagagt gtttatgaca acaactactt atcctggttt 180

cagcagaaac cagggcagcc tcccaagctc ctgatctatg gtgcatccac tctggcatct 240

ggggtcccat cgcggttcgt gggcagtgga tctgggacac agttcactct caccatcaca 300

gacgtgcagt gtgacgatgc tgccacttac tattgtgcag gcgtttatga tgatgatagt 360

gataatgcc 369

<210> 46
<211> 375
<212> DNA
<213> Oryctolagus cuniculus

<400> 46
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tcgctggagg agtccggggg tcgcctggtc acccctggga cacccctgac actcacctgc 120

acagcctctg gattctccct cagtgtctac tacatgaact gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg attcattaca atgagtgata atataaatta cgcgagctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagga gtcgtggctg gggtacaatg 360

ggtcggttgg atctc 375

<210> 47
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 47
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<210> 48
<211> 21
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<400> 48
ggtgcatcca ctctggcatc t 21

<210> 49
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 49
gcaggcgttt atgatgatga tagtgataat gcc 33

<210> 50
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 50
gtctactaca tgaac 15

<210> 51
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 51
ttcattacaa tgagtgataa tataaattac gcgagctggg cgaaaggc 48

<210> 52
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 52
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<210> 53
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<212> PRT
<213> Oryctolagus cuniculus

<400> 53

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Ile Cys Asp Pro Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Pro Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Glu Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Ala Gly Val Tyr Asp Asp Asp Ser Asp Asp Ala
115 120

<210> 54
<211> 126
<212> PRT
<213> Oryctolagus cuniculus

<400> 54

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
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Val Gln Cys Gln Glu Gln Leu Lys Glu Ser Gly Gly Gly Leu Val Thr
20 25 30

Pro Gly Gly Thr Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu
35 40 45

Asn Ala Tyr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Ile Gly Phe Ile Thr Leu Asn Asn Asn Val Ala Tyr Ala Asn
65 70 75 80

Trp Ala Lys Gly Arg Phe Thr Phe Ser Lys Thr Ser Thr Thr Val Asp
85 90 95

Leu Lys Met Thr Ser Pro Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Ala Arg Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
115 120 125

<210> 55
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<212> PRT
<213> Oryctolagus cuniculus

<400> 55

Gln Ala Ser Gln Ser Val Tyr Glu Asn Asn Tyr Leu Ser
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<210> 56
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<400> 56

Gly Ala Ser Thr Leu Asp Ser
1 5

<210> 57
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<212> PRT
<213> Oryctolagus cuniculus

<400> 57

Ala Gly Val Tyr Asp Asp Asp Ser Asp Asp Ala
1 5 10

<210> 58
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 58

Ala Tyr Tyr Met Asn
1 5

<210> 59
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 59

Phe Ile Thr Leu Asn Asn Asn Val Ala Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 60
<211> 12
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<400> 60

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1 5 10

<210> 61
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

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ggggtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccattaca 300

gacgtgcagt gtgacgatgc tgccacttac tattgtgcag gcgtttatga tgatgatagt 360

gatgatgcc 369

<210> 62
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atgggtcggt tggatctc 378

<210> 63
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<210> 64
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<210> 65
<211> 33
<212> DNA
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<400> 65
gcaggcgttt atgatgatga tagtgatgat gcc 33

<210> 66
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<400> 66
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<210> 67
<211> 48
<212> DNA
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<400> 67
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<210> 68
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<210> 69
<211> 122
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<400> 69

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

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Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
        35                  40                  45

Gln Ser Val Asp Asp Asn Asn Trp Leu Gly Trp Tyr Gln Gln Lys Arg
    50                  55                  60

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95

Leu Thr Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala
        115                 120
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<210> 70
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<212> PRT
<213> Oryctolagus cuniculus

<400> 70

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Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
        35                  40                  45

Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Ile Ile Gly Gly Phe Gly Thr Thr Tyr Tyr Ala Thr Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Arg Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Gly Gly Pro Gly Asn Gly Gly Asp Ile
        115                 120
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<210> 71
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<212> PRT
<213> Oryctolagus cuniculus

<400> 71

Gln Ala Ser Gln Ser Val Asp Asp Asn Asn Trp Leu Gly
1 5 10

<210> 72
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<213> Oryctolagus cuniculus

<400> 72

Ser Ala Ser Thr Leu Ala Ser
1 5

<210> 73
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<213> Oryctolagus cuniculus

<400> 73

Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala
1 5 10

<210> 74
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<400> 74

Ser Tyr Ala Met Ser
1 5

<210> 75
<211> 16
<212> PRT
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<400> 75

Ile Ile Gly Gly Phe Gly Thr Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 76
<211> 9
<212> PRT
<213> Oryctolagus cuniculus

<400> 76

Gly Gly Pro Gly Asn Gly Gly Asp Ile
1 5

<210> 77
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 77

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gtcaccatca actgccaggc cagtcagagt gttgatgata acaactggtt aggctggtat 180

cagcagaaac gagggcagcc tcccaagtac ctgatctatt ctgcatccac tctggcatct 240

ggggtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc 300

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tttgct 366

<210> 78
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 78
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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gcttctccct cagtagctat gcaatgagct gggtccgcca ggctccagga 180

aaggggctgg agtggatcgg aatcattggt ggttttggta ccacatacta cgcgacctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag gtggtcctgg taatggtggt 360

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20 25 30

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35 40 45

Gln Ser Val Tyr Asn Asn Phe Leu Ser Trp Tyr Gln Gln Lys Pro Gly
50 55 60

Gln Pro Pro Lys Leu Leu Ile Tyr Gln Ala Ser Lys Leu Ala Ser Gly
65 70 75 80

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu
85 90 95

Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu
100 105 110

Gly Gly Tyr Asp Asp Asp Ala Asp Asn Ala
115 120

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20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
35 40 45

Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Ile Ile Tyr Ala Gly Ser Gly Ser Thr Trp Tyr Ala Ser
65 70 75 80

Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp
85 90 95

Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Ala Arg Asp Gly Tyr Asp Asp Tyr Gly Asp Phe Asp Arg Leu Asp Leu
115 120 125

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Gln Ala Ser Lys Leu Ala Ser
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Asp Tyr Ala Met Ser
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gtcaccatca agtgccagtc cagtcagagt gtttataata atttcttatc gtggtatcag 180

cagaaaccag ggcagcctcc caagctcctg atctaccagg catccaaact ggcatctggg 240

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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac gctcacctgc 120

acagtctctg gaatcgacct cagtgactat gcaatgagct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatcatttat gctggtagtg gtagcacatg gtacgcgagc 240

tgggcgaaag gccgattcac catctccaaa acctcgacca cggtggatct gaaaatcacc 300

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Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
        35                  40                  45

Gln Ser Ile Asn Asn Glu Leu Ser Trp Tyr Gln Gln Lys Ser Gly Gln
    50                  55                  60

Arg Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val
65                  70                  75                  80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                85                  90                  95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
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Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala
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<213> Oryctolagus cuniculus

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            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
        35                  40                  45

Asn Tyr Tyr Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Trp
65                  70                  75                  80

Ala Ile Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110
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<210> 104
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Arg Ala Ser Thr Leu Ala Ser
1 5

<210> 105
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1 5 10

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<210> 107
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1 5 10

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gtcaccatca aatgccaggc cagtcagagc attaacaatg aattatcctg gtatcagcag 180

aaatcagggc agcgtcccaa gctcctgatc tatagggcat ccactctggc atctggggtc 240

tcatcgcggt tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactactgt caacagggtt atagtctgag gaatattgat 360

aatgct 366

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tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagcctctg gattctccct cagtaactac tacatgacct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatgatttat ggtagtgatg aaacagccta cgcgaactgg 240

gcgataggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ctgacagccg cggacacggc cacctatttc tgtgccagag atgatagtag tgactgggat 360

gcaaaattta acttg 375

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<400> 114
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<210> 115
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<400> 115
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<210> 117
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30

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

Gly Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Trp Ala Ile
50 55 60

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

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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
100 105

<210> 118
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<213> Oryctolagus cuniculus

<400> 118

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

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

Gly Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Ser Ala Ile
50 55 60

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

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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
100 105

<210> 119
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<212> PRT
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<400> 119

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

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

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

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

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

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

Ile Asp Asn Ala
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<210> 120

<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 120

Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile Gly
1 5 10 15

<210> 121
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 121

Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Ser Ala Ile Gly
1 5 10 15

<210> 122
<211> 123
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<400> 122

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Ser Cys Gln Ser Ser
35 40 45

Gln Ser Val Gly Asn Asn Gln Asp Leu Ser Trp Phe Gln Gln Arg Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Glu Ile Ser Lys Leu Glu Ser
65 70 75 80

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr
85 90 95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Leu Gly Gly Tyr Asp Asp Asp Ala Asp Asn Ala
115 120

<210> 123
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<212> PRT
<213> Oryctolagus cuniculus

<400> 123

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly

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Val Gln Cys His Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

Ser Arg Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Leu Gly Asp Thr Gly Gly His Ala Tyr Ala Thr Arg Leu Asn Leu
115 120 125

<210> 124
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Gln Ser Ser Gln Ser Val Gly Asn Asn Gln Asp Leu Ser
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<400> 125

Glu Ile Ser Lys Leu Glu Ser
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<210> 126
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Leu Gly Gly Tyr Asp Asp Asp Ala Asp Asn Ala
1 5 10

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Ser Arg Thr Met Ser
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Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
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aaggggctgg agtggatcgg atacatttgg agtggtggta gcacatacta cgcgacctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatcaccagt 300

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gcttatgcta ctcgcttaaa tctc 384

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20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ser Ser
35 40 45

Gln Ser Val Tyr Ser Asn Lys Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Thr Ser Lys Leu Ala Ser
65 70 75 80

Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Leu Gly Ala Tyr Asp Asp Asp Ala Asp Asn Ala
115 120

<210> 139
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<400> 139

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Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Lys Pro
20 25 30

Asp Glu Thr Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Glu
35 40 45

Gly Gly Tyr Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Ile Ser Tyr Asp Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp
85 90 95

Leu Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Val Arg Ser Leu Lys Tyr Pro Thr Val Thr Ser Asp Asp Leu
115 120 125

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1 5 10

<210> 141
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<400> 141

Trp Thr Ser Lys Leu Ala Ser
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<210> 142
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1 5 10

<210> 143
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Gly Gly Tyr Met Thr
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<210> 145
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Ser Leu Lys Tyr Pro Thr Val Thr Ser Asp Asp Leu
1 5 10

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cagcagaaac cagggcagcc tcccaagctc ctgatctact ggacatccaa actggcatct 240

ggggccccat cacggttcag cggcagtgga tctgggacac aattcactct caccatcagc 300

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acagcctctg gattctccct ggagggcggc tacatgacct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatcagttat gatagtggta gcacatacta cgcgagctgg 240

gcgaaaggcc gattcaccat ctccaagacc tcgtcgacca cggtggatct gaaaatgacc 300

agtctgacaa ccgaggacac ggccacctat ttctgcgtca gatcactaaa atatcctact 360

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<212> DNA
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<400> 151
ggcggctaca tgacc 15

<210> 152
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<400> 152
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<210> 153
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<212> DNA
<213> Oryctolagus cuniculus

<400> 153
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<210> 154
<211> 123
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<400> 154

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Ser Cys Gln Ser Ser
35 40 45

Gln Ser Val Tyr Asn Asn Asn Asp Leu Ala Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Ala Tyr Tyr Cys
100 105 110

Leu Gly Gly Tyr Asp Asp Asp Ala Asp Asn Ala
115 120

<210> 155
<211> 129
<212> PRT
<213> Oryctolagus cuniculus

<400> 155

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Leu Ser Leu Ser
35 40 45

Ser Asn Thr Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Ser Trp
65 70 75 80

Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Gly Gly Tyr Ala Ser Gly Gly Tyr Pro Tyr Ala Thr Arg Leu Asp
115 120 125

Leu

<210> 156
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<212> PRT
<213> Oryctolagus cuniculus

<400> 156

Gln Ser Ser Gln Ser Val Tyr Asn Asn Asn Asp Leu Ala
1 5 10

<210> 157
<211> 7
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<213> Oryctolagus cuniculus

<400> 157

Tyr Ala Ser Thr Leu Ala Ser
1 5

<210> 158
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<212> PRT
<213> Oryctolagus cuniculus

<400> 158

Leu Gly Gly Tyr Asp Asp Asp Ala Asp Asn Ala
1 5 10

<210> 159
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 159

Ser Asn Thr Ile Asn
1 5

<210> 160
<211> 16
<212> PRT
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<400> 160

Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Ser Trp Val Asn Gly
1 5 10 15

<210> 161
<211> 16
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<213> Oryctolagus cuniculus

<400> 161

Gly Gly Tyr Ala Ser Gly Gly Tyr Pro Tyr Ala Thr Arg Leu Asp Leu
1 5 10 15

<210> 162
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 162
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acatttgcag ccgtgctgac ccagacacca tcacccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca gttgccagtc cagtcagagt gtttataata ataacgactt agcctggtat 180

cagcagaaac cagggcagcc tcctaaactc ctgatctatt atgcatccac tctggcatct 240

ggggtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc 300

ggcgtgcagt gtgacgatgc tgccgcttac tactgtctag gcggttatga tgatgatgct 360

gataatgct 369

<210> 163
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<212> DNA
<213> Oryctolagus cuniculus

<400> 163
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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtatctg gattatccct cagtagcaat acaataaact gggtccgcca ggctccaggg 180

aaggggctgg agtggatcgg atacatttgg agtggtggta gtacatacta cgcgagctgg 240

gtgaatggtc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag ggggttacgc tagtggtggt 360

tatccttatg ccactcggtt ggatctc 387

<210> 164
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<212> DNA
<213> Oryctolagus cuniculus

<400> 164
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<210> 165
<211> 21
<212> DNA
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<400> 165
tatgcatcca ctctggcatc t 21

<210> 166
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 166
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<210> 167
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 167
agcaatacaa taaac 15

<210> 168
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 168
tacatttgga gtggtggtag tacatactac gcgagctggg tgaatggt 48

<210> 169
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 169
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<210> 170
<211> 123
<212> PRT

<213> Oryctolagus cuniculus

<400> 170

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Ser
            20                  25                  30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
        35                  40                  45

Gln Ser Val Tyr Asn Asn Asp Tyr Leu Ser Trp Tyr Gln Gln Arg Pro
    50                  55                  60

Gly Gln Arg Pro Lys Leu Leu Ile Tyr Gly Ala Ser Lys Leu Ala Ser
65                  70                  75                  80

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Lys Gln Phe Thr
                85                  90                  95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Leu Gly Asp Tyr Asp Asp Asp Ala Asp Asn Thr
        115                 120
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<210> 171
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 171

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                  10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Leu Ser
        35                  40                  45

Thr Asn Tyr Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Gly Ile Ile Tyr Pro Ser Gly Asn Thr Tyr Cys Ala Lys
65                  70                  75                  80

Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val
                85                  90                  95

Asp Leu Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe
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100 105 110

Cys Ala Arg Asn Tyr Gly Gly Asp Glu Ser Leu
115 120

<210> 172
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 172

Gln Ser Ser Gln Ser Val Tyr Asn Asn Asp Tyr Leu Ser
1 5 10

<210> 173
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 173

Gly Ala Ser Lys Leu Ala Ser
1 5

<210> 174
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 174

Leu Gly Asp Tyr Asp Asp Asp Ala Asp Asn Thr
1 5 10

<210> 175
<211> 6
<212> PRT
<213> Oryctolagus cuniculus

<400> 175

Thr Asn Tyr Tyr Leu Ser
1 5

<210> 176
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 176

Ile Ile Tyr Pro Ser Gly Asn Thr Tyr Cys Ala Lys Trp Ala Lys Gly
1 5 10 15

<210> 177
<211> 8
<212> PRT
<213> Oryctolagus cuniculus

<400> 177

Asn Tyr Gly Gly Asp Glu Ser Leu
1 5

<210> 178
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 178
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acatttgcag ccgtgctgac ccagacacca tcctccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca attgccagtc cagtcagagt gtttataata acgactactt atcctggtat 180

caacagaggc cagggcaacg tcccaagctc ctaatctatg gtgcttccaa actggcatct 240

ggggtcccgt cacggttcaa aggcagtgga tctgggaaac agtttactct caccatcagc 300

ggcgtgcagt gtgacgatgc tgccacttac tactgtctgg gcgattatga tgatgatgct 360

gataatact 369

<210> 179
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 179
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tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacttgc 120

acagtctctg gattcaccct cagtaccaac tactacctga gctgggtccg ccaggctcca 180

gggaaggggc tagaatggat cggaatcatt tatcctagtg gtaacacata ttgcgcgaag 240

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgga tctgaaaatg 300

accagtccga caaccgagga cacagccacg tatttctgtg ccagaaatta tggtggtgat 360

gaaagtttg 369

<210> 180
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 180
cagtccagtc agagtgttta taataacgac tacttatcc 39

<210> 181
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 181
ggtgcttcca aactggcatc t 21

<210> 182
<211> 33
<212> DNA

<213> Oryctolagus cuniculus

<400> 182
ctgggcgatt atgatgatga tgctgataat act 33

<210> 183
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 183
accaactact acctgagc 18

<210> 184
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 184
atcatttatc ctagtggtaa cacatattgc gcgaagtggg cgaaaggc 48

<210> 185
<211> 24
<212> DNA
<213> Oryctolagus cuniculus

<400> 185
aattatggtg gtgatgaaag tttg 24

<210> 186
<211> 119
<212> PRT
<213> Oryctolagus cuniculus

<400> 186

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Thr Ile Gly Asn Ala Leu Ala Trp Tyr Gln Gln Lys Ser Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Lys Ala Ser Lys Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Trp
100 105 110

Cys Tyr Phe Gly Asp Ser Val
115

<210> 187
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 187

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Thr Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Glu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Glu Gly Ser Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Asp Phe
35 40 45

Ser Ser Gly Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly
50 55 60

Leu Glu Trp Ile Ala Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Tyr
65 70 75 80

Ala Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
85 90 95

Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
100 105 110

Tyr Leu Cys Ala Arg Gly Ile Tyr Ser Asp Asn Asn Tyr Tyr Ala Leu
115 120 125

<210> 188
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 188

Gln Ala Ser Glu Thr Ile Gly Asn Ala Leu Ala
1 5 10

<210> 189
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 189

Lys Ala Ser Lys Leu Ala Ser
1 5

<210> 190
<211> 9
<212> PRT

<213> Oryctolagus cuniculus

<400> 190

Gln Trp Cys Tyr Phe Gly Asp Ser Val
1 5

<210> 191
<211> 6
<212> PRT
<213> Oryctolagus cuniculus

<400> 191

Ser Gly Tyr Tyr Met Cys
1 5

<210> 192
<211> 17
<212> PRT
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<400> 192

Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
1 5 10 15

Gly

<210> 193
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 193

Gly Ile Tyr Ser Asp Asn Asn Tyr Tyr Ala Leu
1 5 10

<210> 194
<211> 357
<212> DNA
<213> Oryctolagus cuniculus

<400> 194
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agatgtgatg ttgtgatgac ccagactcca gcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtgagacc attggcaatg cattagcctg gtatcagcag 180

aaatcagggc agcctcccaa gctcctgatc tacaaggcat ccaaactggc atctggggtc 240

ccatcgcggt tcaaaggcag tggatctggg acagagtaca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactactgt caatggtgtt attttggtga tagtgtt 357

<210> 195
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 195
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gagcagctgg tggagtccgg gggaggcctg gtccagcctg agggatccct gacactcacc 120

tgcacagcct ctggattcga cttcagtagc ggctactaca tgtgctgggt ccgccaggct 180

ccagggaagg ggctggagtg gatcgcgtgt attttcacta ttactactaa cacttactac 240

gcgagctggg cgaaaggccg attcaccatc tccaagacct cgtcgaccac ggtgactctg 300

caaatgacca gtctgacagc cgcggacacg gccacctatc tctgtgcgag agggatttat 360

tctgataata attattatgc cttg 384

<210> 196
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 196
caggccagtg agaccattgg caatgcatta gcc 33

<210> 197
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 197
aaggcatcca aactggcatc t 21

<210> 198
<211> 27
<212> DNA
<213> Oryctolagus cuniculus

<400> 198
caatggtgtt attttggtga tagtgtt 27

<210> 199
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 199
agcggctact acatgtgc 18

<210> 200
<211> 51
<212> DNA
<213> Oryctolagus cuniculus

<400> 200
tgtattttca ctattactac taacacttac tacgcgagct gggcgaaagg c 51

<210> 201
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 201

gggatttatt ctgataataa ttattatgcc ttg 33

<210> 202
<211> 119
<212> PRT
<213> Oryctolagus cuniculus

<400> 202

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Ser Ile Gly Asn Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Lys Ala Ser Thr Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Gly Val Gln Cys Ala Asp Ala Ala Ala Tyr Tyr Cys Gln Trp
100 105 110

Cys Tyr Phe Gly Asp Ser Val
115

<210> 203
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 203

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Gln Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Ala Ser Leu Thr Leu Thr Cys Lys Ala Ser Gly Phe Ser Phe
35 40 45

Ser Ser Gly Tyr Tyr Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly
50 55 60

Leu Glu Ser Ile Ala Cys Ile Phe Thr Ile Thr Asp Asn Thr Tyr Tyr
65 70 75 80

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Ala Asn Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Pro Ser Ser Pro
                85                  90                  95

Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
            100                 105                 110

Tyr Phe Cys Ala Arg Gly Ile Tyr Ser Thr Asp Asn Tyr Tyr Ala Leu
        115                 120                 125
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<210> 204
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 204

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Gln Ala Ser Glu Ser Ile Gly Asn Ala Leu Ala
1               5                   10
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<210> 205
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 205

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Lys Ala Ser Thr Leu Ala Ser
1               5
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<210> 206
<211> 9
<212> PRT
<213> Oryctolagus cuniculus

<400> 206

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Gln Trp Cys Tyr Phe Gly Asp Ser Val
1               5
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<210> 207
<211> 6
<212> PRT
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<400> 207

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Ser Gly Tyr Tyr Met Cys
1               5
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<210> 208
<211> 17
<212> PRT
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<400> 208

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Cys Ile Phe Thr Ile Thr Asp Asn Thr Tyr Tyr Ala Asn Trp Ala Lys
1               5                   10                  15
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Gly

<210> 209
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 209

Gly Ile Tyr Ser Thr Asp Asn Tyr Tyr Ala Leu
1 5 10

<210> 210
<211> 357
<212> DNA
<213> Oryctolagus cuniculus

<400> 210
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agatgtgatg ttgtgatgac ccagactcca gcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtgagagc attggcaatg cattagcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc tacaaggcat ccactctggc atctggggtc 240

ccatcgcggt tcagcggcag tggatctggg acagagttca ctctcaccat cagcggcgtg 300

cagtgtgccg atgctgccgc ttactactgt caatggtgtt attttggtga tagtgtt 357

<210> 211
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 211
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cagcagctgg tggagtccgg gggaggcctg gtcaagccgg gggcatccct gacactcacc 120

tgcaaagcct ctggattctc cttcagtagc ggctactaca tgtgctgggt ccgccaggct 180

ccagggaagg ggctggagtc gatcgcatgc atttttacta ttactgataa cacttactac 240

gcgaactggg cgaaaggccg attcaccatc tccaagccct cgtcgcccac ggtgactctg 300

caaatgacca gtctgacagc cgcggacacg gccacctatt tctgtgcgag ggggatttat 360

tctactgata attattatgc cttg 384

<210> 212
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 212
caggccagtg agagcattgg caatgcatta gcc 33

<210> 213
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 213
aaggcatcca ctctggcatc t 21

<210> 214
<211> 27
<212> DNA
<213> Oryctolagus cuniculus

<400> 214
caatggtgtt attttggtga tagtgtt 27

<210> 215
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 215
agcggctact acatgtgc 18

<210> 216
<211> 51
<212> DNA
<213> Oryctolagus cuniculus

<400> 216
tgcattttta ctattactga taacacttac tacgcgaact gggcgaaagg c 51

<210> 217
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 217
gggatttatt ctactgataa ttattatgcc ttg 33

<210> 218
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 218

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Gln Ser Val Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Thr Leu Glu Ser Gly Val
65 70 75 80

```
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                85                  90                  95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Cys
            100                 105                 110

Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala
        115                 120
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<210> 219
<211> 133
<212> PRT
<213> Oryctolagus cuniculus

<400> 219

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Ser Leu Ser
        35                  40                  45

Ser Asn Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Ile Ile Ser Tyr Ser Gly Thr Thr Tyr Tyr Ala Ser Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp
                85                  90                  95

Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
            100                 105                 110

Ala Arg Asp Asp Pro Thr Thr Val Met Val Met Leu Ile Pro Phe Gly
        115                 120                 125

Ala Gly Met Asp Leu
    130
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<210> 220
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 220

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Gln Ala Ser Gln Ser Val Ser Ser Tyr Leu Asn
1               5                   10
```

<210> 221
<211> 7

<212> PRT
<213> Oryctolagus cuniculus

<400> 221

Arg Ala Ser Thr Leu Glu Ser
1 5

<210> 222
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 222

Gln Cys Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala
1 5 10

<210> 223
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 223

Ser Asn Ala Ile Ser
1 5

<210> 224
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 224

Ile Ile Ser Tyr Ser Gly Thr Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 225
<211> 19
<212> PRT
<213> Oryctolagus cuniculus

<400> 225

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

Met Asp Leu

<210> 226
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 226
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agatgtgatg ttgtgatgac ccagactcca gcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtcagagc gttagtagct acttaaactg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc tacagggcat ccactctgga atctggggtc 240

ccatcgcggt tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactactgt caatgtactt atggtactag tagtagttat 360

ggtgctgct 369

<210> 227
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<212> DNA
<213> Oryctolagus cuniculus

<400> 227
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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

accgtctctg gtatctccct cagtagcaat gcaataagct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatcattagt tatagtggta ccacatacta cgcgagctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgtcgacca cggtggatct gaaaatcact 300

agtccgacaa ccgaggacac ggccacctac ttctgtgcca gagatgaccc tacgacagtt 360

atggttatgt tgataccttt tggagccggc atggacctc 399

<210> 228
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<212> DNA
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<400> 228
caggccagtc agagcgttag tagctactta aac 33

<210> 229
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<212> DNA
<213> Oryctolagus cuniculus

<400> 229
agggcatcca ctctggaatc t 21

<210> 230
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<400> 230
caatgtactt atggtactag tagtagttat ggtgctgct 39

<210> 231
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 231
agcaatgcaa taagc 15

<210> 232

<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 232
atcattagtt atagtggtac cacatactac gcgagctggg cgaaaggc 48

<210> 233
<211> 57
<212> DNA
<213> Oryctolagus cuniculus

<400> 233
gatgacccta cgacagttat ggttatgttg ataccttttg gagccggcat ggacctc 57

<210> 234
<211> 125
<212> PRT
<213> Oryctolagus cuniculus

<400> 234

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Ala Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Lys Asn Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Leu Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Tyr Ala
115 120 125

<210> 235
<211> 119
<212> PRT
<213> Oryctolagus cuniculus

<400> 235

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro

20 25 30

Glu Gly Ser Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Phe Ser
35 40 45

Ser Tyr Trp Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Ala Cys Ile Val Thr Gly Asn Gly Asn Thr Tyr Tyr Ala Asn
65 70 75 80

Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val
85 90 95

Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr Phe
100 105 110

Cys Ala Lys Ala Tyr Asp Leu
115

<210> 236
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 236

Gln Ala Ser Gln Ser Val Tyr Lys Asn Asn Tyr Leu Ser
1 5 10

<210> 237
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 237

Ser Ala Ser Thr Leu Asp Ser
1 5

<210> 238
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 238

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Tyr Ala
1 5 10

<210> 239
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 239

Ser Tyr Trp Met Cys

1 5

<210> 240
<211> 17
<212> PRT
<213> Oryctolagus cuniculus

<400> 240

Cys Ile Val Thr Gly Asn Gly Asn Thr Tyr Tyr Ala Asn Trp Ala Lys
1 5 10 15

Gly

<210> 241
<211> 4
<212> PRT
<213> Oryctolagus cuniculus

<400> 241

Ala Tyr Asp Leu
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<210> 242
<211> 375
<212> DNA
<213> Oryctolagus cuniculus

<400> 242
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acatttgccc aagtgctgac ccagactgca tcgcccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca actgccaggc cagtcagagt gtttataaga acaactactt atcctggtat 180

cagcagaaac cagggcagcc tcccaaaggc ctgatctatt ctgcatcgac tctagattct 240

ggggtcccat tgcggttcag cggcagtgga tctgggacac agttcactct caccatcagc 300

gacgtgcagt gtgacgatgc tgccacttac tactgtctag gcagttatga ttgtagtagt 360

ggtgattgtt atgct 375

<210> 243
<211> 357
<212> DNA
<213> Oryctolagus cuniculus

<400> 243
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgttggagg agtccggggg agacctggtc aagcctgagg gatccctgac actcacctgc 120

acagcctctg gattctcctt cagtagctac tggatgtgct gggtccgcca ggctccaggg 180

aaggggctgg agtggatcgc atgcattgtt actggtaatg gtaacactta ctacgcgaac 240

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgac tctgcaaatg 300

accagtctga cagccgcgga cacggccacc tatttttgtg cgaaagccta tgacttg 357

<210> 244
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 244
caggccagtc agagtgttta taagaacaac tacttatcc 39

<210> 245
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 245
tctgcatcga ctctagattc t 21

<210> 246
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 246
ctaggcagtt atgattgtag tagtggtgat tgttatgct 39

<210> 247
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 247
agctactgga tgtgc 15

<210> 248
<211> 51
<212> DNA
<213> Oryctolagus cuniculus

<400> 248
tgcattgtta ctggtaatgg taacacttac tacgcgaact gggcgaaagg c 51

<210> 249
<211> 12
<212> DNA
<213> Oryctolagus cuniculus

<400> 249
gcctatgact tg 12

<210> 250
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 250

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ser Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

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Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
        35                  40                  45

Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro
    50                  55                  60

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

Gly Val Pro Ser Arg Phe Lys Gly Thr Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95

Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Ala Gly Val Phe Asn Asp Asp Ser Asp Asp Ala
        115                 120
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<210> 251
<211> 125
<212> PRT
<213> Oryctolagus cuniculus

<400> 251

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1               5                   10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Leu Ser Gly Phe Ser Leu Ser
        35                  40                  45

Ala Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

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

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
        115                 120                 125
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<210> 252
<211> 13
<212> PRT

<213> Oryctolagus cuniculus

<400> 252

Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser
1 5 10

<210> 253
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 253

Gly Ala Ser Thr Leu Ala Ser
1 5

<210> 254
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 254

Ala Gly Val Phe Asn Asp Asp Ser Asp Asp Ala
1 5 10

<210> 255
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 255

Ala Tyr Tyr Met Ser
1 5

<210> 256
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 256

Phe Ile Thr Leu Ser Asp His Ile Ser Tyr Ala Arg Trp Ala Lys Gly
1 5 10 15

<210> 257
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 257

Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
1 5 10

<210> 258
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 258
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggttcc 60

acatttgccg ccgtgctgac ccagactcca tctcccgtgt ctgcagctgt gggaggcaca 120

gtcagcatca gttgccaggc cagtcagagt gtttatgaca acaactattt atcctggtat 180

cagcagaaac caggacagcc tcccaagctc ctgatctatg gtgcatccac tctggcatct 240

ggggtcccat cgcggttcaa aggcacggga tctgggacac agttcactct caccatcaca 300

gacgtgcagt gtgacgatgc tgccacttac tattgtgcag gcgtttttaa tgatgatagt 360

gatgatgcc 369

<210> 259
<211> 375
<212> DNA
<213> Oryctolagus cuniculus

<400> 259
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tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acactctctg gattctccct cagtgcatac tatatgagct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg attcattact ctgagtgatc atatatctta cgcgaggtgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagga gtcgtggctg gggtgcaatg 360

ggtcggttgg atctc 375

<210> 260
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 260
caggccagtc agagtgttta tgacaacaac tatttatcc 39

<210> 261
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 261
ggtgcatcca ctctggcatc t 21

<210> 262
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 262
gcaggcgttt ttaatgatga tagtgatgat gcc 33

<210> 263
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 263
gcatactata tgagc 15

<210> 264
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 264
ttcattactc tgagtgatca tatatcttac gcgaggtggg cgaaaggc 48

<210> 265
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 265
agtcgtggct ggggtgcaat gggtcggttg gatctc 36

<210> 266
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 266

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Ser Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala Trp Tyr Gln Gln Lys Ser
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Leu Ala Ser
65 70 75 80

Gly Val Ser Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Val Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Leu Gly Val Phe Asp Asp Asp Ala Asp Asn Ala
115 120

<210> 267
<211> 121
<212> PRT
<213> Oryctolagus cuniculus

<400> 267

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                  10                  15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
        35                  40                  45

Ser Tyr Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Tyr Ile Gly Val Ile Gly Thr Ser Gly Ser Thr Tyr Tyr Ala Thr Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Ala Leu
                85                  90                  95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Val
            100                 105                 110

Arg Ser Leu Ser Ser Ile Thr Phe Leu
        115                 120
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<210> 268
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 268

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Gln Ala Ser Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala
1               5                  10
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<210> 269
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 269

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Trp Ala Ser Thr Leu Ala Ser
1               5
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<210> 270
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 270

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Leu Gly Val Phe Asp Asp Asp Ala Asp Asn Ala
1               5                  10
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<210> 271
<211> 5

<212> PRT
<213> Oryctolagus cuniculus

<400> 271

Ser Tyr Ser Met Thr
1 5

<210> 272
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 272

Val Ile Gly Thr Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 273
<211> 8
<212> PRT
<213> Oryctolagus cuniculus

<400> 273

Ser Leu Ser Ser Ile Thr Phe Leu
1 5

<210> 274
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 274
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acattcgcag ccgtgctgac ccagacacca tcgcccgtgt ctgcggctgt gggaggcaca 120

gtcaccatca gttgccaggc cagtcagagt gtttataaca acaaaaattt agcctggtat 180

cagcagaaat cagggcagcc tcccaagctc ctgatctact gggcatccac tctggcatct 240

ggggtctcat cgcggttcag cggcagtgga tctgggacac agttcactct caccgtcagc 300

ggcgtgcagt gtgacgatgc tgccacttac tactgtctag gcgtttttga tgatgatgct 360

gataatgct 369

<210> 275
<211> 363
<212> DNA
<213> Oryctolagus cuniculus

<400> 275
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccaatgtcag 60

tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagcctctg gattctccct cagtagctac tccatgacct gggtccgcca ggctccaggg 180

aaggggctgg aatatatcgg agtcattggt actagtggta gcacatacta cgcgacctgg 240

gcgaaaggcc gattcaccat ctccagaacc tcgaccacgg tggctctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgtcagga gtctttcttc tattactttc 360

ttg 363

<210> 276
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 276
caggccagtc agagtgttta taacaacaaa aatttagcc 39

<210> 277
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 277
tgggcatcca ctctggcatc t 21

<210> 278
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 278
ctaggcgttt ttgatgatga tgctgataat gct 33

<210> 279
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 279
agctactcca tgacc 15

<210> 280
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 280
gtcattggta ctagtggtag cacatactac gcgacctggg cgaaaggc 48

<210> 281
<211> 24
<212> DNA
<213> Oryctolagus cuniculus

<400> 281
agtctttctt ctattacttt cttg 24

<210> 282
<211> 120
<212> PRT
<213> Oryctolagus cuniculus

<400> 282

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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Leu Pro Gly Ala Arg Cys Ala Phe Glu Leu Thr Gln Thr Pro Ala Ser
            20                  25                  30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
        35                  40                  45

Gln Asn Ile Tyr Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
    50                  55                  60

Pro Pro Lys Phe Leu Ile Tyr Leu Ala Ser Thr Leu Ala Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                85                  90                  95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Ser
            100                 105                 110

Tyr Tyr Ser Ser Asn Ser Val Ala
        115                 120
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<210> 283
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 283

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Glu Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln
            20                  25                  30

Pro Glu Gly Ser Leu Thr Leu Thr Cys Thr Ala Ser Glu Leu Asp Phe
        35                  40                  45

Ser Ser Gly Tyr Trp Ile Cys Trp Val Arg Gln Val Pro Gly Lys Gly
    50                  55                  60

Leu Glu Trp Ile Gly Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe
65                  70                  75                  80

Tyr Ala Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser
                85                  90                  95

Thr Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala
            100                 105                 110

Thr Tyr Phe Cys Ala Arg Gly Tyr Ser Gly Phe Gly Tyr Phe Lys Leu
        115                 120                 125
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<210> 284
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 284

Gln Ala Ser Gln Asn Ile Tyr Arg Tyr Leu Ala
1 5 10

<210> 285
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 285

Leu Ala Ser Thr Leu Ala Ser
1 5

<210> 286
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 286

Gln Ser Tyr Tyr Ser Ser Asn Ser Val Ala
1 5 10

<210> 287
<211> 6
<212> PRT
<213> Oryctolagus cuniculus

<400> 287

Ser Gly Tyr Trp Ile Cys
1 5

<210> 288
<211> 18
<212> PRT
<213> Oryctolagus cuniculus

<400> 288

Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr Ala Ser Trp Ala
1 5 10 15

Lys Gly

<210> 289
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 289

Gly Tyr Ser Gly Phe Gly Tyr Phe Lys Leu

<210> 290
<211> 360
<212> DNA
<213> Oryctolagus cuniculus

<400> 290
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agatgtgcat tcgaattgac ccagactcca gcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca attgccaggc cagtcagaac atttatagat acttagcctg gtatcagcag 180

aaaccagggc agcctcccaa gttcctgatc tatctggcat ctactctggc atctggggtc 240

ccatcgcggt ttaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactactgt caaagttatt atagtagtaa tagtgtcgct 360

<210> 291
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 291
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

gagcagctgg tggagtccgg gggagacctg gtccagcctg agggatccct gacactcacc 120

tgcacagctt ctgagttaga cttcagtagc ggctactgga tatgctgggt ccgccaggtt 180

ccagggaagg ggctggagtg gatcggatgc atttatactg gtagtagtgg tagcactttt 240

tacgcgagtt gggcgaaagg ccgattcacc atctccaaaa cctcgtcgac cacggtgact 300

ctgcaaatga ccagtctgac agccgcggac acggccacct atttctgtgc gagaggttat 360

agtggctttg gttactttaa gttg 384

<210> 292
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 292
caggccagtc agaacattta tagatactta gcc 33

<210> 293
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 293
ctggcatcta ctctggcatc t 21

<210> 294
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 294
caaagttatt atagtagtaa tagtgtcgct 30

<210> 295
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 295
agcggctact ggatatgc 18

<210> 296
<211> 54
<212> DNA
<213> Oryctolagus cuniculus

<400> 296
tgcatttata ctggtagtag tggtagcact ttttacgcga gttgggcgaa aggc 54

<210> 297
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 297
ggttatagtg gctttggtta ctttaagttg 30

<210> 298
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 298

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Asp Ile Tyr Arg Leu Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Asp Ser Ser Asp Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Ala
85 90 95

Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Ala Trp Ser Tyr Ser Asp Ile Asp Asn Ala
115 120

<210> 299
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 299

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
35 40 45

Ser Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

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

Ala Lys Gly Arg Leu Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Thr Ser Asp Ile Phe Tyr Tyr Arg Asn Leu
115 120

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<400> 301

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<210> 302
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<400> 302

Gln Gln Ala Trp Ser Tyr Ser Asp Ile Asp Asn Ala
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Ser Tyr Tyr Met Ser
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<210> 304
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<213> Oryctolagus cuniculus

<400> 304

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1 5 10

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gtcaccatca agtgccaggc cagtgaggac atttataggt tattggcctg gtatcaacag 180

aaaccagggc agcctcccaa gctcctgatc tatgattcat ccgatctggc atctggggtc 240

ccatcgcggt tcaaaggcag tggatctggg acagagttca ctctcgccat cagcggtgtg 300

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aatgct 366

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acagcctctg gattctccct cagtagctac tacatgagct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aatcattact actagtggta atacatttta cgcgagctgg 240

gcgaaaggcc ggctcaccat ctccagaacc tcgaccacgg tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagaa cttctgatat tttttattat 360

cgtaacttg 369

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<213> Oryctolagus cuniculus

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<210> 309
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<400> 309
gattcatccg atctggcatc t 21

<210> 310
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<213> Oryctolagus cuniculus

<400> 311
agctactaca tgagc 15

<210> 312
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 312
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<210> 313
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<213> Oryctolagus cuniculus

<400> 313
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<210> 314
<211> 123
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<213> Oryctolagus cuniculus

<400> 314

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Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Ala Ser Pro
            20                  25                  30

Val Ser Ala Ala Val Gly Ala Thr Val Thr Ile Asn Cys Gln Ser Ser
        35                  40                  45

Gln Ser Val Tyr Asn Asp Met Asp Leu Ala Trp Phe Gln Gln Lys Pro
    50                  55                  60

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

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
                85                  90                  95

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Leu Gly Ala Phe Asp Asp Asp Ala Asp Asn Thr
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<210> 315
<211> 129
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<213> Oryctolagus cuniculus

<400> 315

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1               5                  10                  15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr
        35                  40                  45

Arg His Ala Ile Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Cys Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Arg Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
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100 105 110

Arg Val Ile Gly Asp Thr Ala Gly Tyr Ala Tyr Phe Thr Gly Leu Asp
115 120 125

Leu

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<212> PRT
<213> Oryctolagus cuniculus

<400> 316

Gln Ser Ser Gln Ser Val Tyr Asn Asp Met Asp Leu Ala
1 5 10

<210> 317
<211> 7
<212> PRT
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<400> 317

Ser Ala Ser Thr Leu Ala Ser
1 5

<210> 318
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<213> Oryctolagus cuniculus

<400> 318

Leu Gly Ala Phe Asp Asp Asp Ala Asp Asn Thr
1 5 10

<210> 319
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<400> 319

Arg His Ala Ile Thr
1 5

<210> 320
<211> 16
<212> PRT
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<400> 320

Cys Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 321
<211> 16

<212> PRT
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<400> 321

Val Ile Gly Asp Thr Ala Gly Tyr Ala Tyr Phe Thr Gly Leu Asp Leu
1 5 10 15

<210> 322
<211> 369
<212> DNA
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acgtttgcag ccgtgctgac ccagactgca tcacccgtgt ctgccgctgt gggagccaca 120

gtcaccatca actgccagtc cagtcagagt gtttataatg acatggactt agcctggttt 180

cagcagaaac cagggcagcc tcccaagctc ctgatctatt ctgcatccac tctggcatct 240

ggggtcccat cgcggttcag cggcagtgga tctgggacag agttcactct caccatcagc 300

ggcgtgcagt gtgacgatgc tgccacttac tactgtctag gcgcttttga tgatgatgct 360

gataatact 369

<210> 323
<211> 387
<212> DNA
<213> Oryctolagus cuniculus

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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gattctccct cactaggcat gcaataacct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg atgcatttgg agtggtggta gcacatacta cgcgacctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctcag aatcaccagt 300

ccgacaaccg aggacacggc cacctacttc tgtgccagag tcattggcga tactgctggt 360

tatgcttatt ttacggggct tgacttg 387

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<210> 325
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<400> 325
tctgcatcca ctctggcatc t 21

<210> 326
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<400> 327
aggcatgcaa taacc 15

<210> 328
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<400> 328
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<210> 329
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<400> 329
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<210> 330
<211> 121
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<400> 330

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Asn Trp Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Thr Ala Ser Ser Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Gly Val Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Tyr Thr Ser Asp Val Asp Asn Val
115 120

<210> 331
<211> 130
<212> PRT
<213> Oryctolagus cuniculus

<400> 331

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
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Val Gln Cys Gln Ser Leu Glu Glu Ala Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
35 40 45

Ser Tyr Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Tyr Ile Gly Ile Ile Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Gln Ala Ser Ser Thr Thr Val Asp
85 90 95

Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Ser Ala Thr Tyr Phe Cys
100 105 110

Ala Arg Gly Gly Ala Gly Ser Gly Gly Val Trp Leu Leu Asp Gly Phe
115 120 125

Asp Pro
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<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 332

Gln Ala Ser Gln Ser Val Tyr Asn Trp Leu Ser
1 5 10

<210> 333
<211> 7
<212> PRT
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<400> 333

Thr Ala Ser Ser Leu Ala Ser
1 5

<210> 334
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<400> 334

Gln Gln Gly Tyr Thr Ser Asp Val Asp Asn Val
1 5 10

<210> 335
<211> 5
<212> PRT
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<400> 335

Ser Tyr Ala Met Gly
1 5

<210> 336
<211> 16
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<213> Oryctolagus cuniculus

<400> 336

Ile Ile Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 337
<211> 16
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<400> 337

Gly Gly Ala Gly Ser Gly Gly Val Trp Leu Leu Asp Gly Phe Asp Pro
1 5 10 15

<210> 338
<211> 363
<212> DNA
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agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtcagagt gtttataatt ggttatcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc tatactgcat ccagtctggc atctggggtc 240

ccatcgcggt tcagtggcag tggatctggg acagagttca ctctcaccat cagcggcgtg 300

gagtgtgccg atgctgccac ttactactgt caacagggtt atactagtga tgttgataat 360

gtt 363

<210> 339
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<212> DNA
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tcgctggagg aggccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gaatcgacct cagtagctat gcaatgggct gggtccgcca ggctccaggg 180

aaggggctgg aatacatcgg aatcattagt agtagtggta gcacatacta cgcgacctgg 240

gcgaaaggcc gattcaccat ctcacaagcc tcgtcgacca cggtggatct gaaaattacc 300

agtccgacaa ccgaggactc ggccacatat ttctgtgcca gaggggggtgc tggtagtggt 360

ggtgtttggc tgcttgatgg ttttgatccc 390

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<210> 341
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<400> 341
actgcatcca gtctggcatc t 21

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caacagggtt atactagtga tgttgataat gtt 33

<210> 343
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<212> DNA
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<400> 343
agctatgcaa tgggc 15

<210> 344
<211> 48
<212> DNA
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<400> 344
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<210> 345
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

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gggggtgctg gtagtggtgg tgtttggctg cttgatggtt ttgatccc 48

<210> 346
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 346

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Lys Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20 25 30

Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala
35 40 45

Ser Glu Asn Ile Tyr Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly
50 55 60

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

Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
85 90 95

Thr Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln
100 105 110

Gln Gly Tyr Ser Ser Ser Tyr Val Asp Asn Val
115 120

<210> 347
<211> 130
<212> PRT
<213> Oryctolagus cuniculus

<400> 347

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Glu Gln Leu Lys Glu Ser Gly Gly Arg Leu Val Thr
20 25 30

Pro Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu
35 40 45

Asn Asp Tyr Ala Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu

50 55 60

Glu Trp Ile Gly Tyr Ile Arg Ser Ser Gly Thr Thr Ala Tyr Ala Thr
65 70 75 80

Trp Ala Lys Gly Arg Phe Thr Ile Ser Ala Thr Ser Thr Thr Val Asp
85 90 95

Leu Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110

Ala Arg Gly Gly Ala Gly Ser Ser Gly Val Trp Ile Leu Asp Gly Phe
115 120 125

Ala Pro
130

<210> 348
<211> 11
<212> PRT
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<400> 348

Gln Ala Ser Glu Asn Ile Tyr Asn Trp Leu Ala
1 5 10

<210> 349
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<400> 349

Thr Val Gly Asp Leu Ala Ser
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<210> 350
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<400> 350

Gln Gln Gly Tyr Ser Ser Ser Tyr Val Asp Asn Val
1 5 10

<210> 351
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<400> 351

Asp Tyr Ala Val Gly
1 5

<210> 352

<211> 16
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<400> 352

Tyr Ile Arg Ser Ser Gly Thr Thr Ala Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 353
<211> 16
<212> PRT
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<400> 353

Gly Gly Ala Gly Ser Ser Gly Val Trp Ile Leu Asp Gly Phe Ala Pro
1 5 10 15

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<212> DNA
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aaatgtgccg atgttgtgat gacccagact ccagcctccg tgtctgcagc tgtgggaggc 120

acagtcacca tcaattgcca ggccagtgag aacatttata attggttagc ctggtatcag 180

cagaaaccag ggcagcctcc caagctcctg atctatactg taggcgatct ggcatctggg 240

gtctcatcgc ggttcaaagg cagtggatct gggacagagt tcactctcac catcagcgac 300

ctggagtgtg ccgatgctgc cacttactat tgtcaacagg gttatagtag tagttatgtt 360

gataatgtt 369

<210> 355
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<212> DNA
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<400> 355
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gagcagctga aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 120

tgcacagtct ctggattctc cctcaatgac tatgcagtgg gctggttccg ccaggctcca 180

gggaaggggc tggaatggat cggatacatt cgtagtagtg gtaccacagc ctacgcgacc 240

tgggcgaaag gccgattcac catctccgct acctcgacca cggtggatct gaaaatcacc 300

agtccgacaa ccgaggacac ggccacctat ttctgtgcca gaggggggtgc tggtagtagt 360

ggtgtgtgga tccttgatgg ttttgctccc 390

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<211> 33
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<210> 357
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<400> 357
actgtaggcg atctggcatc t 21

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<400> 358
caacagggtt atagtagtag ttatgttgat aatgtt 36

<210> 359
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<212> DNA
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<400> 359
gactatgcag tgggc 15

<210> 360
<211> 48
<212> DNA
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<400> 360
tacattcgta gtagtggtac cacagcctac gcgacctggg cgaaaggc 48

<210> 361
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<212> DNA
<213> Oryctolagus cuniculus

<400> 361
gggggtgctg gtagtagtgg tgtgtggatc cttgatggtt ttgctccc 48

<210> 362
<211> 121
<212> PRT
<213> Oryctolagus cuniculus

<400> 362

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Gln Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Ala Gly Ala Tyr Arg Asp Val Asp Ser
115 120

<210> 363
<211> 130
<212> PRT
<213> Oryctolagus cuniculus

<400> 363

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro
20 25 30

Gly Ala Ser Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Phe Thr
35 40 45

Ser Thr Tyr Tyr Ile Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Ile Ala Cys Ile Asp Ala Gly Ser Ser Gly Ser Thr Tyr Tyr
65 70 75 80

Ala Thr Trp Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
85 90 95

Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Ala Lys Trp Asp Tyr Gly Gly Asn Val Gly Trp Gly Tyr
115 120 125

Asp Leu
130

<210> 364
<211> 13
<212> PRT
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<400> 364

Gln Ala Ser Gln Ser Val Tyr Gln Asn Asn Tyr Leu Ser
1 5 10

<210> 365
<211> 7
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<400> 365

Gly Ala Ala Thr Leu Ala Ser
1 5

<210> 366
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<213> Oryctolagus cuniculus

<400> 366

Ala Gly Ala Tyr Arg Asp Val Asp Ser
1 5

<210> 367
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<400> 367

Ser Thr Tyr Tyr Ile Tyr
1 5

<210> 368
<211> 18
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<400> 368

Cys Ile Asp Ala Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Val
1 5 10 15

Asn Gly

<210> 369
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<400> 369

Trp Asp Tyr Gly Gly Asn Val Gly Trp Gly Tyr Asp Leu
1 5 10

<210> 370
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<213> Oryctolagus cuniculus

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acatttgctc aagtgctgac ccagactcca tcctccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca attgccaggc cagtcagagt gtttatcaga acaactactt atcctggttt 180

cagcagaaac cagggcagcc tcccaagctc ctgatctatg gtgcggccac tctggcatct 240

ggggtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc 300

gacctggagt gtgacgatgc tgccacttac tactgtgcag gcgcttatag ggatgtggat 360

tct 363

<210> 371
<211> 390
<212> DNA
<213> Oryctolagus cuniculus

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tcgttggagg agtccggggg agacctggtc aagcctgggg catccctgac actcacctgc 120

acagcctctg gattctcctt tactagtacc tactacatct actgggtccg ccaggctcca 180

gggaaggggc tggagtggat cgcatgtatt gatgctggta gtagtggtag cacttactac 240

gcgacctggg tgaatggccg attcaccatc tccaaaacct cgtcgaccac ggtgactctg 300

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ggtggtaatg ttggttgggg ttatgacttg 390

<210> 372
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 372
caggccagtc agagtgttta tcagaacaac tacttatcc 39

<210> 373
<211> 21
<212> DNA
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<400> 373
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<210> 374
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<212> DNA
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<400> 374
gcaggcgctt atagggatgt ggattct 27

<210> 375
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<212> DNA
<213> Oryctolagus cuniculus

<400> 375
agtacctact acatctac 18

<210> 376
<211> 54
<212> DNA
<213> Oryctolagus cuniculus

<400> 376
tgtattgatg ctggtagtag tggtagcact tactacgcga cctgggtgaa tggc 54

<210> 377
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 377
tgggattatg gtggtaatgt tggttggggt tatgacttg 39

<210> 378
<211> 120
<212> PRT
<213> Oryctolagus cuniculus

<400> 378

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Phe Glu Leu Thr Gln Thr Pro Ser Ser
20 25 30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Gln Ser Ile Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

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

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Ser
100 105 110

Tyr Tyr Asp Ser Val Ser Asn Pro
115 120

<210> 379
<211> 127
<212> PRT
<213> Oryctolagus cuniculus

<400> 379

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                  10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro
            20                  25                  30

Glu Gly Ser Leu Thr Leu Thr Cys Lys Ala Ser Gly Leu Asp Leu Gly
        35                  40                  45

Thr Tyr Trp Phe Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Ala Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr
65                  70                  75                  80

Ala Ser Trp Val Asn Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr
                85                  90                  95

Thr Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr
            100                 105                 110

Tyr Phe Cys Ala Arg Gly Tyr Ser Gly Tyr Gly Tyr Phe Lys Leu
        115                 120                 125
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<210> 380
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<212> PRT
<213> Oryctolagus cuniculus

<400> 380

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1               5                  10
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<210> 381
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<213> Oryctolagus cuniculus

<400> 381

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Arg Ala Ser Thr Leu Ala Ser
1               5
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<210> 382
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 382

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Gln Ser Tyr Tyr Asp Ser Val Ser Asn Pro
1               5                  10
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<210> 383
<211> 6
<212> PRT
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<400> 383

Thr Tyr Trp Phe Met Cys
1 5

<210> 384
<211> 18
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<213> Oryctolagus cuniculus

<400> 384

Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr Ala Ser Trp Val
1 5 10 15

Asn Gly

<210> 385
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 385

Gly Tyr Ser Gly Tyr Gly Tyr Phe Lys Leu
1 5 10

<210> 386
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<212> DNA
<213> Oryctolagus cuniculus

<400> 386
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agatgtgcat tcgaattgac ccagactcca tcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtcagagc attagtagtt acttagcctg gtatcagcag 180

aaaccagggc agcctcccaa gttcctgatc tacagggcgt ccactctggc atctggggtc 240

ccatcgcgat tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactactgt caaagctatt atgatagtgt ttcaaatcct 360

<210> 387
<211> 381
<212> DNA
<213> Oryctolagus cuniculus

<400> 387
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgttggagg agtccggggg agacctggtc aagcctgagg gatccctgac actcacctgc 120

aaagcctctg gactcgacct cggtacctac tggttcatgt gctgggtccg ccaggctcca 180

gggaaggggc tggagtggat cgcttgtatt tatactggta gtagtggttc cactttctac 240

gcgagctggg tgaatggccg attcaccatc tccaaaacct cgtcgaccac ggtgactctg 300

caaatgacca gtctgacagc cgcggacacg gccacttatt tttgtgcgag aggttatagt 360

ggttatggtt attttaagtt g 381

<210> 388
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 388
caggccagtc agagcattag tagttactta gcc 33

<210> 389
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 389
agggcgtcca ctctggcatc t 21

<210> 390
<211> 30
<212> DNA
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<400> 390
caaagctatt atgatagtgt ttcaaatcct 30

<210> 391
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 391
acctactggt tcatgtgc 18

<210> 392
<211> 54
<212> DNA
<213> Oryctolagus cuniculus

<400> 392
tgtatttata ctggtagtag tggttccact ttctacgcga gctgggtgaa tggc 54

<210> 393
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 393
ggttatagtg gttatggtta ttttaagttg 30

<210> 394
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 394

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Val Thr Phe Ala Ile Glu Met Thr Gln Ser Pro Phe Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ala Ser
35 40 45

Gln Ser Val Tyr Lys Asn Asn Gln Leu Ser Trp Tyr Gln Gln Lys Ser
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Ala Leu Ala Ser
65 70 75 80

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr
85 90 95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100 105 110

Ala Gly Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
115 120

<210> 395
<211> 130
<212> PRT
<213> Oryctolagus cuniculus

<400> 395

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Asp Leu Val Lys Pro
20 25 30

Gly Ala Ser Leu Thr Leu Thr Cys Thr Thr Ser Gly Phe Ser Phe Ser
35 40 45

Ser Ser Tyr Phe Ile Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Ile Ala Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Tyr Ala
65 70 75 80

Ser Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr
85 90 95

Val Thr Leu Gln Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr
100 105 110

Phe Cys Ala Arg Glu Trp Ala Tyr Ser Gln Gly Tyr Phe Gly Ala Phe
115 120 125

Asp Leu
130

<210> 396
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 396

Gln Ala Ser Gln Ser Val Tyr Lys Asn Asn Gln Leu Ser
1 5 10

<210> 397
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 397

Gly Ala Ser Ala Leu Ala Ser
1 5

<210> 398
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 398

Ala Gly Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
1 5 10

<210> 399
<211> 6
<212> PRT
<213> Oryctolagus cuniculus

<400> 399

Ser Ser Tyr Phe Ile Cys
1 5

<210> 400
<211> 17
<212> PRT
<213> Oryctolagus cuniculus

<400> 400

Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
1 5 10 15

Gly

<210> 401
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 401

Glu Trp Ala Tyr Ser Gln Gly Tyr Phe Gly Ala Phe Asp Leu
1 5 10

<210> 402
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

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acatttgcca tcgaaatgac ccagagtcca ttctccgtgt ctgcagctgt gggaggcaca 120

gtcagcatca gttgccaggc cagtcagagt gtttataaga acaaccaatt atcctggtat 180

cagcagaaat cagggcagcc tcccaagctc ctgatctatg gtgcatcggc tctggcatct 240

ggggtcccat cgcggttcaa aggcagtgga tctgggacag agttcactct caccatcagc 300

gacgtgcagt gtgacgatgc tgccacttac tactgtgcag gcgctattac tggtagtatt 360

gatacggatg gt 372

<210> 403
<211> 390
<212> DNA
<213> Oryctolagus cuniculus

<400> 403
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgttggagg agtccggggg agacctggtc aagcctgggg catccctgac actcacctgc 120

acaacttctg gattctcctt cagtagcagc tacttcattt gctgggtccg ccaggctcca 180

gggaaggggc tggagtggat cgcatgcatt tatggtggtg atggcagcac atactacgcg 240

agctgggcga aaggccgatt caccatctcc aaaacctcgt cgaccacggt gacgctgcaa 300

atgaccagtc tgacagccgc ggacacggcc acctatttct gtgcgagaga atgggcatat 360

agtcaaggtt attttggtgc ttttgatctc 390

<210> 404
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 404
caggccagtc agagtgttta taagaacaac caattatcc 39

<210> 405
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 405

ggtgcatcgg ctctggcatc t 21

<210> 406
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 406
gcaggcgcta ttactggtag tattgatacg gatggt 36

<210> 407
<211> 18
<212> DNA
<213> Oryctolagus cuniculus

<400> 407
agcagctact tcatttgc 18

<210> 408
<211> 51
<212> DNA
<213> Oryctolagus cuniculus

<400> 408
tgcatttatg gtggtgatgg cagcacatac tacgcgagct gggcgaaagg c 51

<210> 409
<211> 42
<212> DNA
<213> Oryctolagus cuniculus

<400> 409
gaatgggcat atagtcaagg ttattttggt gcttttgatc tc 42

<210> 410
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 410

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Asp Ile Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val
65 70 75 80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Cys
100 105 110

Thr Tyr Gly Thr Ile Ser Ile Ser Asp Gly Asn Ala
115 120

<210> 411
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 411

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

Ser Tyr Phe Met Thr Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
50 55 60

Tyr Ile Gly Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp
65 70 75 80

Val Lys Gly Arg Phe Thr Ile Ser Lys Ser Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
115 120

<210> 412
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 412

Gln Ala Ser Glu Asp Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 413
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 413

Ala Ala Ser Asn Leu Glu Ser

1 5

<210> 414
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 414

Gln Cys Thr Tyr Gly Thr Ile Ser Ile Ser Asp Gly Asn Ala
1 5 10

<210> 415
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 415

Ser Tyr Phe Met Thr
1 5

<210> 416
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 416

Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Val Lys Gly
1 5 10 15

<210> 417
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 417

Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
1 5 10

<210> 418
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 418
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agatgtgatg ttgtgatgac ccagactcca gcctccgtgg aggcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtgaggat attagtagct acttagcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc tatgctgcat ccaatctgga atctggggtc 240

tcatcgcgat tcaaaggcag tggatctggg acagagtaca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ctattactgt caatgtactt atggtactat ttctattagt 360

gatggtaatg ct 372

<210> 419
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 419
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccaatgtcag 60

tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gattctccct cagtagctac ttcatgacct gggtccgcca ggctccaggg 180

gaggggctgg aatacatcgg attcattaat cctggtggta gcgcttacta cgcgagctgg 240

gtgaaaggcc gattcaccat ctccaagtcc tcgaccacgg tagatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccaggg ttctgattgt ttcttatgga 360

gcctttacca tc 372

<210> 420
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 420
caggccagtg aggatattag tagctactta gcc 33

<210> 421
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 421
gctgcatcca atctggaatc t 21

<210> 422
<211> 42
<212> DNA
<213> Oryctolagus cuniculus

<400> 422
caatgtactt atggtactat ttctattagt gatggtaatg ct 42

<210> 423
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 423
agctacttca tgacc 15

<210> 424
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 424
ttcattaatc ctggtggtag cgcttactac gcgagctggg tgaaaggc 48

<210> 425
<211> 33

<212> DNA
<213> Oryctolagus cuniculus

<400> 425
gttctgattg tttcttatgg agcctttacc atc 33

<210> 426
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 426

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Val Val Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
35 40 45

Glu Asp Ile Glu Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Glu Ser Gly Val
65 70 75 80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Cys
100 105 110

Thr Tyr Gly Ile Ile Ser Ile Ser Asp Gly Asn Ala
115 120

<210> 427
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 427

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

Ser Tyr Phe Met Thr Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
50 55 60

Tyr Ile Gly Phe Met Asn Thr Gly Asp Asn Ala Tyr Tyr Ala Ser Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
85 90 95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Val Leu Val Val Ala Tyr Gly Ala Phe Asn Ile
115 120

<210> 428
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 428

Gln Ala Ser Glu Asp Ile Glu Ser Tyr Leu Ala
1 5 10

<210> 429
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 429

Gly Ala Ser Asn Leu Glu Ser
1 5

<210> 430
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 430

Gln Cys Thr Tyr Gly Ile Ile Ser Ile Ser Asp Gly Asn Ala
1 5 10

<210> 431
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 431

Ser Tyr Phe Met Thr
1 5

<210> 432
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 432

Phe Met Asn Thr Gly Asp Asn Ala Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 433
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 433

Val Leu Val Val Ala Tyr Gly Ala Phe Asn Ile
1 5 10

<210> 434
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 434
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agatgtgatg ttgtgatgac ccagactcca gcctccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca agtgccaggc cagtgaggac attgaaagct atctagcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc tatggtgcat ccaatctgga atctggggtc 240

tcatcgcggt tcaaaggcag tggatctggg acagagttca ctctcaccat cagcgacctg 300

gagtgtgccg atgctgccac ttactattgt caatgcactt atggtattat tagtattagt 360

gatggtaatg ct 372

<210> 435
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 435
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tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtgtctg gattctccct cagtagctac ttcatgacct gggtccgcca ggctccaggg 180

gaggggctgg aatacatcgg attcatgaat actggtgata acgcatacta cgcgagctgg 240

gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccaggg ttcttgttgt tgcttatgga 360

gcctttaaca tc 372

<210> 436
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 436
caggccagtg aggacattga aagctatcta gcc 33

<210> 437
<211> 21

<212> DNA
<213> Oryctolagus cuniculus

<400> 437
ggtgcatcca atctggaatc t 21

<210> 438
<211> 42
<212> DNA
<213> Oryctolagus cuniculus

<400> 438
caatgcactt atggtattat tagtattagt gatggtaatg ct 42

<210> 439
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 439
agctacttca tgacc 15

<210> 440
<211> 48
<212> DNA
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<400> 440
ttcatgaata ctggtgataa cgcatactac gcgagctggg cgaaaggc 48

<210> 441
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 441
gttcttgttg ttgcttatgg agcctttaac atc 33

<210> 442
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 442

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Glu Pro Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ser Ser
35 40 45

Lys Ser Val Met Asn Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Ala Ser
65 70 75 80

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Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Gln Gly Gly Tyr Thr Gly Tyr Ser Asp His Gly Thr
        115                 120
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<210> 443
<211> 127
<212> PRT
<213> Oryctolagus cuniculus

<400> 443

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1               5                   10                  15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Lys Pro
            20                  25                  30

Asp Glu Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
        35                  40                  45

Ser Tyr Pro Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

Trp Ile Gly Phe Ile Asn Thr Gly Gly Thr Ile Val Tyr Ala Ser Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Gly Ser Tyr Val Ser Ser Gly Tyr Ala Tyr Tyr Phe Asn Val
        115                 120                 125
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<210> 444
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 444

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Gln Ser Ser Lys Ser Val Met Asn Asn Asn Tyr Leu Ala
1               5                   10
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<210> 445
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 445

Gly Ala Ser Asn Leu Ala Ser
1 5

<210> 446
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 446

Gln Gly Gly Tyr Thr Gly Tyr Ser Asp His Gly Thr
1 5 10

<210> 447
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 447

Ser Tyr Pro Met Asn
1 5

<210> 448
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 448

Phe Ile Asn Thr Gly Gly Thr Ile Val Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 449
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 449

Gly Ser Tyr Val Ser Ser Gly Tyr Ala Tyr Tyr Phe Asn Val
1 5 10

<210> 450
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 450
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

acatttgccg ccgtgctgac ccagactcca tctcccgtgt ctgaacctgt gggaggcaca 120

gtcagcatca gttgccagtc cagtaagagt gttatgaata acaactactt agcctggtat 180

cagcagaaac cagggcagcc tcccaagctc ctgatctatg gtgcatccaa tctggcatct 240

ggggtcccat cacggttcag cggcagtgga tctgggacac agttcactct caccatcagc 300

gacgtgcagt gtgacgatgc tgccacttac tactgtcaag gcggttatac tggttatagt 360

gatcatggga ct 372

<210> 451
<211> 381
<212> DNA
<213> Oryctolagus cuniculus

<400> 451
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcggtggagg agtccggggg tcgcctggtc aagcctgacg aaaccctgac actcacctgc 120

acagtctctg gaatcgacct cagtagctat ccaatgaact gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg attcattaat actggtggta ccatagtcta cgcgagctgg 240

gcaaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag gcagttatgt ttcatctggt 360

tatgcctact attttaatgt c 381

<210> 452
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 452
cagtccagta agagtgttat gaataacaac tacttagcc 39

<210> 453
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 453
ggtgcatcca atctggcatc t 21

<210> 454
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 454
caaggcggtt atactggtta tagtgatcat gggact 36

<210> 455
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 455
agctatccaa tgaac 15

<210> 456
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 456
ttcattaata ctggtggtac catagtctac gcgagctggg caaaaggc 48

<210> 457
<211> 42
<212> DNA
<213> Oryctolagus cuniculus

<400> 457
ggcagttatg tttcatctgg ttatgcctac tattttaatg tc 42

<210> 458
<211> 121
<212> PRT
<213> Oryctolagus cuniculus

<400> 458

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ser Ser
35 40 45

Gln Ser Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
85 90 95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys
100 105 110

Ala Gly Gly Tyr Leu Asp Ser Val Ile
115 120

<210> 459
<211> 126
<212> PRT
<213> Oryctolagus cuniculus

<400> 459

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

```
Thr Tyr Ser Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    50                  55                  60

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

Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Glu Ser Gly Met Tyr Asn Glu Tyr Gly Lys Phe Asn Ile
        115                 120                 125
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<210> 460
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 460

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Gln Ser Ser Gln Ser Val Tyr Asn Asn Asn Trp Leu Ser
1               5                   10
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<210> 461
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 461

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Lys Ala Ser Thr Leu Ala Ser
1               5
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<210> 462
<211> 9
<212> PRT
<213> Oryctolagus cuniculus

<400> 462

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Ala Gly Gly Tyr Leu Asp Ser Val Ile
1               5
```

<210> 463
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 463

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Thr Tyr Ser Ile Asn
1               5
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<210> 464
<211> 16
<212> PRT

<213> Oryctolagus cuniculus

<400> 464

Ile Ile Ala Asn Ser Gly Thr Thr Phe Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 465
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 465

Glu Ser Gly Met Tyr Asn Glu Tyr Gly Lys Phe Asn Ile
1 5 10

<210> 466
<211> 363
<212> DNA
<213> Oryctolagus cuniculus

<400> 466
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acatttgccg ccgtgctgac ccagactcca tctcccgtgt ctgcagctgt gggaggcaca 120

gtcagcatca gttgccagtc cagtcagagt gtttataata acaactggtt atcctggttt 180

cagcagaaac cagggcagcc tcccaagctc ctgatctaca aggcatccac tctggcatct 240

ggggtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc 300

gacgtgcagt gtgacgatgt tgccacttac tactgtgcgg gcggttatct tgatagtgtt 360

att 363

<210> 467
<211> 378
<212> DNA
<213> Oryctolagus cuniculus

<400> 467
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gattctccct cagtacctat tcaataaact gggtccgcca ggctccaggg 180

aagggcctgg aatggatcgg aatcattgct aatagtggta ccacattcta cgcgaactgg 240

gcgaaaggcc gattcaccgt ctccaaaacc tcgaccacgg tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag agagtggaat gtacaatgaa 360

tatggtaaat ttaacatc 378

<210> 468
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 468
cagtccagtc agagtgttta taataacaac tggttatcc 39

<210> 469
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 469
aaggcatcca ctctggcatc t 21

<210> 470
<211> 27
<212> DNA
<213> Oryctolagus cuniculus

<400> 470
gcgggcggtt atcttgatag tgttatt 27

<210> 471
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 471
acctattcaa taaac 15

<210> 472
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 472
atcattgcta atagtggtac cacattctac gcgaactggg cgaaaggc 48

<210> 473
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 473
gagagtggaa tgtacaatga atatggtaaa tttaacatc 39

<210> 474
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 474

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ser Asp Met Thr Gln Thr Pro Ser Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45

Glu Asn Ile Tyr Ser Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

```
Pro Pro Lys Leu Leu Ile Phe Lys Ala Ser Thr Leu Ala Ser Gly Val
65                  70                  75                  80

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
                85                  90                  95

Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
        115                 120
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<210> 475
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 475

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
        35                  40                  45

Ala Tyr Ala Met Ile Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60

Trp Ile Thr Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Tyr Ala Asn Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Ala Met Asp Leu
                85                  90                  95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
        115                 120                 125
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<210> 476
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 476

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Gln Ala Ser Glu Asn Ile Tyr Ser Phe Leu Ala
1               5                   10
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<210> 477
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 477

Lys Ala Ser Thr Leu Ala Ser
1 5

<210> 478
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 478

Gln Gln Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
1 5 10

<210> 479
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 479

Ala Tyr Ala Met Ile
1 5

<210> 480
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 480

Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 481
<211> 15
<212> PRT
<213> Oryctolagus cuniculus

<400> 481

Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
1 5 10 15

<210> 482
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 482
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

agatgtgcct ctgatatgac ccagactcca tcctccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca attgccaggc cagtgagaac atttatagct ttttggcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc ttcaaggctt ccactctggc atctggggtc 240

tcatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat cagcgacctg 300

gagtgtgacg atgctgccac ttactactgt caacagggtg ctactgtgta tgatattgat 360

aataat 366

<210> 483
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 483
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtttctg gaatcgacct cagtgcctat gcaatgatct gggtccgcca ggctccaggg 180

gaggggctgg aatggatcac aatcatttat cctaatggta tcacatacta cgcgaactgg 240

gcgaaaggcc gattcaccgt ctccaaaacc tcgaccgcga tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag atgcagaaag tagtaagaat 360

gcttattggg gctactttaa cgtc 384

<210> 484
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 484
caggccagtg agaacattta tagctttttg gcc 33

<210> 485
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 485
aaggcttcca ctctggcatc t 21

<210> 486
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 486
caacagggtg ctactgtgta tgatattgat aataat 36

<210> 487
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 487
gcctatgcaa tgatc 15

<210> 488
<211> 48
<212> DNA

<213> Oryctolagus cuniculus

<400> 488
atcatttatc ctaatggtat cacatactac gcgaactggg cgaaaggc 48

<210> 489
<211> 45
<212> DNA
<213> Oryctolagus cuniculus

<400> 489
gatgcagaaa gtagtaagaa tgcttattgg ggctacttta acgtc 45

<210> 490
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 490

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ser Asp Met Thr Gln Thr Pro Ser Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45

Glu Asn Ile Tyr Ser Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

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

Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85 90 95

Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
115 120

<210> 491
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 491

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

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Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
        35                  40                  45

Ala Tyr Ala Met Ile Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60

Trp Ile Thr Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Tyr Ala Asn Trp
65                  70                  75                  80

Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Ala Met Asp Leu
                85                  90                  95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
        115                 120                 125
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<210> 492
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 492

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Gln Ala Ser Glu Asn Ile Tyr Ser Phe Leu Ala
1               5                   10
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<210> 493
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 493

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Arg Ala Ser Thr Leu Ala Ser
1               5
```

<210> 494
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 494

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Gln Gln Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
1               5                   10
```

<210> 495
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 495

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Ala Tyr Ala Met Ile
1               5
```

<210> 496
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 496

Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 497
<211> 15
<212> PRT
<213> Oryctolagus cuniculus

<400> 497

Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
1 5 10 15

<210> 498
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 498
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agatgtgcct ctgatatgac ccagactcca tcctccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca attgccaggc cagtgagaac atttatagct ttttggcctg gtatcagcag 180

aaaccagggc agcctcccaa gctcctgatc ttcagggctt ccactctggc atctggggtc 240

tcatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat cagcgacctg 300

gagtgtgacg atgctgccac ttactactgt caacagggtg ctactgtgta tgatattgat 360

aataat 366

<210> 499
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 499
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtttctg gaatcgacct cagtgcctat gcaatgatct gggtccgcca ggctccaggg 180

gaggggctgg aatggatcac aatcatttat cctaatggta tcacatacta cgcgaactgg 240

gcgaaaggcc gattcaccgt ctccaaaacc tcgaccgcga tggatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag atgcagaaag tagtaagaat 360

gcttattggg gctactttaa cgtc 384

<210> 500
<211> 33
<212> DNA

<213> Oryctolagus cuniculus

<400> 500
caggccagtg agaacattta tagctttttg gcc 33

<210> 501
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 501
agggcttcca ctctggcatc t 21

<210> 502
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 502
caacagggtg ctactgtgta tgatattgat aataat 36

<210> 503
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 503
gcctatgcaa tgatc 15

<210> 504
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 504
atcatttatc ctaatggtat cacatactac gcgaactggg cgaaaggc 48

<210> 505
<211> 45
<212> DNA
<213> Oryctolagus cuniculus

<400> 505
gatgcagaaa gtagtaagaa tgcttattgg ggctacttta acgtc 45

<210> 506
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 506

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Ile Glu Met Thr Gln Thr Pro Ser Pro
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45

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Glu Ser Val Phe Asn Asn Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly
    50                  55                  60

His Ser Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly
65                  70                  75                  80

Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu
                85                  90                  95

Thr Ile Ser Gly Val Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Ala
            100                 105                 110

Gly Tyr Lys Ser Asp Ser Asn Asp Gly Asp Asn Val
        115                 120
```

<210> 507
<211> 123
<212> PRT
<213> Oryctolagus cuniculus

<400> 507

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Asn
        35                  40                  45

Arg Asn Ser Ile Thr Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60

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

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Gly His Pro Gly Leu Gly Ser Gly Asn Ile
        115                 120
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<210> 508
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 508

Gln Ala Ser Glu Ser Val Phe Asn Asn Met Leu Ser
1 5 10

<210> 509
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 509

Asp Ala Ser Asp Leu Ala Ser
1 5

<210> 510
<211> 13
<212> PRT
<213> Oryctolagus cuniculus

<400> 510

Ala Gly Tyr Lys Ser Asp Ser Asn Asp Gly Asp Asn Val
1 5 10

<210> 511
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 511

Arg Asn Ser Ile Thr
1 5

<210> 512
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 512

Ile Ile Thr Gly Ser Gly Arg Thr Tyr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 513
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 513

Gly His Pro Gly Leu Gly Ser Gly Asn Ile
1 5 10

<210> 514
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 514
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

acatttgcca ttgaaatgac ccagactcca tcccccgtgt ctgccgctgt gggaggcaca 120

gtcaccatca attgccaggc cagtgagagt gtttttaata atatgttatc ctggtatcag 180

cagaaaccag ggcactctcc taagctcctg atctatgatg catccgatct ggcatctggg 240

gtcccatcgc ggttcaaagg cagtggatct gggacacagt tcactctcac catcagtggc 300

gtggagtgtg acgatgctgc cacttactat tgtgcagggt ataaaagtga tagtaatgat 360

ggcgataatg tt 372

<210> 515
<211> 369
<212> DNA
<213> Oryctolagus cuniculus

<400> 515
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtctctg gattctccct caacaggaat tcaataacct gggtccgcca ggctccaggg 180

gaggggctgg aatggatcgg aatcattact ggtagtggta gaacgtacta cgcgaactgg 240

gcaaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatgaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagag gccatcctgg tcttggtagt 360

ggtaacatc 369

<210> 516
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 516
caggccagtg agagtgtttt taataatatg ttatcc 36

<210> 517
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 517
gatgcatccg atctggcatc t 21

<210> 518
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 518
gcagggtata aaagtgatag taatgatggc gataatgtt 39

<210> 519
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 519
aggaattcaa taacc 15

<210> 520
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 520
atcattactg gtagtggtag aacgtactac gcgaactggg caaaaggc 48

<210> 521
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 521
ggccatcctg gtcttggtag tggtaacatc 30

<210> 522
<211> 121
<212> PRT
<213> Oryctolagus cuniculus

<400> 522

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Ala Ser Ser
20 25 30

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
35 40 45

Gln Ser Val Tyr Asn Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
50 55 60

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

Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu
85 90 95

Thr Ile Ser Glu Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln
100 105 110

Gly Tyr Tyr Ser Gly Pro Ile Ile Thr
115 120

<210> 523
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 523

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

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Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Asn
        35                  40                  45

Asn Tyr Tyr Ile Gln Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60

Trp Ile Gly Ile Ile Tyr Ala Gly Gly Ser Ala Tyr Tyr Ala Thr Trp
65                  70                  75                  80

Ala Asn Gly Arg Phe Thr Ile Ala Lys Thr Ser Ser Thr Thr Val Asp
                85                  90                  95

Leu Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
            100                 105                 110

Ala Arg Gly Thr Phe Asp Gly Tyr Glu Leu
        115                 120
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<210> 524
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 524

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Gln Ser Ser Gln Ser Val Tyr Asn Asn Tyr Leu Ser
1               5                   10
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<210> 525
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 525

```
Thr Ala Ser Ser Leu Ala Ser
1               5
```

<210> 526
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 526

```
Gln Gly Tyr Tyr Ser Gly Pro Ile Ile Thr
1               5                   10
```

<210> 527
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 527

Asn Tyr Tyr Ile Gln
1 5

<210> 528
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 528

Ile Ile Tyr Ala Gly Gly Ser Ala Tyr Tyr Ala Thr Trp Ala Asn Gly
1 5 10 15

<210> 529
<211> 8
<212> PRT
<213> Oryctolagus cuniculus

<400> 529

Gly Thr Phe Asp Gly Tyr Glu Leu
1 5

<210> 530
<211> 363
<212> DNA
<213> Oryctolagus cuniculus

<400> 530
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

acatttgcgc aagtgctgac ccagactgca tcgtccgtgt ctgcagctgt gggaggcaca 120

gtcaccatca attgccagtc cagtcagagt gtttataata actacttatc ctggtatcag 180

cagaaaccag ggcagcctcc caagctcctg atctatactg catccagcct ggcatctggg 240

gtcccatcgc ggttcaaagg cagtggatct gggacacagt tcactctcac catcagcgaa 300

gtgcagtgtg acgatgctgc cacttactac tgtcaaggct attatagtgg tcctataatt 360

act 363

<210> 531
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 531
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagcctctg gattctccct caataactac tacatacaat gggtccgcca ggctccaggg 180

gaggggctgg aatggatcgg gatcatttat gctggtggta gcgcatacta cgcgacctgg 240

gcaaacggcc gattcaccat cgccaaaacc tcgtcgacca cggtggatct gaagatgacc 300

agtctgacaa ccgaggacac ggccacctat ttctgtgcca gagggacatt tgatggttat 360

gagttg 366

<210> 532
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 532
cagtccagtc agagtgttta taataactac ttatcc 36

<210> 533
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 533
actgcatcca gcctggcatc t 21

<210> 534
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 534
caaggctatt atagtggtcc tataattact 30

<210> 535
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 535
aactactaca tacaa 15

<210> 536
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 536
atcatttatg ctggtggtag cgcatactac gcgacctggg caaacggc 48

<210> 537
<211> 24
<212> DNA
<213> Oryctolagus cuniculus

<400> 537
gggacatttg atggttatga gttg 24

<210> 538
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 538

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro
20 25 30

```
Val Ser Val Pro Val Gly Asp Thr Val Thr Ile Ser Cys Gln Ser Ser
        35                  40                  45

Glu Ser Val Tyr Ser Asn Asn Leu Leu Ser Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Ala Ser
65                  70                  75                  80

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
                85                  90                  95

Leu Thr Ile Ser Gly Ala Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Gln Gly Tyr Tyr Ser Gly Val Ile Asn Ser
        115                 120
```

<210> 539
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 539

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
        35                  40                  45

Ser Tyr Phe Met Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu
    50                  55                  60

Tyr Ile Gly Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp
65                  70                  75                  80

Ala Ser Gly Arg Leu Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
                85                  90                  95

Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
            100                 105                 110

Arg Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
        115                 120
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<210> 540
<211> 13
<212> PRT

<213> Oryctolagus cuniculus

<400> 540

Gln Ser Ser Glu Ser Val Tyr Ser Asn Asn Leu Leu Ser
1 5 10

<210> 541
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 541

Arg Ala Ser Asn Leu Ala Ser
1 5

<210> 542
<211> 10
<212> PRT
<213> Oryctolagus cuniculus

<400> 542

Gln Gly Tyr Tyr Ser Gly Val Ile Asn Ser
1 5 10

<210> 543
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 543

Ser Tyr Phe Met Ser
1 5

<210> 544
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 544

Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Ala Ser Gly
1 5 10 15

<210> 545
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 545

Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
1 5 10

<210> 546
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 546
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

acatttgccc aagtgctgac ccagactcca tcccctgtgt ctgtccctgt gggagacaca 120

gtcaccatca gttgccagtc cagtgagagc gtttatagta ataacctctt atcctggtat 180

cagcagaaac cagggcagcc tcccaagctc ctgatctaca gggcatccaa tctggcatct 240

ggtgtcccat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc 300

ggcgcacagt gtgacgatgc tgccacttac tactgtcaag gctattatag tggtgtcatt 360

aatagt 366

<210> 547
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 547
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcggtggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

acagtgtctg gattctccct cagtagctac ttcatgagct gggtccgcca ggctccaggg 180

gaggggctgg aatacatcgg attcattaat cctggtggta gcgcatacta cgcgagctgg 240

gcgagtggcc gactcaccat ctccaaaacc tcgaccacgg tagatctgaa aatcaccagt 300

ccgacaaccg aggacacggc cacctatttc tgtgccagga ttcttattgt ttcttatgga 360

gcctttacca tc 372

<210> 548
<211> 39
<212> DNA
<213> Oryctolagus cuniculus

<400> 548
cagtccagtg agagcgttta tagtaataac ctcttatcc 39

<210> 549
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 549
agggcatcca atctggcatc t 21

<210> 550
<211> 30
<212> DNA
<213> Oryctolagus cuniculus

<400> 550
caaggctatt atagtggtgt cattaatagt 30

<210> 551
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 551
agctacttca tgagc 15

<210> 552
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 552
ttcattaatc ctggtggtag cgcatactac gcgagctggg cgagtggc 48

<210> 553
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 553
attcttattg tttcttatgg agcctttacc atc 33

<210> 554
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 554

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Thr
35 40 45

Glu Ser Ile Gly Asn Glu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85 90 95

Ile Thr Gly Val Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
115 120

<210> 555
<211> 128
<212> PRT
<213> Oryctolagus cuniculus

<400> 555

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1               5                  10                  15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
            20                  25                  30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
        35                  40                  45

Lys Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Lys
    50                  55                  60

Tyr Ile Gly Tyr Ile Asp Ser Thr Thr Val Asn Thr Tyr Tyr Ala Thr
65                  70                  75                  80

Trp Ala Arg Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp
                85                  90                  95

Leu Lys Ile Thr Ser Pro Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys
            100                 105                 110

Ala Arg Gly Ser Thr Tyr Phe Thr Asp Gly Gly His Arg Leu Asp Leu
        115                 120                 125
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<210> 556
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 556

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Gln Ala Thr Glu Ser Ile Gly Asn Glu Leu Ser
1               5                  10
```

<210> 557
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 557

```
Ser Ala Ser Thr Leu Ala Ser
1               5
```

<210> 558
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 558

```
Gln Gln Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
1               5                  10
```

<210> 559
<211> 5

<212> PRT
<213> Oryctolagus cuniculus

<400> 559

Lys Tyr Tyr Met Ser
1 5

<210> 560
<211> 17
<212> PRT
<213> Oryctolagus cuniculus

<400> 560

Tyr Ile Asp Ser Thr Thr Val Asn Thr Tyr Tyr Ala Thr Trp Ala Arg
1 5 10 15

Gly

<210> 561
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 561

Gly Ser Thr Tyr Phe Thr Asp Gly Gly His Arg Leu Asp Leu
1 5 10

<210> 562
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 562
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120

gtcaccatca agtgccaggc cactgagagc attggcaatg agttatcctg gtatcagcag 180

aaaccagggc aggctcccaa gctcctgatc tattctgcat ccactctggc atctggggtc 240

ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat caccggcgtg 300

gagtgtgatg atgctgccac ttactactgt caacagggtt atagtagtgc taatattgat 360

aatgct 366

<210> 563
<211> 384
<212> DNA
<213> Oryctolagus cuniculus

<400> 563
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggtc acgcctggga cacccctgac actcacctgc 120

accgtctctg gattctccct cagtaagtac tacatgagct gggtccgcca ggctccagag 180

aaggggctga aatacatcgg atacattgat agtactactg ttaatacata ctacgcgacc 240

tgggcgagag gccgattcac catctccaaa acctcgacca cggtggatct gaagatcacc 300

agtccgacaa gtgaggacac ggccacctat ttctgtgcca gaggaagtac ttattttact 360

gatggaggcc atcggttgga tctc 384

<210> 564
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 564
caggccactg agagcattgg caatgagtta tcc 33

<210> 565
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 565
tctgcatcca ctctggcatc t 21

<210> 566
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 566
caacagggtt atagtagtgc taatattgat aatgct 36

<210> 567
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 567
aagtactaca tgagc 15

<210> 568
<211> 51
<212> DNA
<213> Oryctolagus cuniculus

<400> 568
tacattgata gtactactgt taatacatac tacgcgacct gggcgagagg c 51

<210> 569
<211> 42
<212> DNA
<213> Oryctolagus cuniculus

<400> 569
ggaagtactt attttactga tggaggccat cggttggatc tc 42

<210> 570
<211> 122
<212> PRT
<213> Oryctolagus cuniculus

<400> 570

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
20 25 30

Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Thr
35 40 45

Glu Ser Ile Gly Asn Glu Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
85 90 95

Ile Thr Gly Val Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
115 120

<210> 571
<211> 124
<212> PRT
<213> Oryctolagus cuniculus

<400> 571

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
35 40 45

Thr Tyr Asn Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60

Trp Ile Gly Ser Ile Thr Ile Asp Gly Arg Thr Tyr Tyr Ala Ser Trp
65 70 75 80

Ala Lys Gly Arg Phe Thr Val Ser Lys Ser Ser Thr Thr Val Asp Leu
85 90 95

Lys Met Thr Ser Leu Thr Thr Gly Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110

Arg Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
115 120

<210> 572
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 572

Gln Ala Thr Glu Ser Ile Gly Asn Glu Leu Ser
1 5 10

<210> 573
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 573

Ser Ala Ser Thr Leu Ala Ser
1 5

<210> 574
<211> 12
<212> PRT
<213> Oryctolagus cuniculus

<400> 574

Gln Gln Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
1 5 10

<210> 575
<211> 5
<212> PRT
<213> Oryctolagus cuniculus

<400> 575

Thr Tyr Asn Met Gly
1 5

<210> 576
<211> 16
<212> PRT
<213> Oryctolagus cuniculus

<400> 576

Ser Ile Thr Ile Asp Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 577
<211> 11
<212> PRT
<213> Oryctolagus cuniculus

<400> 577

Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile

<210> 578
<211> 366
<212> DNA
<213> Oryctolagus cuniculus

<400> 578
atggacacga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc 60

agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120

gtcaccatca agtgccaggc cactgagagc attggcaatg agttatcctg gtatcagcag 180

aaaccagggc aggctcccaa gctcctgatc tattctgcat ccactctggc atctggggtc 240

ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat caccggcgtg 300

gagtgtgatg atgctgccac ttactactgt caacagggtt atagtagtgc taatattgat 360

aatgct 366

<210> 579
<211> 372
<212> DNA
<213> Oryctolagus cuniculus

<400> 579
atggagactg ggctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag 60

tcgctggagg agtccggggg tcgcctggta acgcctggga cacccctgac actcacctgc 120

acagtctctg gattctccct cagtacctac aacatgggct gggtccgcca ggctccaggg 180

aaggggctgg aatggatcgg aagtattact attgatggtc gcacatacta cgcgagctgg 240

gcgaaaggcc gattcaccgt ctccaaaagc tcgaccacgg tggatctgaa aatgaccagt 300

ctgacaaccg gggacacggc cacctatttc tgtgccagga ttcttattgt ttcttatggg 360

gcctttacca tc 372

<210> 580
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 580
caggccactg agagcattgg caatgagtta tcc 33

<210> 581
<211> 21
<212> DNA
<213> Oryctolagus cuniculus

<400> 581
tctgcatcca ctctggcatc t 21

<210> 582
<211> 36
<212> DNA
<213> Oryctolagus cuniculus

<400> 582
caacagggtt atagtagtgc taatattgat aatgct 36

<210> 583
<211> 15
<212> DNA
<213> Oryctolagus cuniculus

<400> 583
acctacaaca tgggc 15

<210> 584
<211> 48
<212> DNA
<213> Oryctolagus cuniculus

<400> 584
agtattacta ttgatggtcg cacatactac gcgagctggg cgaaaggc 48

<210> 585
<211> 33
<212> DNA
<213> Oryctolagus cuniculus

<400> 585
attcttattg tttcttatgg ggcctttacc atc 33

<210> 586
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<223> Kappa constant domain of Ab1

<400> 586

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

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
20 25 30

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

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
50 55 60

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
65 70 75 80

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
85 90 95

Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 587
<211> 315
<212> DNA
<213> Artificial Sequence

<220>
<223> Kappa constant domain of Ab1

<400> 587
gtggctgcac catctgtctt catcttcccg ccatctgatg agcagttgaa atctggaact 60

gcctctgttg tgtgcctgct gaataacttc tatcccagag aggccaaagt acagtggaag 120

gtggataacg ccctccaatc gggtaactcc caggagagtg tcacagagca ggacagcaag 180

gacagcacct acagcctcag cagcaccctg acgctgagca aagcagacta cgagaaacac 240

aaagtctacg cctgcgaagt cacccatcag ggcctgagct cgcccgtcac aaagagcttc 300

aacaggggag agtgt 315

<210> 588
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Gamma-1 constant domain of Ab1

<400> 588

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
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<210> 589
<211> 990
<212> DNA
<213> Artificial Sequence

<220>
<223> Gamma-1 constant domain of Ab1

<400> 589

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Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser
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Pro Lys Met Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn
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Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr
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Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile
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Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu
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Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe
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Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr
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Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu
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Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala
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Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val
1 5 10 15

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Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln Met Ser
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Ser Ser Glu Glu Gln Ala Arg Ala Val Gln Met Ser Thr Lys Val
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Glu Gln Ala Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile Gln
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Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln
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Gln Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala
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Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn Leu
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Phe Leu Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro
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<400> 632

Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr
1 5 10 15

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Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu
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Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu Thr Lys Leu
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Asp Pro Thr Thr Asn Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln
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Thr Asn Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp
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Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp
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Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala Leu Arg Gln Met
1 5 10 15