NUCLEIC ACIDS ENCODING ANTI-IL-6 ANTIBODIES OF DEFINED EPITOP SPECIFICITY

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Abstract

The invention relates to nucleic acids encoding antibody or antibody fragments that specifically bind to an epitope on an intact human IL-6 polypeptide, which epitope when ascertained by epitopic mapping includes one or more residues comprised in each of the following IL-6 fragments (i) a fragment consisting of amino acid residues 37-51 of human IL-6, (ii) a fragment consisting of amino acid residues 70-84 of human IL-6, (iii) a fragment consisting of amino acid residues 169-183 of human IL-6, (iv) a fragment consisting of amino acid residues 31-45 of human IL-6 and (v) a fragment consisting of amino acid residues 58-72 of human IL-6.
FIG. 1
## FIG. 2

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### Notes
- The diagram illustrates the amino acid sequences for various regions of a protein.
- The sequences are arranged in a tabular format, with columns for different regions of the protein.
- The sequences include both variable (FR, CDR) and constant (FR3) regions, as well as specific labels for different sections (RbtVL, L12A, V1, Vx02, Vlh).
- The sequences are aligned to show conservation and variation across different regions.

### References
- [Further details and context for the sequences can be found in the patent application.]
FIG. 3

460

461

462

463

Just IgG
IL-6 or B-IL-6
IgG and IL-6
or B-IL-6
FIG. 4

- **ID$_{50}$ = 0.09273 mg/kg**
- $r^2 = 0.9701$

- Dose: 0.03 mg/kg Ab1
- Dose: 0.1 mg/kg Ab1
- Dose: 0.3 mg/kg Ab1
- Dose: 1 mg/kg Ab1
- Dose: 3 mg/kg Ab1

Graph shows the 24h A2M level (µg/ml) against the log dose of Ab1.
FIG. 5

Polyclonal IgG (n=9)
PBS (n=10)
Ab1 (n=30)
FIG. 6

- Polyclonal IgG (n=9)
- PBS (n=10)
- Ab1 (n=30)
FIG. 8

- Polyclonal IgG (400-527mg TW)
- Ab1 (400-527mg TW)
FIG. 9

Plasma Ab1 (µg/ml)

Time (h)

Male Cyno dose 1
Male Cyno dose 2
Female Cyno dose 1
Female cyno dose 2
FIG. 10A

Ab4 BLOCKS GP130 BINDING

BINDING (mM)

0.0000

0.5000

1.0000

1.5000

2.0000

TIME (SECONDS)

0

500

1000

1500

2000

2500

3000

3500

4000

ANTIBODY

IL6

IL6R1

GP130

Ab4

BUFFER CONTROL

GP130

IL6R1
FIG. 10B

Ab3 BLOCKS GP130 BINDING

BINDING (nm)

ANTIBODY

IL6R1

GP130

BUFFER CONTROL

IL6

0.0000

0.5000

1.0000

1.5000

2.0000

2.5000

0 500 1000 1500 2000 2500 3000 3500

TIME (SECONDS)
FIG. 10C

Ab8 BLOCKS GP130 BINDING

CONTROL ANTIBODY

IL6R1

GP130

Ab8

BINDING (nm)

0.0000

0.2000

0.4000

0.6000

0.8000

1.0000

1.2000

1.4000

0

200

400

600

800

1000

1200

1400

1600

1800

TIME (SECONDS)
FIG. 10D

Ab2 inhibits GP130 binding

- Control Antibody
- Ab2

Graph showing binding over time (seconds) with markers for IL6R1, IL6, GP130, and antibody binding.
FIG. 10E

Ab1, Ab6, AND Ab7 BLOCK IL6R1 AND GP130 BINDING

BINDING (fm)

0.0000
0.2000
0.4000
0.6000
0.8000
1.0000
1.2000
1.4000

TIME (SECONDS)

0 200 400 600 800 1000 1200 1400 1600 1800

CONTROL ANTIBODY

IL6R1

IL6

GP130

Ab6

Ab1

Ab7

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FIG. 15

Preferred anti-IL-6 antibody humanization

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NUCLEIC ACIDS ENCODING ANTI-IL-6 ANTIBODIES OF DEFINED EPITOPIC SPECIFICITY

RELATED PRIORITY APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 12/323,666 filed Nov. 25, 2008, which is a continuation-in-part of U.S. Ser. No. 12/153,612 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,550 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/153,611 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,551 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/142,723 filed May 21, 2008;

[0002] this application is also a continuation-in-part of U.S. Ser. No. 12/323,147 filed Nov. 25, 2008, which is a continuation-in-part of U.S. Ser. No. 12/153,612 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,550 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/153,611 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,551 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/142,723 filed May 21, 2008;

[0003] this application is also a continuation-in-part of U.S. Ser. No. 12/323,194 filed Nov. 25, 2008, which is a continuation-in-part of U.S. Ser. No. 12/153,612 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,550 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/153,611 filed May 21, 2008, which claims the benefit of U.S. Ser. No. 60/924,551 filed May 21, 2007, and is a continuation-in-part of U.S. Ser. No. 12/142,723 filed May 21, 2008;

[0004] the disclosure of each of the foregoing is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0006] 1. Field of the Invention

[0007] This invention pertains to antibodies and fragments thereof especially humanized versions 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.

[0008] 2. Description of Related Art

[0009] Interleukin-6 (hereinafter “IL-6”) (also known as interferon-β₂; 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. Papassotriopoulou, et al, Neurobiology of Aging, 22:863-871 (2001).

[0010] 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, S A, J. Immunology, 175:3463-3468 (2005).

[0011] 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, S A, J. Immunology, 175:3463-3468 (2005).

[0012] 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

[0013] The present invention is directed to specific antibodies and fragments thereof especially humanized version 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 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.

Another embodiment of this invention relates to the antibodies described herein, comprising the sequences of the V₃, V₄, 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 Kₐ values less than or equal to 10⁻⁴ S⁻¹.

[0014] 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.

[0015] 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 stimulated HepC2 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.

[0017] 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.

[0018] 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.

[0019] 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**

[0020] 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).

[0021] FIG. 2 shows alignments of variable light and variable heavy sequences between a rabbit antibody variable light and heavy sequences and homologous human sequences and the final humanized sequences. Framework regions are identified FR1- FR4. Complementarity determining regions are identified as CDRI-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.

[0022] 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.

[0023] FIG. 4 provides the α2-macroglobulin (A2M) dose response curve for antibody Ab1 administered intravenously at different doses one hour after a 100 µg/kg s.c. dose of human IL-6.

[0024] FIG. 5 provides survival data for the antibody Ab1 progression groups versus control groups.

[0025] FIG. 6 provides additional survival data for the antibody Ab1 progression groups versus control groups.

[0026] FIG. 7 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (270-320 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size).

[0027] FIG. 8 provides survival data for polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) versus antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size).

[0028] FIG. 9 provides a pharmacokinetic 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.

[0029] FIGS. 10A-D provide binding data for antibodies Ab4, Ab5, Ab8 and Ab2, respectively. FIG. 10E provides binding data for antibodies Ab1, Ab6 and Ab7.

[0030] FIG. 11 summarizes the binding data of FIGS. 10A-E in tabular form.

[0031] FIG. 12 presents the sequences of the 15 amino acid peptides used in the peptide mapping experiment of Example 14.

[0032] FIG. 13 presents the results of the blots prepared in Example 14.

[0033] FIG. 14 presents the results of the blots prepared in Example 14.

[0034] FIG. 15 depicts preferred humanized heavy and light chain regions derived from Ab1. These sequences are contained in SEQ ID NO:s 647-657.

**DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

**Definitions**

[0035] 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.

[0036] As used herein the singular forms “a”, “and”, and “the” include plural refers 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 their fragments as they occur in 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.

[0037] Interleukin-6 (IL-6):

[0038] As used herein, interleukin-6 (IL-6) encompasses not only the 212 amino acid sequence available as GenBank Protein Accession No. NP_000591: MNSFST-SAEVFVSLGGLLLVPAAFAPVPGEDSKVDAHHRQILSSERIDQPLRVIHDGISALR-KETCNGKSMCCESSKEALAEHNLNLKPMAEKDGCF- QSGFNEETCLY KITTLGIEFFVYLQNYRFSSES-FEQRARAVQSTMKVLIQFLQKAKNLIDAITTPDPT TNASLLTTLQANQOWLQDMTHHILRSFKEFLOSLRLARQM (SEQ ID NO: 1), but also any pro-, pre-, and mature forms of this IL-6 amino acid sequence, as well as mutants and variants including allelic variants of this sequence.

[0039] Mating Competent Yeast Species:

[0040] 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 polyplioid yeast cells are preferably produced by mating or spheroplast fusion.

[0041] In one embodiment of the invention, the mating competent yeast is a member of the Saccharomyces cerevisiae family, which includes the genera Arxiozyma; Ascosobryozyma; Citeromyces; Debaromyces; Dekkeria; Eremothecium; Issatchenka; Kazachstania; Kluyveromyces; Kodamaea; Loddermyces; Pichia; Saccharomyces; Saturnispora; Tetrapisispora; Torulaspora; Willipatis; and Zygosaccharomyces. Other types of yeast potentially useful in the invention include Yarrowia, Rhodosporidium, Candida, Hansenula, Filobasidium, Filobasidella, Sporidiobolus, Bullera, Leucosporidium and Filobasidella.

[0042] 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.

[0043] Haploid Yeast Cell:

[0044] A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0045] Polyplioid Yeast Cell:

[0046] A cell having more than one copy of its normal genomic (chromosomal) complement.

[0047] Diploid Yeast Cell:

[0048] A cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (matting) of two haploid cells.

[0049] 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 (matting) 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]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.

[0050] Yeast Mating:

[0051] The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0052] Meiosis:

[0053] 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.

[0054] Selectable Marker:

[0055] 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 are 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 is 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.

[0056] Expression Vector:

[0057] 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., & Storms, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0058] 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.
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.

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.

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 preproteins 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® Technology; Invitrogen, Carlsbad Calif.). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

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.

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.


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.

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 maybe 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 signals are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 pre-protoxin 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).

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' or 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.

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.

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 religated 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.

As an alternative to restriction and ligation of fragments, recombination methods based on site 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, N.Y.: 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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, camelodies, 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 Strelets V A, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early developmental isotype, Protein Sci. 2005 November; 14(11):2901-9. EPub 2005 Sep 30; Greenberg A S, 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 S D, et al., Isolation of the new antigen receptor from wobegong sharks, and use as a scaffold for the display of protein loop libraries, Mol. Immunol. 2001 August; 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 D S, et al., Biopharmaceutical drug discovery using novel protein scaffolds, Curr Opin Biotechnol. 2006 December; 17(6):653-8. EPub 2006 October 19.

[0077] 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.

[0078] 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 func-
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. Pat. 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.

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. Pat. No. 6,187,287, incorporated fully herein by reference.

In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab, 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), camemboids, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

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.

The term “polyploid 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.

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.

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.

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.

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, plague 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 polypeptide encoded by said polynucleotide sequence.
“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.

The general structure of antibodies in vertebrates now is well understood (Eidelman, 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 Fc 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.

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 Immunchemistry, 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.

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 (VH) followed by a number of constant domains. Each light chain has a variable domain (VL) 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.

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 hyper-variable 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 hyper-variable 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 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 antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)).

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.
SEQ ID NO: 2 or SEQ ID NO: 651, and/or one or more of the polypeptide sequences of SEQ ID NO: 7; SEQ ID NO: 8 or SEQ ID NO: 659; 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 SEQ ID NO: 656 or SEQ ID NO: 657 or SEQ ID NO: 658; 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.

[0098] In another embodiment, the invention contemplates other antibodies, such as for example chimeric or humanized 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 or SEQ ID NO: 651, and/or one or more of the polypeptide sequences of SEQ ID NO: 7 (CDR1); SEQ ID NO: 8 (CDR2); SEQ ID NO: 659 (CDR2), and SEQ ID NO: 9 (CDR3) which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or SEQ ID NO: 656 or SEQ ID NO: 657 or SEQ ID NO: 658, 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.

[0099] 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 or SEQ ID NO: 651 or humanized versions including those set forth in FIG. 15. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 3 or those contained in any one of SEQ ID NO: 652, 653, 654, 655, 656, 657, or 658.

[0100] 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 or SEQ ID NO: 651 or humanized versions including those depicted in FIG. 15.

[0101] 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 or SEQ ID NO: 659 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 SEQ ID NO: 656 or SEQ ID NO: 657 or SEQ ID NO: 658.

[0102] 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 or SEQ ID NO: 651; the variable heavy chain region of SEQ ID NO: 3, 652, 653, 654, 655, 656, 657, or 658; 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 or SEQ ID NO: 651; and the complementarity-determining regions (SEQ ID NO: 7; SEQ ID NO: 8 or SEQ ID NO: 659; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 3 or SEQ ID NO: 656 or SEQ ID NO: 657 or SEQ ID NO: 658.

[0103] 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, 652, 653, 654, 655, 656, 657, or 658; the light chain polypeptide sequence of SEQ ID NO: 20 is substituted for the light chain polypeptide sequence of SEQ ID NO: 2, 647, 648, 649, 650, or 651; and the heavy chain CDR sequence of SEQ ID NO: 120 is substituted for the heavy chain CDR sequence of SEQ ID NO: 8 or SEQ ID NO: 659.

[0104] 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 an antibody comprising any combination of the variable heavy and light chain region sequences depicted in FIG. 15 especially one comprising the variable light region in SEQ ID NO: 651 and the heavy region in or SEQ ID NO: 656 or SEQ ID NO: 657 or the alternative SEQ ID NOs set forth in paragraph [0087] above, and having at least one of the biological activities set forth herein.

[0105] 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:

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MDTRAPTOLLGLLLLWLPGARCAYDMTOTPASVEAVGQVVVTIMCQASEMT
IWSLWYQEQFFQPPKLLIYQASDLACGTVPLSPGSGCGATYETVLTGSG
QCDDAAYYQQGYSQGHDNVWVGGTVEKKTAPASVFPVFPSSDEQL
KGTGATVVLNHPY
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[0106] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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MBTAPFQLLLLLMLGPARCAYDMQTAPASVEAVGQVVVTIMCQAERST
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[0107] 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.
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.

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.

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.

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.

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.

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.

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:

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DVCDDAAATYICAVYDDDDSNAPGGEVEVWRRWSAAPSFIPPPSEDQ
LEGSQASVCLLLN

[0115] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] 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 sequence of SEQ ID NO: 38.
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.

[0121] 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.

[0122] 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.

[0123] 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:

(QETGKFTCGGKRIKYEKHICLSYKTVTQKVP) 18

[0124] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(QETGKFTCGGKRIKYEKHICLSYKTVTQKVP) 18

[0125] 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.

[0126] 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.
[0133] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 70)
METGLRWMLLAVLKVQGVCQVEESGSGLVTPGPSLTLCTVSGFELSSY
AMSWRQAPKQEGLEMWIGIGGTTTAYAWKGRPTISKSTYDVLKITS
PTTEDATYPFRQGQOGHGDWIQGQTVLTVSASTKPSVFPAPSSSS
TSGSATAALGCLVDF.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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:

(SEQ ID NO: 85)
MTRAPFTQLLWLQLWLPGATFAVLVQTPGVSPVQVTSTETFSTITIKCSOS
VYHNPLSWYQQRKPPFELILLYQGKLASYVRFPSGSQEQTQTTLITSEG
VQCDDAATYYCLGSVDADDANAGGGITREVKVTVAAPPSVFPSSDEQL
KSSTATSVCVLNSF.

[0142] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 86)
METGLRWMLLAVLKVQGVCQVEESGSGLVTPGPSLTLCTVSGFELSDY
AMSWRQAPKQEGLEMWIGIGGTTTAYAWKGRPTISKSTYDVLKITS
PTTEDATYPFRQGQOGHGDWIQGQTVLTVSASTKPSVFPAPSSSS
TSGSATAALGCLVDF.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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 variable heavy chain sequence of SEQ ID NO: 86.

[0148] 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.

[0149] 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.

[0150] 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:

\[
\text{(SEQ ID NO: 101)}
\]

\[
\text{MDTRAPTOLLGLLLLWLPGARCAYDMTOTPASWSAAWGGTWTIKCOASOS INNELSWYOOKSGORPKLLIYRASTLASGVSSRFKGSGSGTEFTLTISDCEADAATYYCOOGYSLRNIDNAFGGGTEVVVKRTVAAPSVFIFPPSDEOLKSGTASWWCLLNNF}
\]

[0151] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{(SEQ ID NO: 102)}
\]

\[
\text{METGLRWLLLVAVLSGVOCOSLEESGGRLVTPGTPULTCTAGSFFLHNY YMTVQRAPKKGSLWNGYVSDAYAYMAIGRTFSKSTTVLDUMTS LTAADATATIPCARSSDSSDWDKAFHWQQTTLVTVSSASTKPSVVFPLAPS SKESTNGTAALGCLVK.}
\]

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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.

[0158] 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.

[0159] 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.

[0160] 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:

```
(METGLRMLLLLAVLKEVQCHSVBESSGRRLVPTPPPTLTLTCTVSSGSLSS
TMSGVRQPGKELQGVINGKGYTTYATAMKEEPITSFSTTVDIKTS
PTTCTATYFCARLDGOTQGHAYTSLWL
```

[0161] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(MDRAPTQLQLLLNLPGATFAAVLQTGPPSVSVAOGTVSTISQCGS
VYSHKYLANYYQKPQPKLIIYWTSLAGPSRFSGSGGTQFTLTS
GVCQDDAAATYCLGNYDDADDNA
```

[0164] 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.

[0165] 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: 128; and SEQ ID NO: 129 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 122.

[0166] 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: 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.

[0167] 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.

[0168] 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.

[0169] 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:

```
(METGLRMLLLLAVLKEVQCHSVBESSGRRLVPTPPPTLTLTCTVSSGSLSS
TMSGVRQPGKELQGVINGKGYTTYATAMKEEPITSFSTTVDIKTS
PTTCTATYFCARLDGOTQGHAYTSLWL
```

[0170] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:
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.

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.

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 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.

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.

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.

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.

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.

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:

```
(METGLRWLLLVAVLKVGQCSVEGGLLKVPDLTTLTCTCTASGFLKDETLTLTCTASGFSLEGG)
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```svn
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In one 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.

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(METGLRWLLLVAVLKVGQCSVEGGLLKVPDLTTLTCTCTASGFLKDETLTLTCTASGFSLEGG)
```

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.

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 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.

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 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.
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.

[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: 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.

[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: 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.

[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: 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.

[0186] 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.

[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:

```
(HQQD ID NO: 170)
MDTREPThrLLGLLILPLGPGPAVLTQTQPPgVgRVGQGCTG
YVNNYELsWgQgPQgPQgPKgLgVgKgLGQgPQgPQgSgQgQgPQgLgT
GVCQDAATTYGCLgYDDgADD
```

[0188] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(HQQD ID NO: 171)
METGQKLLLVAVGKQCCSlhEgSGQLVTPPFLPTCTWQgPFLST
YLGWgQAPgKgKgWgIIgIPgQgNTgYgKgAKgAPQgPTISgKSTgSTSgTDgLgMg
TSPPTEDTAYFYgCRgHCgYgODgSL.
```

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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.

[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: 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.

[0194] 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.

[0195] 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.
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:

(SEQ ID NO: 186)

MDTRAPTQLLGLLLLWLGPARCHQVMTTPASVEAMGGVTVIKCOASEST
IGNALAYQQRSQPKLLYKAAALLGSFQEPKSGGTYSLD
ECADAATYYCQCFPSDV

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 187)

METGLRKLLLVTVLKQVCQRLVESGGGLVQEPKLSLCTCAFGPSS
GYNWCRQAPQGKLYAWACPIHTDTTNTYAGWAKGRFTISETSSVTL
QMTSITAATATYLCARGYSIDNYAL.

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.

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.

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 202)

MDTRAPTQLLGLLLLWLGPARCHQVMTTPASVEAMGGVTVIKCOASES
IGNALAYQQRSQPKLLYKAAALLGSFQEPKSGGTYSLD
QCADAAYCQCFPSDV

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.

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.

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.
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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] 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.

[0213] 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.

[0214] 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:

```
MDTARPTQLGLLLLHLANVKACDVTQSPASVEAVAVQYTVTICQASQS
VSYLYNVQKQFQPKLLIIYRATLS6S0VPVRKPGGSGSTETLTLSDL
ECDADTVYOCYCTTGTSSSYQAAA
```

[0215] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
METGLRWLLLVAVLKVCOSESEGGRLVTPGPPVTCTVNGISGSLSE
A1SWSRQPAGKHLWGIISGTYYASMAKGRFTIKSTTVLKLIT
```

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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.

[0220] 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.

[0221] 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; and the variable heavy chain region of SEQ ID NO: 219.
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.

**[0222]** 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.

**[0223]** 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:

```
MTDAPTQLLGLLILLWLPGATFAQVLTQASPVAAVVGVTITNCCASQSG
YVSNYLSKVQPGPQPLGKLYATLDSGVPLRFSGSGSGTFTLTIS
DVQCDQDAATYCCGLYDCSSGCAYA
```

**[0224]** The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
METGLRLWLLLVALEVGVQCSLRSQGSVLKPEGSLLLLCTCATSGFSQSS
YMYWVRQAPGKLEHACIVTOKHIPYYAKRCSPTIESTSSDVL
QMTSSTADATATYPCACAYDL
```

**[0225]** 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.

**[0226]** 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.

**[0227]** 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.

**[0228]** 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.

**[0229]** 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.

**[0230]** 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.

**[0231]** 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.

**[0232]** 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:

```
MTDAPTQLLGLLILLWLPGATFAQVLTQASPVAAVVGVTITNCCASQSG
YVSNYLSKVQPGPQPLGKLYATLDSGVPLRFSGSGSGTFTLTIS
DVQCDQDAATYCCGLYDCSSGCAYA
```

**[0233]** The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MTDAPTQLLGLLILLWLPGATFAQVLTQASPVAAVVGVTITNCCASQSG
YVSNYLSKVQPGPQPLGKLYATLDSGVPLRFSGSGSGTFTLTIS
DVQCDQDAATYCCGLYDCSSGCAYA
```

**[0234]** 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.

[0235] 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.

[0236] 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.

[0237] 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.

[0238] 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: 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.

[0239] 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.

[0240] 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.

[0241] 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:

```
MDTRAPTOLLGLLLLWLPGATFAAVLTOTPSPWSAAWGGTWTISCOASQ
SVEHKKNLAWQQESQPPPFLL1YMASTLHGVSSRPSGSGSTQPTLT
```

[0242] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
VSGYQCDDDAATYCLVGPDDDDANA
```

[0243] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 266; 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.

[0244] 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: 266; 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.

[0245] The invention also contemplates fragments of the antibody having binding specificity to IL-6, comprising one or more of the polypeptide sequences 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.

[0246] 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: 266; 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.
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.

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.

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.

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:

(MDTRAPTQLLLLWPGHCAFETQIPTPSVEAVGAVIYNCPQGKFQVTVMDTRAPTQLLLLWPGHCAFETQIPTPSVEAVGAVIYNCPQGKFQVTVMD
NDYMLWYQKPPKFLYILAJTASLAVPSRFKSGSGETFLLTIS
DLECDAAAYTGSTYSINVA)

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, 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.

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.

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.

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:

(MDTRAPTQLLLLWPGHCAFETQIPTPSVEAVGAVIYNCPQGKFQVTVMDTRAPTQLLLLWPGHCAFETQIPTPSVEAVGAVIYNCPQGKFQVTVMD
NDYMLWYQKPPKFLYILAJTASLAVPSRFKSGSGETFLLTIS
DLECDAAAYTGSTYSINVA)

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, 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.
[0261] 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.

[0262] 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.

[0263] 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: 291.

[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: 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.

[0265] 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.

[0266] 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.

[0267] 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.

[0268] 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:

[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:

[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, the 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:

```
<table>
<thead>
<tr>
<th>Seq ID NO: 320</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDTARPQLLLILGLPARGCAVTNQTQPASVEAVGSQTVTIECQAS</td>
</tr>
<tr>
<td>Q5VNYSLGWQ1FQQPQPKIIYTVASSLAVGSEPESGGSQTEFTLT</td>
</tr>
<tr>
<td>ISGVECDAAAATYTCQQSYTSDVIN</td>
</tr>
</tbody>
</table>
```

[0278] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
<table>
<thead>
<tr>
<th>Seq ID NO: 331</th>
</tr>
</thead>
<tbody>
<tr>
<td>METQLEHLLVAVLEKVCQSLIESAGKGLVPFTPFLTFCVSGDISS</td>
</tr>
<tr>
<td>YAMGWRQAPKQGKLY10I010S0G0T0N0AK0RPT0S0Q0SSTTVDLK</td>
</tr>
<tr>
<td>I15SSPPDTSATYFCGANQAGCGNWILGDFP</td>
</tr>
</tbody>
</table>
```

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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.

[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: 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.

[0284] 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.

[0285] 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.
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:

```
MDTRAPTQMLLLLSLPAGKECADVMQTPASVSAVQSTTVCACQA
SEHNWLAQIIPQQQPKQFELILITGTSLGSVERSGRKQGGSTEPL
TSIQLCADDAYYQSYYYSSVNV
```

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MDTRAPTQLGGLLLSLLPGKLGKACGVMQTPASVSAVQSTTVACQA
SEHNWLAQIIPQQQPKQFELILITGTSLGSVERSGRKQGGSTEPL
TSIQLCADDAYYQSYYYSSVNV
```

In another embodiment, the invention contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 354; and SEQ ID NO: 355 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 354, or/and one or more of the polypeptide sequences of SEQ ID NO: 355; and SEQ ID NO: 356 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

In a further embodiment of the invention, the invention also contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 354; and SEQ ID NO: 355 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 356.

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:

```
MDTRAPTQLGGLLLSLLPGKLGKACGVMQTPASVSAVQSTTVACQA
SEHNWLAQIIPQQQPKQFELILITGTSLGSVERSGRKQGGSTEPL
TSIQLCADDAYYQSYYYSSVNV
```

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:

```
MDTRAPTQLGGLLLSLLPGKLGKACGVMQTPASVSAVQSTTVACQA
SEHNWLAQIIPQQQPKQFELILITGTSLGSVERSGRKQGGSTEPL
TSIQLCADDAYYQSYYYSSVNV
```

In another embodiment, the invention contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 354; and SEQ ID NO: 355 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 354, or/and one or more of the polypeptide sequences of SEQ ID NO: 355; and SEQ ID NO: 356 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

In a further embodiment of the invention, the invention includes antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 354; and SEQ ID NO: 355 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 354, or/and one or more of the polypeptide sequences of SEQ ID NO: 355; and SEQ ID NO: 356 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.

In another embodiment, the invention contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 354; and SEQ ID NO: 355 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 354, or/and one or more of the polypeptide sequences of SEQ ID NO: 355; and SEQ ID NO: 356 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 347.
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.

[0299] 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.

[0300] 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.

[0301] 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.

[0302] 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, 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.

[0303] 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.

[0304] 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:

(SEQ ID NO: 378)

MDTAPQ7GQLGQGFLPAGC6ELQYQPSV2GENAAGGTVTTIKCQASQ
SIIYLYWQKQGPKPLFLYRASL3AGVPSFPGKSGSGT6PFLT1S
DLCG6AATYYC5Q7GDVSNP

[0305] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 379)

MGTGRWLLLVAVLKGCTQPSV2GENAAGGTVTTIKCQASQ
YFMK6CVQAPGK6M6AC51YGT66GGTST6FPAWENGRFT1SKTSSTTV
TLQMTSLTAAG5ATYFCARGYSGGVIFKFL

[0306] 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.

[0307] 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.

[0308] 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.

[0309] 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.

[0310] 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.

[0311] 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.

[0312] 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.

[0313] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MDTAPQQLLGLLLLWLPQVPSTQPSVSVAAVQGTVSISQCAQ
```

[0314] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MTGLRLLVVAVLKVQCSQSLBEGSGSLVPAGSULTLCITSSGSPSS
```

[0315] 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.

[0316] 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.

[0317] 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.

[0318] 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.

[0319] 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.

[0320] 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.

[0321] 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.

[0322] 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:

```
MDTAPQQLLGLLLLWLPQVPSTQPSVSVAAVQGTVSISQCAQ
```

[0323] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MTGLRLLVVAVLKVQCSQSLBEGSGSLVPAGSULTLCITSSGSPSS
```

[0324] 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.

[0325] 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.

[0326] 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.

[0327] 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.

[0328] 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.

[0329] 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.

[0330] 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.

[0331] 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:

(SEQ ID NO: 426)
MDTRAPTLLLKLWLGLPGAGPHLVMTOTPAVTSAAVGGTVTIKCOAS EDIESYLAVQEGFQKLEINSNLESGVSSRFKGSGSGTEFTLTI ...

[0332] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 427)
MTRTLKOEVLVVAVLQGQQVPGQKLEINSNLESGVSSRFKGSGSGTEFTLTI ...

[0333] 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.

[0334] 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.

[0335] The invention also contemplates fragments of the antibody having binding specificity to IL-6 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.

[0336] 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.
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: 441; SEQ ID NO: 442; and SEQ ID NO: 443 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 427.

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.

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.

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:

\[
\text{MDTRAPTQ LLGLLLLLPLAGTFPAVLTQVIYSPSVSEPVGTVSISICQQSK}
\]
\[
\text{SVMNYLAWYQQPQQPKLIYAGNLASGVPSTFGSGGSQTPLT}
\]
\[
\text{ISVQCCDOATTYQCGTICDNGT}
\]

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

\[
\text{MDTRAPTQLLLLLLLPLAGTFPAVLTVQVIPVSPPVSEPVGTVSISICQ}
\]
\[
\text{SQSK}
\]
\[
\text{SVMNYLAWYQQPQQPKLIYAGNLASGVPSTFGSGGSQTPLT}
\]
\[
\text{ISVQCCDOATTYQCGTICDNGT}
\]

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.

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: 447; 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.

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.

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:

\[
\text{MDTRAPTQLLLLLLLPLAGTFPAVLTVQVIPVSPPVSEPVGTVSISICQ}
\]
\[
\text{SQSK}
\]
\[
\text{SVMNYLAWYQQPQQPKLIYAGNLASGVPSTFGSGGSQTPLT}
\]
\[
\text{ISVQCCDOATTYQCGTICDNGT}
\]

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below.

\[
\text{MDTRAPTQQLLLLLLPLAGTFPAVLTVQVIPVSPPVSEPVGTVSISICQ}
\]
\[
\text{SQSK}
\]
\[
\text{SVMNYLAWYQQPQQPKLIYAGNLASGVPSTFGSGGSQTPLT}
\]
\[
\text{ISVQCCDOATTYQCGTICDNGT}
\]
[0351] 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.

[0352] 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.

[0353] 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: 458.

[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: 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.

[0355] 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.

[0356] The invention also contains antibody fragments which include one or more of the antibody fragments described herein. In one embodiments 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.

[0357] 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.

[0358] 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:

(SEQ ID NO: 474)

METHRLAVLALAVLQGQGSQGSQGSLVTPGTPPLITCCSSGIDSAY

[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:

(SEQ ID NO: 475)

METHRLAVLALAVLQGQGSQGSQGSLVTPGTPPLITCCSSGIDSAY

[0360] 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.

[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: 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.

[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: 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.

[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: 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.

[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: 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.

[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: 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.

[0366] 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.

[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:

```
(M SEQ ID NO: 490)
MDRTAPQLLLGILLLGLGRCASNTQIPSSYSPAVQGVTVIQASBN
IYSPFAHQQKCPQPKLLIFPASTLACSN/S2SPKGGSSGTQFPLTLSDL
ECCDAATYQCCQ9ATYIDNN
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[0368] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
(M SEQ ID NO: 491)
MELGRHKLLLVALEKVCQCSICSGKLVPTPFLTLTCSEQYGLSAY
AMINVRQAPGBLEWIIYIIPGNTYNSWAKGRFTVSKTSMDELEITS
PTTDEATYPCARDABSSOSNAWYGNV.
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[0369] 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.

[0370] 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.

[0371] 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.

[0372] 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.

[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: 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.

[0374] 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.

[0375] In a preferred embodiment of the invention, the anti-IL-6 antibody is Ab31, comprising SEQ ID NO: 400 and SEQ ID NO: 491, and having at least one of the biological activities set forth herein.
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:

(SEQ ID NO: 506)

MDTRAPTQLLGLLSSLWPLGATFAIAMQTQPSPVASSAAGAGTVTINCOASSS
VPENLWYQTPQFQSPFPSSLLLYDAASAGVPSQFSGGQTQFSLTEISG
VCCDAAATTCAHYESNEDDDIV

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 507)

METGLRLLLVAVLKEVQCGLSRESGRLVTPTQPAILTTCTYSFLRNH
SITWVRQAPGELWIGIITSGRTRYANNWAKRSPTKSIYTTVDMNTS
PTTETDTATYPFCGRHGLGSGQNI.

The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 506; 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.

The invention also contemplates other antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 506; 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.

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.

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 light chain sequence of SEQ ID NO: 507.

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.

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.

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:

(SEQ ID NO: 522)

MDTRAPTQLLGLLSSLWPLGATFAIAMQTQPSPVASSAAGAGTVTINCOASSS
VPENLWYQTPQFQSPFPSSLLLYDAASAGVPSQFSGGQTQFSLTEISG
VCCDAAATTCAHYESNEDDDIV

The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 523)

METGLRLLLVAVLKEVQCGLSRESGRLVTPTQPAILTTCTYSFLRNH
SITWVRQAPGELWIGIITSGRTRYANNWAKRSPTKSIYTTVDMNTS
PTTETDTATYPFCGRHGLGSGQNI.

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: 506, 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: 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.

In another embodiment, the invention comprises antibodies, such as for example chimeric antibodies, comprising one or more of the polypeptide sequences of SEQ ID NO: 506; 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.
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.

[0389] 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.

[0390] 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.

[0391] 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.

[0392] 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.

[0393] 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.

[0394] 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:

```plaintext
MDTRAPTOLLGLLLLWLPGATFAOVLTOTPSPVSVPVGDTVTISCOSSES WYSNNLLSWYOOKPGOPPKLLIYRASNLASGVPSRFKGSGSGTOFTL TIS ... binding specificity to IL-6 and possessing a variable light chain sequence comprising the sequence set forth above:

[0396] 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.

[0397] 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.

[0398] 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.

[0399] 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. In another 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.

[0400] In a further embodiment of the invention, fragments of the antibody having binding specificity to IL-6 comprise, or alternatively consists 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.

[0401] 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.

[0402] 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.

[0403] In another embodiment, the invention includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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MDTRAPTQGNGGGLMLWLPQACDNYMTQTPASVEVAVGVVTITQAGQTES
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[0404] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

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MDTGRTPQGNGGGLMLWLPQACDNYMTQTPASVEVAVGVVTITQAGQTES
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[0405] 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.

[0406] 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.

[0407] 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.

[0408] 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.

[0409] 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.

[0410] 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.

[0411] 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.

[0412] 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:

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MDTGRTPQGNGGGLMLWLPQACDNYMTQTPASVEVAVGVVTITQAGQTES
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[0413] The invention also includes antibodies having binding specificity to IL-6 and possessing a variable heavy chain sequence comprising the sequence set forth below:

```
MDTGRTPQGNGGGLMLWLPQACDNYMTQTPASVEVAVGVVTITQAGQTES
```

[0414] 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) 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.

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) 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) 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.

The invention also contemplates fragments of the antibody having binding specificity to IL-6. In one embodiment, 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.

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) of the variable light chain sequence of SEQ ID NO: 570.

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) of the variable heavy chain sequence of SEQ ID NO: 571.

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.

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.

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:

```
[SEQ ID NO: 598]
AGTGRPSVVFPLAPSSKSTSGTACGLVQIVVSQTLVSPKVSLQALGSVELT
HTFPLAVLSGLYSLSSVVTFTVSSLLGTVYQCVNHKFSSTKVEKDPVP
KSCDIIHTCPAPELLGNSPVSFLPPFEPDKTLMIERTPETCVVYVDS
HDPKIVKPRNYVQVGVSHIAKTFKRESQYASTYRVSVTLVQWNLKIK
EYKKCVSNKALFAP1KTI1SAGQEPREFQYVTLPFSREHETIHVQYLTCT
LUKGRPSDSIAVENESGQPSNPNHETYTPFVLDSGEFPFLEKTVKDESW
QCGPFFSCSVMEEAHHNHTQKSLGSFPGK.
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The invention also 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, 23, 28, 54, 70, 86, 102, 117, 118, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 421, 443, 459, 475, 491, 507, 523, 555 and SEQ ID NO: 571 or those contained in SEQ ID NO: 652, 653, 654, 655, 656 or 657; and further comprising a V_L polypeptide sequence selected from the group consisting of: SEQ ID NO: 2, 651, 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 in SEQ ID NO: 647, 648, 649, 650 or 651; or a variant thereof wherein one or more of the framework residues (FR residues) or CDR 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 Fe derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

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.

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 anti-
odies and fragments thereof inhibits the association of IL-6
with IL-6R, and/or the production of IL-6/IL-6R/gp130 com-
plexes and/or the production of IL-6/IL-6R/gp130 multimers and/or antagonizes the biological effects of one or more of the foregoing.

[0426] 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, sub-
strates, bioluminescent materials, radioactive materials, and
chemiluminescent moieties, or functional moieties such as
for example streptavidin, avidin, biotin, a cytotoxic, a cyto-
toxic agent, and/or radioactive materials.

[0427] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxy-
dase, acetylcholinesterase, alkaline phosphatase, beta-galac-
tosidase and luciferase. Further exemplary fluorescent mate-
rials include, but are not limited to, rhodamine, fluorescein,
fluorescein isothiocyanate, umbelliferone, dichlorotriazinyl-
lamine, phycocyanin and dansyl chloride. Further exam-
plary chemiluminescent moieties include, but are not limited
to, luminol. Further exemplary bioluminescent materials in-
clude, but are not limited to, luciferin and aequorin. Further
exemplary radioactively labeled materials include, but are not limited
to, iodine 125 (125I), carbon 14 (14C), sulfur 35 (35S), tri-
tium (3H) and phosphorus 32 (32P).

[0428] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminop-
terin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluo-
rouracil decarbazine; alkylating agents such as melpho-
theoremine, thioepa chlorambucil, melphalan, carbustone
(BSNU), mitomycin C, lonustone (CCNU), 1-methylhi-
trosourea, cyclophosphamide, meflothrin, busulfan, dibromodimethylstilbestrol, streptozotocin, mitomycin C, cis-dichlo-
rodiamine platinum (II) (DDP) cisplatin and carboptatin
(paraplatin); anthraeyclines include daunorubicin (formerly
daunomycin), doxorubicin (adriamycin), etoposide, tenosine, colchicine, dihydroxyanthranilic acid, 1-dehydrotestosterone, gluco corticoids, propranolol, etoposide, tenosine, colchicine, dihydroxyan-
rine, vincristine and vinblastine. Other cytotoxic agents include
paclitaxel (taxol), ricin, pseudomonas exotoxin, gemicatibine,
cytocinsolin B, gramicidin D, ethidium bromide, emetine,
etoposide, tenosine, colchicine, dihydroxyanacin dione, 1-
dehydrotestosterone, glucocorticoids, propranolol, etoposide,
lidocaine, propranolol, puromycin, procarbazine, hydroy-
uen, asparaginase, corticosteroids, mytopyrine (O.P-
(DDD)), interferons, and mixtures of these cytotoxic agents.

[0429] Further cytotoxic agents include, but are not limited
to, chemotherapeutic agents such as carboplatin, cisplatin,
paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluo-
rouracil, 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-kill-
(1980)).

[0430] Other cytotoxic agents include cytoxic ribonu-
cles classes as described by Goldenberg in U.S. Pat. No. 6,653,
104. Embodiments of the invention also relate to radioimmu-
nocojugates where a radionuclide that emits alpha or beta
particles is stably coupled to the antibody, or binding frag-
ments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as
Phosphorus-32 (32P), Scandium-47 (47Sc), Copper-67 (67Cu),
Gallium-67 (67Ga), Yttrium-88 (88Y), Yttrium-90 (90Y),
Iodine-125 (125I), Iodine-131 (131I), Samarium-153 (153Sm),
Lutetium-177 (177Lu), Rhenium-186 (186Re) or Rhenium-
188 (188Re), and alpha-emitters such as Actinatine-211 (211At),
Lead-212 (212Pb), Bismuth-212 (212Bi) or -213 (213Bi) or Actinium-225 (225Ac).

[0431] Methods are known in the art for conjugating an
antibody or binding fragment thereof to a detectable moeity
and the like, such as for example those methods described by
(1981); and Nygren, J. Histochem. and Cytochem. 30:407
(1982).

[0432] Embodiments described herein further include vari-
ts and equivalents that are substantially homologous to the
antibodies, antibody fragments, diabodies, SMIs, camel-
odies, nanobodies, IgNAR, polypeptides, variable regions
and CDRs set forth herein. These may contain, e.g., conser-
ervative substitution nutations, (i.e., the substitution of one or
more amino acids by similar amino acids). For example, conser-
ervative 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 neu-
tral amino acid by another neutral amino acid. What is
intended by a conservative amino acid substitution is well
known in the art.

[0433] 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.

[0434] In another embodiment, the invention further con-
templates the above-recited polypeptide homologies of the
antibody fragments, variable regions and CDRs set forth
herein further having anti-IL-6 activity. Non-limiting exam-
ple examples of anti-IL-6 activity are set forth herein, for
example, in paragraphs [0731]-[0736] infra.

[0435] In another embodiment, the invention further con-
templates 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 admin-
istered 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.

[0436] 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. As noted preferred anti-IL-6 antibodies or fragments may contain a variable heavy and/or light sequence as shown in FIG. 15, such as SEQ ID NO:651 and 657 or variants thereof wherein one or more CDR or FR residues are modified without adversely affecting antibody binding to IL-6 or other desired functional activity.

Additional Exemplary Embodiments of the Invention

[0437] 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 compete 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 or humanized versions such as those containing the heavy and light chain region humanized versions depicted in FIG. 15. 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.

[0438] In another embodiment of the invention, the anti-human IL-6 antibody which specifically binds to the same linear or conformational epitope(s) 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.

[0439] 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 and humanized or chimeric or other variants including those containing the humanized variable heavy and/or light regions contained in FIG. 15.

[0440] In another embodiment, the invention is also directed to an isolated anti-IL-6 antibody or antibody fragment comprising one or more of the CDR sequences contained in the V\textsubscript{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, 559, 555 and SEQ ID NO: 571 or in one of SEQ ID NOs: 652-658 and/or one or more of the CDRs contained in the V\textsubscript{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 or in one of SEQ ID NO:647-651.

[0441] 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.

[0442] 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 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 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 the variable heavy and light chain polypeptides contained in SEQ ID NO:651 and 657 as shown in FIG. 15.

[0443] The invention further contemplates that the one or more anti-human IL-6 antibodies discussed above are glycosylated; that contain an Fe 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.

[0444] 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 least 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.
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.

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, and inflammation-related cachexia. In another embodiment, the disease is selected from 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.

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 radiocolloid 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

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 as shown below or the humanized versions thereof contained in SEQ ID NO: 647, 648, 649, 650 or 651.

```
[SEQ ID NO: 10]
ATGGACACAGGGGCCGCCCACTGAGGTTGGCTCCCTTGCTGCTGCTTG
GCTCCAGGTGCACGATGTTTGGTATGCTAGTATATGGCCACCTGCTGCTG
TGCTCTGAGCATGTTAAGGCACACTCATCAGTGGACACATGTGAACG
AGCAATTACAAATATTAGCTTCTGCATACGACGAAACCAAGGCAACGCTC
CAAGCTGGTATGCTGCGCAATCATCCTGCTGCTGCTGCTGCTGCTGCT
GGTTCAAGGCGATGCACTTTGCGGAGCGGAGCTGACCTGACCTGACCT
CTGGAAGCTGACGTGGCTGAGCTGAGCTGACCTGACCTGACCTGACCT
GTAACCTAGGGCCGCACTGCTGGGTGGAAGCAGGGGAGCTGACCTGACCT
TTYGAANCCTGGAGATCTTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
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[SEQ ID NO: 11]
ATGGACACAGGGGCCGCCCACTGAGGTTGGCTCCCTTGCTGCTGCTTG
GCTCCAGGTGCACGATGTTTGGTATGCTAGTATATGGCCACCTGCTGCTG
TGCTCTGAGCATGTTAAGGCACACTCATCAGTGGACACATGTGAACG
AGCAATTACAAATATTAGCTTCTGCATACGACGAAACCAAGGCAACGCTC
CAAGCTGGTATGCTGCGCAATCATCCTGCTGCTGCTGCTGCTGCTGCT
GGTTCAAGGCGATGCACTTTGCGGAGCGGAGCTGACCTGACCTGACCT
CTGGAAGCTGACGTGGCTGAGCTGAGCTGACCTGACCTGACCTGACCT
GTAACCTAGGGCCGCACTGCTGGGTGGAAGCAGGGGAGCTGACCTGACCT
TTYGAANCCTGGAGATCTTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
```

The invention also contemplates one or more nucleic acid sequences which result in 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 diploid yeast cell. In a more preferred embodiment, the yeast cell is a Pichia yeast.

The invention also contemplates a method of treating 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.
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 segment of SEQ ID NO: 2.

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 region of SEQ ID NO: 3 or SEQ ID NO:657 or others depicted in Fig. 15.

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 or a polynucleotide encoding the variable light chain region in SEQ ID NO:650 or SEQ ID NO:651 or others depicted in Fig. 15; the polynucleotide SEQ ID NO: 11 encoding the heavy chain variable region of SEQ ID NO:3 or a polynucleotide encoding the variable heavy chain region in SEQ ID NO:656 or SEQ ID NO:657 or SEQ ID NO:658 or others depicted in Fig. 15; 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 or those encoding the CDRs in the variable chain heavy region contained in SEQ ID NO:656 or SEQ ID NO:657 or SEQ ID NO:658.

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 encoding the variable light chain polypeptide sequence of SEQ ID NO: 21: TGGAGTGAGCTGTGGGAGGCCACACCTGATCAATTGTGAGCTGATCGAGGTGCTGAGCAAGGATGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG

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: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG

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 heavy chain variable region of SEQ ID NO: 21.

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.

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 poly-
nucleotide 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.

[0461] 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:

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AGTGACACGCGGCCCCCACTGCCGTCTGGCGCT
GCTCCCGGTGGCCACATTGCCTCGGCTCTACCACATCTCCGGCC
TGCTTTGCTGGCGCAATGCAGCTGACAGCTGACGGGTCA
AGTGTTTATAAGACACGTCACTATTTACGTTTACGAACTGGGCA
GCTCCTAACGTCGTACCTGTGGATGCTCGGATCC
ACAGACCTGGCACTGCGCCACATCTCCGGCC
ACGGTGAACGTGAACTGGCCCTGTCCCTGGCCCTG
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[0462] 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:

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ATGGAGATCTGGCTGCTGCTCTCCTCTTCTGGCTGCTGCTAAGG
GTCAGCTGATCTGGCGCTCTCTGTCCCTGGCTGTGTCT
GGCACCTCCAGACCTCCACCTCGGATCTGCGGATCC
GCTACAGCTGAGTGAGTGGCTTGGTCCTGGCTGTGTCT
GCTGGGTGTTAATGTTTATATATGGACCATCTATTTACGTTTACGAACTGGGCA
GCTCCTAACGTCGTACCTGTGGATGCTCGGATCC
ACAGACCTGGCACTGCGCCACATCTCCGGCC
ACGGTGAACGTGAACTGGCCCTGTCCCTGGCCCTG
```

[0463] 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.

[0464] 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.

[0465] 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.

[0466] 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:

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ATGGAGACGCGGCCCCCACTGCCGTCTGGCGCT
GCTCCCGGTGGCCACATTGCCTCGGCTCTACCACATCTCCGGCC
TGCTTTGCTGGCGCAATGCAGCTGACAGCTGACGGGTCA
AGTGTTTATAAGACACGTCACTATTTACGTTTACGAACTGGGCA
GCTCCTAACGTCGTACCTGTGGATGCTCGGATCC
ACAGACCTGGCACTGCGCCACATCTCCGGCC
ACGGTGAACGTGAACTGGCCCTGTCCCTGGCCCTG
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[0467] 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:

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ATGGAGATCTGGCTGCTGCTCTCCTCTTCTGGCTGCTGCTAAGG
GTCAGCTGATCTGGCGCTCTCTGTCCCTGGCTGTGTCT
GGCACCTCCAGACCTCCACCTCGGATCTGCGGATCC
GCTACAGCTGAGTGAGTGGCTTGGTCCTGGCTGTGTCT
GCTGGGTGTTAATGTTTATATATGGACCATCTATTTACGTTTACGAACTGGGCA
GCTCCTAACGTCGTACCTGTGGATGCTCGGATCC
ACAGACCTGGCACTGCGCCACATCTCCGGCC
ACGGTGAACGTGAACTGGCCCTGTCCCTGGCCCTG
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[0468] 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.
[0468] In another 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.

[0469] In another 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.

[0470] 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.

[0471] The invention is further directed to polynucleotides encoding peptides 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 variable region of SEQ ID NO: 69:

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AGGAGCCATTCACCTCTCCAAACTCGACCACGGTGGATCTGAAAATGC
ACCAGTCCGACACCCGAGGACACGGCCACCTATTTCTGTGCCAGGAGTCG
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[0472] 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:

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ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCCAAGTGCTGACCCAGACTCCATCGCCTG
TGTCGCTGGCTGCTGCTTCTGGGCTTCTCCCTCAGTAGC
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[0473] In another 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.

[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: 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.

[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: 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.
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:

ATGGACACAGGGCCACCTACAGCTG (SEQ ID NO: 93)

CTGGGGCTCTCTCGCTCGGCTCCAGTGACAATTTGACACGGTTGCCT

GACCCAGACCATGCCTGGCTTCACCATGTGCAGCAAAGTTCTACCT

TCAAGTCCAGGCTGCTACAGTTATACCTTTCTGTGGCTATAT

CAGCCAGAACGAGGCGCCCTCAAGAGCTGCTGCTGCTGCTGCTGCTG

AGTCACTCTCAGCAGCTGGCCCTGAGAATCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG

CTGCTGAAATACCTC

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

ATGGAGACTGGGCGCTGCTCTCGGCTCCAGTGACAATTTGACACGGTTGCCT

CTGGGGCTCTCTCGCTCGGCTCCAGTGACAATTTGACACGGTTGCCT

GACCCAGACCATGCCTGGCTTCACCATGTGCAGCAAAGTTCTACCT

TCAAGTCCAGGCTGCTACAGTTATACCTTTCTGTGGCTATAT

CAGCCAGAACGAGGCGCCCTCAAGAGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG

AGTCACTCTCAGCAGCTGGCCCTGAGAATCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG

CTGCTGAAATACCTC

In another 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.

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.
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.

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.

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 polynucleotide sequences 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.

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:

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:

[Continued]
[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: 139:

(SEQ ID NO: 147)
ATGGACACGAGGGCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCT
CCAGGTGACCATTTGGAGCAGGGCTGGGGCTCCTCTGGCCCTTATGA
TGATGTAGCTAGTTACGCTGCTGCAGTCCCTACTCTCTACCTAGGCT

[0493] 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.

[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: 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.

[0495] 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 polynucleotide sequences 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.

[0496] 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:

(SEQ ID NO: 162)
ATGGACACGAGGGCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCT
CCAGGTGACCATTTGGAGCAGGGCTGGGGCTCCTCTGGCCCTTATGA
TGATGTAGCTAGTTACGCTGCTGCAGTCCCTACTCTCTACCTAGGCT

[0497] 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:

(SEQ ID NO: 163)
ATGGACACGAGGGCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTGGCT
CCAGGTGACCATTTGGAGCAGGGCTGGGGCTCCTCTGGCCCTTATGA
TGATGTAGCTAGTTACGCTGCTGCAGTCCCTACTCTCTACCTAGGCT

[0498] 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 heavy chain variable sequence of SEQ ID NO: 154.

[0499] 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: 154.

[0500] 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 polynucleotide sequences 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: 154; 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 polynucle-
otides 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.

[0501] 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:

(SEQ ID NO: 170)
ATGGACACGAGGCGCCCACCTGAGCCGGCTCTGTGACACTCTTCCCTATTATCGGAGCTGCGATACAGCTG
CCAGGTCGCCAGTGGTGGATCTGGGGACAGAGTACACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGGTGTTATTTTGGTGA
TAGTGTT

[0502] 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:

(SEQ ID NO: 171)
ATGGACACTGGCTGGCTGCTCTGCTCTGCTCTGCTGCTCTGCTGCT
CCAGGTGCTACGCTGAGGAGGCCGGCTCTGCTGCTGCTGCTGCTGCTGCT
CACCCTGCTCACTCTGAACTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
TACATCTGGCTGGGCTGGCGAGCAGCAGGAGGGGGGGAATGAT
CGGCGATTATTTCTACATTATAGGTACACATTTGCACCAATTGGTGCCAGCGGACG
ACAGGGCCGCCACACCCAGGACAGGGGCGGTGCAATTTTTCAGGCTGCCAGATT
TAGGTT

[0503] 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.

[0504] 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.

[0505] 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.

[0506] 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:

(SEQ ID NO: 194)
ATGGACACGAGGCGCCCACCTGAGCCGGCTCTGTGACACTCTTCCCTATTATCGGAGCTGCGATACAGCTG
CCAGGTCGCCAGTGGTGGATCTGGGGACAGAGTACACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAATGGTGTTATTTTGGTGA
TAGTGTT

[0507] 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:

(SEQ ID NO: 195)
ATGGACACTGGCTGGCTGCTCTGCTCTGCTCTGCTGCTGCTGCTGCT
CCAGGTGCTACGCTGAGGAGGCCGGCTCTGCTGCTGCTGCTGCTGCTGCT
CACCCTGCTCACTCTGAACTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
TACATCTGGCTGGGCTGGCGAGCAGCAGGAGGGGGGGAATGAT
CGGCGATTATTTCTACATTATAGGTACACATTTGCACCAATTGGTGCCAGCGGACG
ACAGGGCCGCCACACCCAGGACAGGGGCGGTGCAATTTTTCAGGCTGCCAGATT
TAGGTT

[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: 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.
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.

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.

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:

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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.

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: 205.

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.

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:

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[0518] In another 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.

[0519] In another 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.

[0520] 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.

[0521] 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:

[0522] 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:

[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: 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.

[0524] 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.

[0525] 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.

[0526] 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:
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TGTCTGGCTGGCAGGACACGACATCGCTGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTGCA ...

[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: 251:

AGTCAACGCTGCTGGGACACATCGCTGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTGCA...

[0528] 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 complementary-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 250.

[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: 263; SEQ ID NO: 264; and SEQ ID NO: 265 which correspond to polynucleotides encoding the complementary-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 251.

[0530] 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, the 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 polynucleotide sequences 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 complementary-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 complementary-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.

[0531] 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:

AGTCAACGCTGCTGGGACACATCGCTGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTGCA...

[0532] 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:

AGTCAACGCTGCTGGGACACATCGCTGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACACTCTCTGGATTCTCCCTCAGTGCA...

[0533] 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 complementary-determining regions (CDRs), or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 266.

[0534] 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 complementary-determining regions (CDRs), or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 267.

[0535] 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 polynucleotide sequences encoding anti-
body 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.

[0536] 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:

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ATGKACACAGAGGCCCTCACTGCGTGTCTGCTGGTGTTCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTGCTGGCTG
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.

[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: 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.

[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: 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.

[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: 314:

-continued

[0547] In another embodiment of the invention, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 315:

-continued

[0548] 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.

[0549] 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.

[0550] 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.

[0551] 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: 350:

-continued
[0552] 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:

```
ATGAGAATGCGGCTGCACTCGCTTGCCCTTGCTCCTGCACTGCTACCAGGTGCGATGTTGTGATGACCCAGACTCCAGCCTCCAGGATCTGAAAAATT
```

[0555] 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 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.

[0557] 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:

```
ATGGAGAATGCGGCTGCACTCGCTTGCCCTTGCTCCTGCACTGCTACCAGGTGCGATGTTGTGATGACCCAGACTCCAGCCTCCAGGATCTGAAAAATT
```

[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: 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.

[0559] 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.

[0560] 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 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 heavy chain variable sequence of SEQ ID NO: 347.
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:

```
AAGCAAGACGAGGCCGCCACACTGCTCTGCGAGCTCTCTCTC
GCTCCAGTATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
```

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:

```
AAGCAAGACGAGGCCGCCACACTGCTCTGCGAGCTCTCTCTC
GCTCCAGTATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
```

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: 370:

```
AAGCAAGACGAGGCCGCCACACTGCTCTGCGAGCTCTCTCTC
GCTCCAGTATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
```

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.

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.

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 heavy 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.

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:

```
AAGCAAGACGAGGCCGCCACACTGCTCTGCGAGCTCTCTCTC
GCTCCAGTATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
```

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:

```
AAGCAAGACGAGGCCGCCACACTGCTCTGCGAGCTCTCTCTC
GCTCCAGTATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
TGTCGCAGATCGTGGTCTCCCAAGCAAGCAAGCAAGCAAGC
AGTATCTACTACACTACACTACACTACACTACACTACACTAC
ACGTCTGACTCAGCTGACTCAGCTGACTCAGCTGACTCAGCT
```

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.

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

[0570] 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.

[0571] 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:

```
ATGGAACCGAGGGCCCTCCCCCTACTCGTGGGCTCCCTCTGCTGCTG
GCTCCACGGTTCAATGGTCCACTGAGAGAAGGGATTACCTG
GTTACCTGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GAGCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
```

[0572] 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:

```
ATGGAACCGAGGGCCCTCCCCCTACTCGTGGGCTCCCTCTGCTGCTG
GCTCCACGGTTCAATGGTCCACTGAGAGAAGGGATTACCTG
GTTACCTGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GAGCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
```

[0573] 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.

[0574] 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.

[0575] 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.

[0576] 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:

```
ATGGAACCGAGGGCCCTCCCCCTACTCGTGGGCTCCCTCTGCTGCTG
GCTCCACGGTTCAATGGTCCACTGAGAGAAGGGATTACCTG
GTTACCTGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GAGCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
```

[0577] 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:

```
ATGGAACCGAGGGCCCTCCCCCTACTCGTGGGCTCCCTCTGCTGCTG
GCTCCACGGTTCAATGGTCCACTGAGAGAAGGGATTACCTG
GTTACCTGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GAGCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
GCTCCACGGATGGTGGCCGAGCACTGACCATGACATCGAGGCACG
```

[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: 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.
[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: 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 heavy chain variable sequence of SEQ ID NO: 410.

[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: 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 light chain variable sequence of SEQ ID NO: 411.

[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: 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.

[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: 426:

```
GCTACCTCTGACCTGGCTGCCGAGGCTGGCTGCCAAGGAGGTCTGGAAAA
CATGGATTTCATATTCCTCTGATGAGCTTTACAGCAGGAGCTGGATTG
AAAGGGCATTCACCCACCTCCGATGCTCGTGGGAGGCTGGATCGAAA
TCACCATGAGCAGACTCAGGAGACCAACCCACCTTTTCTCTGGACAGG
CTCTGATTCTTTTCTGAGGACCATCTACACATCATCCATCCATCATCAT
```

[0582] 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:

```
ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
```

[0583] 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.

[0584] 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.

[0585] 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.

[0586] 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:

```
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
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GCTACCTCTGACCTGGCTGCCGAGGCTGGCTGCCAAGGAGGTCTGGAAAA
CATGGATTTCATATTCCTCTGATGAGCTTTACAGCAGGAGCTGGATTG
AAAGGGCATTCACCCACCTCCGATGCTCGTGGGAGGCTGGATCGAAA
TCACCATGAGCAGACTCAGGAGACCAACCCACCTTTTCTCTGGACAGG
CTCTGATTCTTTTCTGAGGACCATCTACACATCATCCATCCATCATCAT
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ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
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ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
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ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
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ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
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ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
TGTCGGCTGGGGAATGAGGATGCTGCTGCTGCTGCTGCTGAAAGG
ATGGACACGAGGGCCCCCACTCAGCTGCTGGGGCTCCTGCTGCTCTG
GCTCCCAGGTGCCACATTTGCCGCCGTGCTGACCCAGACTCCATCTCCC
```
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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

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

53 Jan. 17, 2013

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:

[0591] 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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

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

53 Jan. 17, 2013

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:

[0591] 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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

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

53 Jan. 17, 2013

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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

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

53 Jan. 17, 2013

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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

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

53 Jan. 17, 2013

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:

[0591] 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:

(AQ TGGGAGACGGTGCTGGGGCTGCTGGCCACCCATCTGTACAGTTGCCAGTCCAGTA AGAGTGTTATGAATAACAACTACTTAGCCTGGTATCAGCAGAAACCAGG ... heavy chain polypeptide sequence of SEQ ID NO: 443: (SEQ ID NO: ATGGAGACTGGGCTGCGCTGGCTTCTCCTGGTCGCTGTGCTCAAAGG 451)

TGTCCAGTGTCAGTCGGTGGAGGAGTCCGGGGGTCGCCTGGTCAAGCGCT GACGAAACCCTGACACTCACCTGCACAGTCTCTGGAATCGACCTCAGTA ... regions (SEQ ID NO:455; SEQID NO. 456; and SEQID NO:457) of the heavy chain variable region of SEQID NO: 443.
body 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.

[0596] The invention is further directed to polynucleotides encoding peptides 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 chain sequence of SEQ ID NO: 474:

(SEQ ID NO: 492)

[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 chain sequence of SEQ ID NO: 475:

(SEQ ID NO: 493)

[0598] 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.

[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: 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.

[0600] 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.

[0601] The invention is further directed to polynucleotides encoding peptides of the antibodies having binding specificity to IL-6. In one embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide chain sequence of SEQ ID NO: 490:

(SEQ ID NO: 498)

[0602] 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 chain sequence of SEQ ID NO: 491:

(SEQ ID NO: 499)
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 complementary-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 490.

[0604] 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 complementary-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 491.

[0605] 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 complementary-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 complementary-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.

[0606] 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:

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ATGGAACAGGAGGCCCAAGCCCATCGGCGGTCCTGCTCCTGGC
TCCAAAGGTCGAGTACTAGGAACTTCAGGCTATCTGCCTGGCC
GGCGGTGAGTACGGAAACGCTTTGCGATCTGCTCCGAGT
CTCTGGTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AGTGTTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AAGCCGACTGAGGACTGAGGACTGAGGACTGAGGACTGAGG
```

[0607] 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:

```
ATGGAACAGGAGGCCCAAGCCCATCGGCGGTCCTGCTCCTGGC
TCCAAAGGTCGAGTACTAGGAACTTCAGGCTATCTGCCTGGCC
GGCGGTGAGTACGGAAACGCTTTGCGATCTGCTCCGAGT
CTCTGGTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AGTGTTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AAGCCGACTGAGGACTGAGGACTGAGGACTGAGGACTGAGG
```

[0608] 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 complementary-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 506.

[0609] 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 complementary-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 507.

[0610] 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 complementary-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 complementary-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.

[0611] 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:

```
ATGGAACAGGAGGCCCAAGCCCATCGGCGGTCCTGCTCCTGGC
TCCAAAGGTCGAGTACTAGGAACTTCAGGCTATCTGCCTGGCC
GGCGGTGAGTACGGAAACGCTTTGCGATCTGCTCCGAGT
CTCTGGTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AGTGTTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AAGCCGACTGAGGACTGAGGACTGAGGACTGAGGACTGAGG
```

[0612] 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:

```
ATGGAACAGGAGGCCCAAGCCCATCGGCGGTCCTGCTCCTGGC
TCCAAAGGTCGAGTACTAGGAACTTCAGGCTATCTGCCTGGCC
GGCGGTGAGTACGGAAACGCTTTGCGATCTGCTCCGAGT
CTCTGGTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AGTGTTTATATGCTATGCTAGGCCGTGAGGGATGATGATGC
AAGCCGACTGAGGACTGAGGACTGAGGACTGAGGACTGAGG
```
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:

(SEQ ID NO: 531)

ATGGAGACTGGGCTGCGCTCTCTGCTGGCCCTGGTCTGACCAGGATG
TCCAGTGTACGCTGGAGATCCGCGGCTCCTGCTGAGCTTGAGCT
GACACTCCGCTAGCACTTGACAGGCTGGGTTCATATCTGGAGTCA
TACTACATACAAATGGTTCGACAGCTTCAGGGAGGAGGCTGTTTGGGA
TCGGGACATTTATATCCGTCTGGGAGCCATCTACGACACCCGGG
CGAGACATTGAGGTTATAGATCTGAA

In another 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.

In another 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.

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 polynucleotide sequences 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.

The invention is further directed to polynucleotides encoding peptides 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:

(SEQ ID NO: 546)

ATGAGACATGCGCTGGGCTGCGCTCTCTGCTGGCCCTGGTCTTCCAGTGTACGCTGGAGATCCGCGGCTCCTGCTGAGCTTGAGCT
GACACTCCGCTAGCACTTGACAGGCTGGGTTCATATCTGGAGTCA
TACTACATACAAATGGTTCGACAGCTTCAGGGAGGAGGCTGTTTGGGA
TCGGGACATTTATATCCGTCTGGGAGCCATCTACGACACCCGGG
CGAGACATTGAGGTTATAGATCTGAA

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:

(SEQ ID NO: 547)

ATGAGACATGCGCTGGGCTGCGCTCTCTGCTGGCCCTGGTCTTCCAGTGTACGCTGGAGATCCGCGGCTCCTGCTGAGCTTGAGCT
GACACTCCGCTAGCACTTGACAGGCTGGGTTCATATCTGGAGTCA
TACTACATACAAATGGTTCGACAGCTTCAGGGAGGAGGCTGTTTGGGA
TCGGGACATTTATATCCGTCTGGGAGCCATCTACGACACCCGGG
CGAGACATTGAGGTTATAGATCTGAA

In another 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.

In another 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.

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 polynucleotide sequences 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.
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:

```
(SEQ ID NO: 562)
ATGGAACAGAGGAGCGTCCACCTCTACCTGCTGCTGAGGCTGGGC
CCGGTGCGAGACGAGCTCGTGCTGAGGCTGGGC
AGTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
ATTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
GTCCTCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TCAAAGCAGGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
GACGTGAGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TATAATGCAGAATGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
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[0621] 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:

```
(SEQ ID NO: 563)
ATGGGAACAGAGGAGCGTCCACCTCTACCTGCTGCTGAGGCTGGGC
CCGGTGCGAGACGAGCTCGTGCTGAGGCTGGGC
AGTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
ATTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
GTCCTCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TCAAAGCAGGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
GACGTGAGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TATAATGCAGAATGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
```

[0622] 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:

```
(SEQ ID NO: 564)
ATGGAACAGAGGAGCGTCCACCTCTACCTGCTGCTGAGGCTGGGC
CCGGTGCGAGACGAGCTCGTGCTGAGGCTGGGC
AGTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
ATTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
GTCCTCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TCAAAGCAGGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
GACGTGAGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TATAATGCAGAATGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
```

[0623] 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 NOs: 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.

[0624] 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 NOs: 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.

[0625] 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.

[0626] 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 heavy chain polypeptide sequence of SEQ ID NO: 570:

```
(SEQ ID NO: 578)
ATGGGAACAGAGGAGCGTCCACCTCTACCTGCTGCTGAGGCTGGGC
CCGGTGCGAGACGAGCTCGTGCTGAGGCTGGGC
AGTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
ATTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
GTCCTCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TCAAAGCAGGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
GACGTGAGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
```

[0627] 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:

```
(SEQ ID NO: 579)
ATGGGAACAGAGGAGCGTCCACCTCTACCTGCTGCTGAGGCTGGGC
CCGGTGCGAGACGAGCTCGTGCTGAGGCTGGGC
AGTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
ATTGGTGAGCTGAGCTCGTGCTGAGGCTGGGC
GTCCTCTGAGCTGAGCTCGTGCTGAGGCTGGGC
TCAAAGCAGGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
GACGTGAGAGCTGAGCTGAGCTGAGCTCGTGCTGAGGCTGGGC
```

[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 NOs: 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.

[0629] 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 NOs: 583; SEQ ID NO: 584; and SEQ ID NO: 585 which corre-
spond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 571.

[0630] 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.

[0631] 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:

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GAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA
ACCATCTCCAAAGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
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[0632] 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:

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GCCTCACCAGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
ACGGAGATTCCAGCGACCGGGCGACAGCGGCCCTGCGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
CGGACCGGCTGAGCGGCCTGGCTCTCTGGAGTACCTTCC
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[0633] In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-IL-6 V\textsubscript{H} antibody amino acid sequence selected from SEQ ID NO: 3, 656, 657, 658, 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 those contained in FIG. 15 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\textsubscript{H} polypeptide or a conservative amino acid substitution. In addition, the invention specifically encompasses humanized anti-I-6 antibodies or humanized antibody binding fragments and nucleic acid sequences encoding the foregoing comprising the variable heavy chain and or light chain polypeptides depicted in the sequences contained in FIG. 15 or variants thereof wherein one or more framework or CDR residues may be modified. Preferably, if any modifications are introduced they will not affect adversely the binding affinity of the resulting humanized anti-IL-6 antibody or fragment.

[0634] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-IL-6 V\textsubscript{H} antibody amino acid sequence of 2, 651, 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 others depicted in FIG. 15 or another polynucleotide 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\textsubscript{H} polypeptide or a conservative amino acid substitution.

[0635] 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 or 651 and SEQ ID NO:30R SEQ ID NO:656 or SEQ ID NO:657 or SEQ ID NO:658; SEQ ID NO:2 or 651 and SEQ ID NO:18; SEQ ID NO:2 or 651, and SEQ ID NO:19; SEQ ID NO:20 and SEQ ID NO:30R SEQ ID NO:656 or SEQ ID NO:657 or SEQ ID NO:658; SEQ ID NO:20 and SEQ ID NO:18; SEQ ID NO:20 and SEQ ID NO:19; SEQ ID NO:20 and 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:119 and SEQ ID NO:119; SEQ ID NO:119 and SEQ ID NO:122 and SEQ ID NO:123; SEQ ID NO:138 and SEQ ID NO:139; SEQ ID
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.

[0642] 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}.

[0643] 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.

[0644] 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.

[0645] 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

[0646] 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 pro-
duce a monoclonal antibody, which is specific to a desired antigen, or a nucleic acid sequence corresponding to such an antibody.

[0647] In one embodiment, the present invention provides a method comprising the steps of:

[0648] a. preparing a cell population comprising at least one antigen-specific B cell;

[0649] b. enriching the cell population, e.g., by chromatography, to form an enriched cell population comprising at least one antigen-specific B cell;

[0650] c. isolating a single B cell from the enriched B cell population; and

[0651] d. determining whether the single B cell produces an antibody specific to the antigen.

[0652] 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.

[0653] 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.

[0654] 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.

[0655] The general term “cell population” encompasses pre- and 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:

[0656] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[0657] b. creating at least one single cell suspension from the harvested cell population;

[0658] c. enriching at least one single cell suspension to form a first enriched cell population;

[0659] d. enriching the first enriched cell population to form a second enriched cell population;

[0660] e. enriching the second enriched cell population to form a third enriched cell population; and

[0661] f. selecting an antibody produced by an antigen-specific cell of the third enriched cell population.

[0662] 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.

[0663] 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%.

[0664] 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.

[0665] 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.

[0666] 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.

[0667] 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.

[0668] 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.

[0669] Methods of “enriching” a cell population by size or density are known in the art. See, e.g., U.S. Pat. No. 5,627,052. These steps can be used in the present method in addition to enriching the cell population by antigen-specificity.

[0670] 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.

[0671] In such an 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.

[0672] 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 or/and a desired property.

[0673] 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.

[0674] 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).

[0675] 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.

[0676] 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 5×10^{-10} M, preferably about 1×10^{-13} to 5×10^{-10}, 1×10^{-13} to 1×10^{-10}, 1×10^{-12} to 7.5×10^{-10}, 1×10^{-11} to 2×10^{-10}, about 1.5×10^{-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® (trastuzumab), Mylotarg® (gentuzumab), Campath® (alemtuzumab), Zevalin® (ibritumomab), Erbitux™ (cetuximab), Avastin® (bevacizumab), 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.
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, techniques known in the art such as CDR grafting or selectivity determining residue grafting (SDR).

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.

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:

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.

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.

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.

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.

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.

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.

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, cytolitic activity, and the like by a process including the following steps:

- immunizing a host against an antigen;
- harvesting B cells from the host;
- enriching the harvested B cells to increase the frequency of antigen-specific cells;
- creating at least one single cell suspension;
- 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;
- determining whether the single B cell produces an antibody specific to the antigen;

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.

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 anti-
bodies 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 grafted. This enhances the probability of complete activity recovery in the humanized antibody protein.

[0696] The methods of antibody selection using an enrichment step disclosed herein include a step of obtaining a immune cell-containing cell population from an immobilized host. Methods of obtaining an immune cell-containing cell population from an immobilized 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.

[0697] 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.

[0698] 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.

[0699] 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%.

[0700] 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., EL4 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 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 correlated 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 form 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.

[0701] 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.

[0702] 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 thereof, 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.

[0703] The identified antigen-specific cell can be used to derive the corresponding nucleic acid sequences encoding the desired monoclonal antibody. (An Alu 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.

[0704] 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.

[0705] Thus, in one embodiment, the present invention provides a method comprising:

[0706] a. harvesting a cell population from an immunized host to obtain a harvested cell population;

[0707] b. creating at least one single cell suspension from a harvested cell population;

[0708] c. enriching at least one single cell suspension, preferably by chromatography, to form a first enriched cell population;

[0709] 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;

[0710] 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

[0711] f. selecting an antibody produced by an antigen-specific cell isolated from the third enriched cell population.

[0712] 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.

[0713] Similarly, the method can include one or more steps of screening the second enriched cell population for antibody binding strength and/or antibody functionality.

[0714] 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, chimerization, 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 polyplidic yeast cells, i.e., diploid yeast cells, particularly Pichia.

[0715] In one embodiment, the method comprises:

[0716] a. immunizing a host against an antigen to yield host antibodies;

[0717] b. screening the host antibodies for antigen specificity and neutralization;

[0718] c. harvesting B cells from the host;

[0719] d. enriching the harvested B cells to create an enriched cell population having an increased frequency of antigen-specific cells;

[0720] 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;

[0721] f. determining whether the clonal population produces an antibody specific to the antigen;

[0722] g. isolating a single B cell; and

[0723] h. sequencing the nucleic acid sequence of the antibody produced by the single B cell.

Methods of Humanizing Antibodies

[0724] 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:

[0725] Light Chain

[0726] 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.

[0727] Example: RbTVL. Amino acid residue 1 in FIG. 2, starting ‘AYDM . . . ’
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.

Example: RbVL amino acid residue 88 in FIG. 2, ending as ‘TYYC’

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).

Example: RbVL amino acid sequence from residues numbered 1 through 88 in FIG. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in FIG. 2 as L12A, V1 and Vx02.

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.

Example: In FIG. 2, L12A was the most homologous human germline variable light chain sequence and is used as the basis for the humanization of RbVL.

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.

Example: In FIG. 2, the RbVL sequence is aligned with the human homologous sequence L12A, and the framework and CDR domains are indicated.

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.

Example: In FIG. 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 RbVL rabbit antibody light chain sequence. The human L12A frameworks 1, 2 and 3 are unaltered. The resulting humanized sequence is shown below as V1h 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.

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.

Example: In FIG. 2, the CDR3 of RbVL (amino acid residues numbered 89-100) is added after the end of framework 3 in the humanized sequence indicated as VLh.

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.

Example: In FIG. 2, Framework 4 (FR4) of the RbVL 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 CDR3 region added in Step 7 above.

Heavy Chain 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.

Example: RbVH Amino acid residue 1 in FIG. 2, starting ‘QEQL . . . ‘

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.

Example: RbVH amino acid residue 98 in FIG. 2, ending as ‘. . . FCVR’.

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 matura-
tion 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).

Example: RbtVH amino acid sequence from residues numbered 1 through 98 in FIG. 2 is BLASTed against a human antibody germline database. The top three unique returned sequences are shown in FIGS. 2 as 3-64-04, 3-66-04, and 3-53-02.

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.

Example: 3-64-04 in FIG. 2 was the most homologous human germline variable heavy chain sequence and is used as the basis for the humanization of RbtVH.

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.

Example: In FIG. 2, the RbtVH sequence is aligned with the human homologous sequence 3-64-04, and the framework and CDR domains are indicated.

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 successfully used, 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 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.

Example: In FIG. 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.

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 WGVXG . . . (where X is usually Q or P), however some variation may exist in these residues.

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.

8. The rabbit heavy chain framework 4, which is 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 of is of the sequence ‘WGVQTLTVSS’. 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.

Example: In FIG. 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.

In addition, FIG. 15 depicts preferred humanized anti-IL-6 variable heavy and variable light chain sequences humanized from the variable heavy and light regions in Ab1 according to the invention. These humanized light and heavy chain regions are respectively contained in the polypeptides contained in SEQ ID NO:647, 648, 649, 650, or 651 and in SEQ ID NO:652, 653, 654, 655, 656, 657 or 658. The CDR2 of the humanized variable heavy region in SEQ ID NO:657 (containing a serine substitution in CDR2) is contained in SEQ ID NO:659.

Methods of Producing Antibodies and Fragments Thereof.

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 polyplodial, 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 polyplodial 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 polyplodial 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).

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 polyplodial 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.

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.

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.

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.

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. Pat. Nos. 5,959,177; and 5,202,422).

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.

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 significant 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.

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.

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.

[0769] 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 L C, 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.

[0770] 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.

[0771] 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.

[0772] 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.

[0773] 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 inhibit 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.

[0774] 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.

[0775] 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.

[0776] 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.

[0777] 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. Pat. Nos. 4,816,567 to Cabilly et al.; Morrison et al., P.N.A.S. USA, 81:8651-55 (1984); Neuherger, M. S et al., Nature, 314:268-270 (1985); Boulianne, G. L. et al., Nature, 312:643-46 (1984), the disclosures of which are herein incorporated by reference in their entireties).

[0778] Likewise, other methods of producing humanized antibodies are now well known in the art (See, for example, U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen et al; U.S. Pat. Nos. 5,225,539 and 6,548,640 to Winter; U.S. Pat. Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al; U.S. Pat. No. 6,632,927 to Adair; Jones, P. T. et al,
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 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.

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.

The expression vectors are transfected into a host cell by conventional 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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucus, 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.

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.


In another embodiment of the invention, anti-IL-6 antibodies described herein, or fragments thereof, are useful as a wakefulness aid.

Administration

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.

[0804] 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., Loza, J. S., & Parker, K. L. (2006). Goodman & Gilman’s the pharmacological basis of therapeutics. New York: McGraw-Hill; Hollain, 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.

[0805] 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.

[0806] 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, epidermal, 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.

[0807] 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-1, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-α, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepciklin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include 2-Arylpropionic acids, Aceclofenac, Acemectin, Acetylsalicylic acid (Aspirin), Aleclofenac, Alminopropen, Amoxiprin, Amyprone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxapropen, Brofenac, Carprofen, Celecoxib, Choline magnesium salicylate, Cleofzone, COX-2 inhibitors, Dextubiprofen, Dexketoprofen, Dieloferac, Diflunisal, Droxicam, Ethamizamide, Etodolac, Etoricoxib, Fiasilamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Fluoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indometacin, Indoprofen, Kebuzon, Ketorolac, Loroxinate, Loxoprofen, Lumira- cocoxib, Magnesium salicylate, Meclofenamic acid, Mefenamic acid, Meloxicam, Metambutol, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylanthranilic acids, Oxametacin, Oxaoprozin, Oxicams, Oxphenbutazone, Parecoxib, Phenazonia, Phenylbutazone, Phenylbutyzone, Pirprofen, Pirprofen, profens, Proglumetacin, Pyrazolide derivatives, Rosofex, Salicyl salicylate, Salicylamide, Salicylates, Sulfinpyrazone, Sulindac, Suprofen, Tenoxicam, Tiafenac acid, Tolnfanamic acid, Tolumetin, and Valdecoxib. Antibiotics include Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arspenamines, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbencillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefamandole, Cefazolin, Cefdinir, Cefotoren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Cefazidime, Cefibuten, Cefitoxime, Ceflobiprofen, Cefetaxone, Cefuroxime, Ceplaphorosin, Chloramphenicol, Cilastatin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacin, Colistin, Co-trimoxazole, Dalfopristin, Demeocycline, Diectoxacillin, Dirithromycin, Doripenem, Doxycycline, Enoxacin, Erup- enem, Erythromycin, Ethambutol, Fluoxacillin, Fosfornyacin, Furazolidone, Fusidic acid, Gatifloxacin, Geldanamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Iso- nitizid, Kanamycin, Levofloxacin, Lincomycin, Linezolid, Lomefloxacin, Loraneurbin, Macrolydes, Mafenide, Mercopenem, Metacinlin, Metronidazole, Mezlocillin, Minecycline, Monobactams, Moxifloxacin, Mupirocin, Nacillin, Neomy- cin, Netilmicin, Nitrofurantoin, Norloxacin, Ofloxacin, Oxacillin, Oxytetracycline, Paromycin, Penicillin, Penicil- lians, Pipracillin, Platensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinaiprin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulametamide, Sulfamethizole, Sulfinam- hilde, Sulfasalazine, Sulfoisoxazole, Sulfinamides, Teicoplanin, Telithromycin, Tetracycline, Tetracyclines, Ticarcillin, Timi- dazole, Tobramycin, Trimethoprim, Trimethoprin-Sulfamethoxazole, Trokindomycin, Troxifloxacin, and Vancomyc- mycin. Active agents also include Aldosterone, Beclometasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, DEXYcorticosterone acetate, Dexamethasone, Fludrocortisone acetate, Glucocorticoids, Hydrocorti- sone, Methylprednisolone, Prednisolone, Prednisone, Steroids, and Triaminocolone. Antiviral agents include abacavir, aciclovir, acyclovir, adefovir, amantadine, amphenavir, an antiretroviral fixed dose combination, an antiretroviral synergistic enhancer, arbidol, atazanavir, atipra, brivudine, cido- fovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, entry inhibitors, famiclovir, fomiviren, fosam- prenavir, foscarnet, fosfonat, fusion inhibitor, ganciclovir, garsulis, lbidactinam, idoxuridine, imiquimod, immunovir, iniclovir, inosine, integrase inhibitor, interferon, interferon type I, interferon type II, interferon type III, lamivudine,
lopinavir, loviride, maraviroc, MK-0518, moroxydine, nelﬁnavir, nevirapine, nevir, nucleoside analogues, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxin, protease inhibitor, reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tramontadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, and zidovudine. Any suitable combination of these active agents is also contemplated.

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., Gennaro, A., Ed., 1995 which is incorporated by reference.

As used herein “pharmaceutically acceptable carrier” or “excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonics 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.

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.

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, polyactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

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 intradernal), infusions, and combinations thereof.

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.

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.

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.

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.

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. PCT/EP02/04838, 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.

Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. patent application Ser. No. 11/429,053, filed May 8, 2006, (U.S. Patent Application Publication No. US20060270045), the disclosure of which is herein incorporated by reference in its entirety.

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.
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.

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 entirety.

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 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

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.

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.

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 Millenyi 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

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 % 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

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). Antibody-positive well supernatants are then optionally tested in a function-modifying assay that is strictly dependent 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

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-Ig light 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 repipetted 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

[0829] 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 Alul 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

[0830] 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

[0831] 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 (T165 and HepG2). Furthermore, the collection of antibodies display distinct modes of antagonism toward IL-6-driven processes.

Immunization Strategy

[0832] 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.

[0833] Antibody Selection Titer Assessment

[0834] 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 5 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-ERP (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 Prism software, and titers were determined.

[0835] Functional Titer Assessment

[0836] 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 Heps, 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 Owen. Cells were set aside at room temperature.

[0837] 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 4× 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 CellTitre96 (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.

[0838] Tissue Harvesting

[0839] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[0840] Spleen and lymph nodes were processed into a single cell suspension by dissociating 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 hulL-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 PBS (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.

[0841] 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/PBS medium and frozen as described above.

[0842] B Cell Culture

[0843] 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 medium. Cell density and viability was determined by trypan blue. Cells were washed again and resuspended at 1E07 cells/80 ul medium. Biotinylated hulL-6 (B hulL-6) was added to the cell suspension at the final concentration of 3 ng/ml and incubated for 30 minutes at 4°C. Unbound B hulL-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 (Miltenyi) 1E07 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/1E07 cells. After washing, the cells were resuspended at 1E08 cells/500 µl of PBF and set aside. A MACS® MS column (Miltenyi) was pre-rinsed with 500 ml of PBF on a magnetic stand (Miltenyi). 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 Polystyrene 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.

[0844] 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 (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.

[0845] Identification of Selective Antibody Secreting B Cells

[0846] Cultures were tested for antigen recognition and functional activity between days 5 and 7.

[0847] Antigen Recognition Screening

[0848] 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.

[0849] Functional Activity Screening

[0850] 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 hulL-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.

[0851] B Cell Recovery

[0852] 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.
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.

20 µl of cell/beads/FITC suspension was removed, and 5 µl droplets were prepared on a glass slide (Coming) previously treated with SigmaCoat (Sigma). 35 to 40 droplets/slide. An impermeable barrier of parafilm 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.

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

Antibody Genes:

Genes were cloned and constructed that directed the synthesis of a chimeric humanized rabbit monoclonal antibody.

Expression Vector:

The vector contains the following functional components: 1) an 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 glycerol-dehyde dehydrogenase gene (GAP gene) promoter, fused to sequences encoding the Saccharomyces cerevisiae alpha mating factor pre pro secretion leader sequence, followed by sequences encoding a P. pastoris transcriptional termination signal from the P. pastoris alcohol oxidase 1 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.

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.

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).

Methods

Construction of pGAZP-Z-Alpha Expression Vectors for Transcription of Light and Heavy Chain Antibody Genes.

The humanized light and heavy chain fragments were cloned into the pGAZP 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 cycles; (5) 72°C 2 minutes) employing the following primers (1) light chain forward

AGCGTTAATCCTGATATCCAGTGACCGAGTC-the Aatel 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 CTTAGCTTGTGAGTCTCCACCTTG.

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 pGAZP vector using the human HAS leader sequence in frame with the human kappa light chain constant region for export. (2) A similar strategy is performed for the heavy chain. The forward primer employed is AGCGTTAATCCTGAGGTGACGCTGGTTGAGTC. The Aatel 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 CTCAGACCGTGACGGGTT.

The Xhol site is underlined, followed by the reverse complement for the 3′ end of the variable heavy chain. This allows cloning of the heavy chain in-frame with IgG-γ1 CH1-CH2-CH3 region previous inserted within pGAZP using a comparable directional cloning strategy.

Transformation of Expression Vectors into Haploid Ade1 Ura3, Met1 and Lys3 Host Strains of P. pastoris.


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 and/or by 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.

[0869] 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 arise 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.

[0870] 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.

[0871] 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/CaCl2. 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.

[0872] 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.

[0873] 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 Coomassie blue stained SDS-PAGE and immunoblotting for antibody protein. Antibody is characterized using the ELISA described above for IL-6 recognition.


[0875] 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

[0876] 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 Oreg., cat. no.—E-25AZM). The endpoint was the difference in the plasma concentration of A2M at the 24 hour time point (post-Ab1). The results are presented in FIG. 4.

[0877] 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 I

[0878] Introduction

[0879] 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 10 ng/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 hematological parameters in athymic nude mice transplanted with the human renal cell cancer cell line, RXF393.

[0880] Methods

[0881] Eighty six week old, male athymic nude mice were implanted with RXF393 tumor fragments (30-40 mg) subcutaneously in the right flank. Animals were then divided into eight groups of ten mice. Three groups were given either antibody Ab1 at 3 mg/kg, 10 mg/kg, or 30 mg/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 3 mg/kg, 10 mg/kg, or 30 mg/kg intravenously weekly on day 8, day 15 and day 22 after...
transplantation (regression groups). Finally, one control
group was given polyclonal human IgG 30 mg/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. (0882) Animals were euthanized at either
day 28, when the tumor reached 4,000 mm³ 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 hematological
and serum amyloid A protein (SAA) concentration. An addi-
tional group of 10 non-tumor bearing 6 week old, athy
mic nude male mice had blood samples taken for hematological
and SAA concentration estimation to act as a baseline set
of values. (0883) Results—Survival
(0884) 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 buff-
ered 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. (0885) The survival curves for the two control groups
and the antibody Ab1 progression (dosed from day 1 of the study)
groups are presented in FIG. 5. (0886) The survival curves for the two control groups
and the antibody Ab1 regression (dosed from day 8 of the study)
groups are presented in FIG. 6. (0887) There was no 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). (0888) Results—Plasma Serum Amyloid A
(0889) 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 pre-
sented in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean Plasma SAA - antibody Ab1, all groups versus control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Plasma SAA ± SEM</td>
</tr>
<tr>
<td></td>
<td>Day 5 (µg/ml)</td>
</tr>
<tr>
<td>Polyclonal IgG iv</td>
<td>675 ± 240</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>PBS iv weekly</td>
<td>355 ± 207</td>
</tr>
<tr>
<td>from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 30 mg/kg iv</td>
<td>246 ± 100</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Ab1 10 mg/kg iv</td>
<td>3629 ± 624</td>
</tr>
<tr>
<td>weekly from day 1</td>
<td>(n = 5)</td>
</tr>
</tbody>
</table>

(0890) SAA is up-regulated via the stimulation of hl-6 and
this response is directly correlated with circulating levels of
hl-6 derived from the implanted tumor. The surrogate
marker provides an indirect readout for active hl-6. Thus in
the two treatment groups described above there are signifi-
cantly decreased levels of SAA due to the neutralization of
tumor-derived hl-6. This further supports the contention
that antibody Ab1 displays in vivo efficacy. (0891) Example 11

RXF393 Cachexia Model Study 2

(0892) Introduction

(0893) 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 consump-
tion was measured. There was also an attempt to standardize
the tumor sizes at the time of initiating dosing with antibody
Ab1.

(0894) Methods

(0895) Eighty, 6 week old, male athymic nude mice were
implanted with RXF393 tumor fragments (30-40 mg) subcu-
taneously in the right flank. 20 mice were selected whose
tumors had reached between 270-320 mg in size and divided
into two groups. One group received antibody Ab1 at 10
mg/kg i.v. every three days and the other group received
polyclonal human IgG 10 mg/kg every 3 days from that
timepoint (day 10 after transplantation). Another 20 mice
were selected when their tumor size had reached 400-527 mg
in size and divided into two groups. One group received
antibody Ab1 at 10 mg/kg i.v. every three days and the other

group received polyclonal human IgG 10 mg/kg every 3 days
from that time-point (day 13 after transplantation). The remain-
ing 40 mice took no further part in the study and were

euthanized at either day 49, when the tumor reached 4,000
mm³ or if they became very debilitated (>50% loss of
body weight).

(0896) 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 mea-
sured (amount consumed in 24 hours by weight (g) by each
treatment group) every day from day 10 for the 270-320 mg
tumor groups and day 13 for the 400-527 mg tumor groups.
[0897] Results—Survival

[0898] The survival curves for antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size) and for the polyclonal human IgG 10 mg/kg i.v. every three days (270-320 mg tumor size) are presented in FIG. 7.

[0899] Median survival for the antibody Ab1 at 10 mg/kg i.v. every three days (270-320 mg tumor size) was 46 days and for the polyclonal human IgG at 10 mg/kg i.v. every three days (270-320 mg tumor size) was 52 days (p = 0.0071).

[0900] The survival curves for the antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size) and for the polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) are presented in FIG. 8. Median survival for the antibody Ab1 at 10 mg/kg i.v. every three days (400-527 mg tumor size) was 46.5 days and for the polyclonal human IgG at 10 mg/kg i.v. every three days (400-527 mg tumor size) was 27 days (p = 0.0481).

Example 12

Multi-Dose Pharmacokinetic Evaluation of Antibody Ab1 in Non-Human Primates

[0901] Antibody Ab1 was dosed in a single bolus infusion to a single male and single female cynomolgous monkey in phosphate buffered saline. Plasma samples were removed at fixed time intervals and the level of antibody Ab1 was quantified through the use of an antigen capture ELISA assay. Biotinylated IL-6 (50 μg of 3 mg/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.

[0902] 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 cynomolgous monkeys and the experiment replicated using an identical sampling plan. The resulting concentrations are then plotted vs. time as shown in FIG. 9.

[0903] This humanized full length aglycosylated antibody expressed and purified with 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

[0904] 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 (ForteoBio; Menlo Park, Calif.). Studies were performed in two different configurations. In the first orientation, biotinylated IL-6 (R&D systems part number 206-IL-001 MG/CF, biotinylated using Pierce EZ-link sulfo-NHS-EDC-LC-biotin product number 21338 according to manufacturer’s protocols) was initially bound to a streptavidin coated biosensor (ForteoBio part number 18-5006). Binding is monitored as an increase in signal.

[0905] 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.

[0906] In the second orientation, the antibody was bound to a biosensor coated with an anti-human IgG1 Fe-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/GP 130 interactions. All studies were performed in a 200 μl final volume, at 30 C and 1000 rpm. For these studies, all proteins were diluted using ForteBio’s sample diluent buffer (part number 18-5028).

[0907] Results are presented in FIGS. 10A-E and 11.

Example 14

Peptide Mapping

[0908] 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 FIG. 12. Blots were prepared and probed according to the manufacturer’s recommendations.

[0909] 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 (Alphalumina). The results of the blots is shown in FIGS. 13 and 14.

[0910] The sequence of the form of human IL-6 utilized to generate peptide library is set forth:

```
SEQ ID NO: 1

VPQGQDGKDAVAPRQLQSLERDRQYIRLYLDDGAQLKATEKCKKNSCE
SSIKELAENRLIPKQAKDGCFQGSGHNHCLVVKITTQLEFQSTYEL
QNPQFESWIEQRVQKSTYLVQGLQKPAKQHaDATTIDPDNTSNLTL
QGQKQLQDQMTSLILRFSKELQGSSLRLQRM.
```
SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 659
<210> SEQ ID NO 1
<211> LENGTH: 183
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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

<210> SEQ ID NO 2
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 2

Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Trp 1 5 10 15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gin Thr Pro Ala Ser 20 25 30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gin Ala Ser 35 40 45
Gln Ser Ile Asn Asn Gin Gin Ser Gin Ser Tyr Gin Gin Lys Pro Gly Gin 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 Gin Ser Gin Ser Gin Thr Glu Phe Thr Leu Thr 85 90 95
Ile Ser Asp Leu Glu Cys Ala Gin Ala Ala Thr Tyr Tyr Cys Gin Gin 100 105 110
Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala

115
120

<210> SEQ ID NO 3
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 3

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 Ser Gly Gly 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

Asn Tyr Tyr Val Thr Trp Val Arg Asn Ala Pro Gly Lys Gly Leu Glu
50    55    60

Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr 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

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
115
120
125

<210> SEQ ID NO 4
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 4

Gln Ala Ser Gln Ser Ile Asn Asn Glu Leu Ser
1     5     10

<210> SEQ ID NO 5
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 5

Arg Ala Ser Thr Leu Ala Ser
1     5

<210> SEQ ID NO 6
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 6

Gln Gln Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala
1     5     10

<210> SEQ ID NO 7
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 7

Asn Tyr Tyr Val Thr

-continued
-continued

1

<210> SEQ ID NO 8
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 8

Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Trp Ala Ile Gly
1   5   10  15

<210> SEQ ID NO 9
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 9

Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
1   5   10

<210> SEQ ID NO 10
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 10

atggaacagg ggccccacac tcacgctctg gggtctttgg ctcggctgct cccaggtgcc  60
agatgtgtct atgtatagac ccagacttcc gtttctgggt gttgagcttg ggaggtcaca 120
gtcacacatca aagtggacag cactcaggcc attaacaatg aatcttctgg gtatcagcag 180
aaacacgagc agctgtgcac gttcctgcat tattaaggcat ccactctggc atctggttgtc 240
tcaggtgcgt tcacagcgtgc ttgatctgag acagagttcc ctctccactt cagcagcttg 300
gaggtgctcag atcgtgctccc tctactctg caaaccagtt atgcttctg gasatattgat 360
aagctc 366

<210> SEQ ID NO 11
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 11

atgcggactg ggctggcgtgc gtctttctgct gttgttgctgc tctaaagtgtg ccaagttctg  60
tctctggagg actccgggag tcctgctgct cagccctgga caccctgac actcactgc 120
aacagccttg gattctcctc cagtactac ctgctgaccc ggtctggcga ggtcctgccag 180
aagggcgtgg aatgcatcgg aactcttctt ggtagtgtag aaagggctca cggcagcttg 240
gccatggtgc gatccaccat cttccaaacc tcgaccagg tcgatctgaa aatgaccagt 300
tcagcagcag cggacagcgc cacccttctc tctgaccagag atgatagtag tcactgggt 360
gcagaatatta ccttgt 375

<210> SEQ ID NO 12
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 12

caggccagtc agagcacattc ctaatgatttt ctc 33
<210> SEQ ID NO 13
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 13
agggcatcctcttggtcatc t 21

<210> SEQ ID NO 14
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 14
cacaagggtt atagtctgag gaattggtat aatgt 36

<210> SEQ ID NO 15
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 15
aactactacg tgcac 15

<210> SEQ ID NO 16
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 16
atcatttag tgtagttaga aacgctcctc gcgccttgggg gcctagc 48

<210> SEQ ID NO 17
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 17
gtagtagtactgta ctgctgcttgg ggtaaaattg aacttg 36

<210> SEQ ID NO 18
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 18
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 Gln 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 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> SEQ ID NO 19
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 46
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 Asp Ala Lys Phe Asn Leu
100 105

<210> SEQ ID NO 20
<211> LENGTH: 99
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Gin Ser Ile Asn Asn Glu Leu
20 25 30
Ser Trp Tyr Glu Gln Gly Pro Gly Lys Ala Pro Gly 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
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 Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn Ile
85 90 95
Asp Asn Ala

<210> SEQ ID NO 21
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 21
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 Aasp 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
<210> SEQ ID NO 22
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 22

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 Arg Leu Val Thr
20  25  30
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 Gin Ala Pro Gly Lys Gly Leu
50  55  60
Glu Tyr Ile Gly Phe Ile Asn Ser Gly Ser Ala Arg Tyr Ala Ser
65  70  75  80
Trp Ala Glu Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Val Asp
85  90  95
Leu Lys Met Thr Ser Leu Thr Glu Asp Thr Ala Thr Tyr Phe Cys
100 105 110
Val Arg Gly Gln Ala Val Trp Ser Ile His Ser Phe Asp Pro
115 120 125

<210> SEQ ID NO 23
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 23

Gln Ala Ser Glu Thr Ile Tyr Ser Trp Leu Ser
1  5  10

<210> SEQ ID NO 24
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 24

Gln Ala Ser Asp Leu Ala Ser
1  5

<210> SEQ ID NO 25
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 25
Gln Gln Gly Tyr Ser Gly Ser Asn Val Asp Asn Val
1  5  10

<210> SEQ ID NO 26  
<211> LENGTH:  5  
<212> TYPE:   PRT  
<213> ORGANISM:  Oryctolagus cuniculus  

<400> SEQUENCE:  26  
Asp His Ala Met Gly
1  5

<210> SEQ ID NO 27  
<211> LENGTH:  16  
<212> TYPE:   PRT  
<213> ORGANISM:  Oryctolagus cuniculus  

<400> SEQUENCE:  27  
Phe Ile Asn Ser Gly Ser Ala Arg Tyr Ala Ser Trp Ala Glu Gly
1  5  10  15

<210> SEQ ID NO 28  
<211> LENGTH:  12  
<212> TYPE:   PRT  
<213> ORGANISM:  Oryctolagus cuniculus  

<400> SEQUENCE:  28  
Gly Gly Ala Val Trp Ser Ile His Ser Phe Asp Pro
1  5  10

<210> SEQ ID NO 29  
<211> LENGTH:  366  
<212> TYPE:   DNA  
<213> ORGANISM:  Oryctolagus cuniculus  

<400> SEQUENCE:  29
atgacacag gcgcccccac tcagatcgtg gggtctctgc tgctctgtgc ccaacagttc  60
agatgtggtc atgataagac ccagacacta gcctctgttg agatgtcgtg gggaggccac 120
gctaccatac atgcgcagcc cagtgacacc atttacagtt ggttatcttg gtagctgca  180
agaagacggc agccctctcaac gcctctgatt tacatgacat cgagtctgacc atctggtgtc 240
cctagcagt tcagtgccag tggggtgctg acaagagtcac ctctcaccct cagccgctgt 300
cagtgctgcag atcagcgcac ttactactgt ccaaggggtt atagttgtag taatggttgt 360
aatgtt  366

<210> SEQ ID NO 30  
<211> LENGTH:  378  
<212> TYPE:   DNA  
<213> ORGANISM:  Oryctolagus cuniculus  

<400> SEQUENCE:  30
atggagactg gggtgcgtcg gcctctcttg gctgctgtgc tcacaggtgt ccaggtcag  60
gacgacgtga agagttcgg gggtgcgtcg gtagggtctgt gcacacccct gcacattacc 120
tgacacagct ctgtagttca ccctataagct ccagcaatgg ggtggtggcc ccaaggtcct 180
gggagggggc tggaattcct ccagttgctg aagttggtg gtatgcacgg ctgtgctgac 240
tggggcagag gcagttcagc ccctccagcc acctcagacc ccggagagct gaaatgac 300
agctcggaca ccacagaccc ggcacactat ttctgtgtca ggggggtgc ttgctgctg 360
attcatagtt ttgatcc

<210> SEQ ID NO 31
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 31
cagggcagtg agaccattta cagttggtta tcc

<210> SEQ ID NO 32
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 32
cagggcatccg atctggcacac t

<210> SEQ ID NO 33
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 33
caacagggtt taagtggtag taagttgtgat aatgtt

<210> SEQ ID NO 34
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 34
gacacctgca g tggg

<210> SEQ ID NO 35
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 35
ttcattaata gttggtgtag cgacagctac ggcagctggg cagasgcg

<210> SEQ ID NO 36
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 36
ggagggtgtct tttggagatct tcatagtttt gatccc

<210> SEQ ID NO 37
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 37
Met Asp Thr Arg Ala Pro Thr Gin Leu Leu Gly Leu Leu Leu Leu Trp
1  5  10  15
Leu Pro Gly Ala Thr Phe Ala Ala Val Leu Thr Gin 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
Gln Ser Val Tyr Asp 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 Ser Asp Asn Ala 115 120

<210> SEQ ID NO 38
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 38
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 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 Glu 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 Val Asp Leu 85 90 95
Lys Met Thr Ser Pro Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala 100 105 110
Arg Ser Arg Gly Thr Gly Thr Met Gly Arg Leu Asp Leu 115 120 125

<210> SEQ ID NO 39
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 39
Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ser 1 5 10

<210> SEQ ID NO 40
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 40
Gly Ala Ser Thr Leu Ala Ser 1 5

<210> SEQ ID NO 41
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 41

Ala Gly Val Tyr Asp Asp Asp Ser Asp Asn Ala
1    5

<210> SEQ ID NO 42
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 42

Val Tyr Tyr Met Asn
1    5

<210> SEQ ID NO 43
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 43

Phe Ile Thr Met Ser Asp Asn Ile Asn Tyr Ala Ser Trp Ala Lys Gly
1    5    10

<210> SEQ ID NO 44
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 44

Ser Arg Gly Trp Gly Thr Met Gly Leu Asp Leu
1    5

<210> SEQ ID NO 45
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 45

atggacacg gggcccccc ac at gctgtgcg gggtctgctg tgcctggtct cccaggtgcc
  60
acatttgcc gc gctggtcgg cca gactccca tctcgcgtgt tctgcagctg gggaggcaac
 120
gtctcagta cgtcgcaggc cagtcagagt gtttacacaa cacaacctct atctcgcatt
 180
cagcgaaac cagggcagcc tccacaccc tctatctagt gtgcacccag tctggcatct
 240
ggggtccatt gc gggtgttgag ggccaggtga tctgggacac agtctactct caccatcaca
 300
gagctcaggt gtgcaggtgc tggcacttac tattgtgcag gctgttatga tgaattagct
 360
gataatgccc
 369

<210> SEQ ID NO 46
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 46

atggagacgt ggcgcggccg tctttcatct gtggcgggtgc tcaaggggtg cagagtcgca
  60
tgctgaggg agtccggggg gcgcgtcggc aaccgggctg aaccggctac actaacgtgc
 120
acagctctgg cagtcgctct acatggagcc ggtgctgcca ggtccaggg
 180
aaggggctgg atagatcgg atccattaca atagatgta atataatta cgcgagcgtgg
 240
-continued

gccaaagggc gatcagatg cttccaaacc tggacccaggg tgagatctgaa aatgaccagt 300
ccgacacacg aggacacagc cacctatcc tggccagagcg tgcggggttc gggtcatctg 360
gtctgtggtg atctc 375

<210> SEQ ID NO 47
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 47
cagggcagtc agatgtttta tgacacacac taattatcc 39

<210> SEQ ID NO 48
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 48
gtctacatca cttcagcatct t 21

<210> SEQ ID NO 49
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 49
gcagggcttt atatgtgagta tagtgaat ggc 33

<210> SEQ ID NO 50
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 50
gttactaca tgaac 15

<210> SEQ ID NO 51
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 51
tttcattcgc tgaagtgttag tataattac gcaagtgggg cgaagggc 48

<210> SEQ ID NO 52
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 52
agtagagtct ggggtacatt ggtcggtttg gatctc 36

<210> SEQ ID NO 53
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 53
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15
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<th>Protein Sequence</th>
<th>Position</th>
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<tbody>
<tr>
<td>Leu Pro Gly Ala Ile Cys Asp Pro Val Leu Thr Gln Thr Pro Ser Pro</td>
<td>20 25 30</td>
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<tr>
<td>Val Ser Ala Pro Val Gly Gly Thr Val Ser Ile Ser Cys Gln Ala Ser</td>
<td>35 40 45</td>
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<td>Gln Ser Val Tyr Glu Asn Asn Tyr Leu Ser Trp Phe Gln Gln Lys Pro</td>
<td>50 55 60</td>
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<td>Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Leu Asp Ser</td>
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<td>Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr</td>
<td>85 90 95</td>
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<td>Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys</td>
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<td>115 120</td>
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SEQ ID NO: 54
LENGTH: 126
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

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<tr>
<td>Val Gln Cys Glu Glu Glu Leu Lys Glu Ser Gly Gly Gly Leu Val Thr</td>
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<td>Asn Ala Tyr Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu</td>
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<td>Trp Ala Lys Gly Arg Phe Thr Phe Ser Lys Thr Ser Thr Thr Thr Val Asp</td>
<td>85 90 95</td>
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<td>Leu Lys Met Thr Ser Pro Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys</td>
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SEQ ID NO: 55
LENGTH: 13
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

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<td>1 5 10</td>
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SEQ ID NO: 56
LENGTH: 7
TYPE: PRT
ORGANISM: Oryctolagus cuniculus

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<td>Gly Ala Ser Thr Leu Asp Ser</td>
<td>1 5</td>
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SEQ ID NO: 57
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 57

Ala Gly Val Tyr Asp Asp Ser Asp Asp Ala
1  5       10

<210> SEQ ID NO 58
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 58

Ala Tyr Tyr Met Asn
1  5

<210> SEQ ID NO 59
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 59

Phe Ile Thr Leu Asn Asn Val Ala Tyr Ala Asn Trp Ala Lys Gly
1  5 10 15

<210> SEQ ID NO 60
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 60

Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
1  5 10

<210> SEQ ID NO 61
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 61

atgagacagc ggcccctcac tcagctgtga gggtctctgc tgctcttgct cccaggtgcc 60
atatgtgacc ctggtgtagc ccagatctaa tctccgtatat ttgcaacctg gggagggaca 120
gtcaagcata gtttgccagccc gatcagagct gttatataga aacaactattt atcttggttt 180
cagcagaaac caggggagcc tcccacactc tctgactctatg ttgcaatctac ctcctgattt 240
ggggggctcat cgcgtccaca aggcagttga ttggtggacac aacccatctact caccattaca 300
gacgtgctgt gtaagagatag tggccaaagtag ggttttatga tggtgatagt 360
gatgatgcc 369

<210> SEQ ID NO 62
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 62

agagacctgg ggtgcgctgt gttctctctg gtggctgtag tcasaagttgt ccagtttcag 60
gagcagctga aggagttcggaggggctgt ctgaaactgc gacaoctaccac 120
tgcaacgcttt gcgattctcct catcaagtgc actggtcctgg caaggtcctaa 180
gggaaggggc tggaatggat cggatcatt actctgaaata ataatgtagc ttacgcgaac 240
tgppgcaag gcggacac ctcttccaa actctgacca cggtgcatc gaaaatgacc 300
agtcggacac cgagggacac ggccacctat ttcttgccca ggatcggtg gctgggtgca 360
atgggttgt tggatctc 378

<210> SEQ ID NO 63
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 63
cagggcagtc agagtgttta tgagaacaac tattttatcc 39

<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 64
ggtgcatcca cttctggatct t 21

<210> SEQ ID NO 65
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 65
gcagggggtt atatgtgata tagtgatgat gcc 33

<210> SEQ ID NO 66
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 66
gcctactaca tgaac 15

<210> SEQ ID NO 67
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 67
ttcattattc tgaatataaa gtatgcttac gcgaactgga cgaagggc 48

<210> SEQ ID NO 68
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 68
agtcggtgct ggggtcaat gggtcggttg gatctc 36

<210> SEQ ID NO 69
<211> LENGTH: 122
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 69
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Leu Gly Leu Leu Leu Leu Leu Trp
1 5 10 35
Leu Pro Gly Ala Thr Phe Ala Gln Val Leu Thr Gln Thr Pro Ser Pro
20 25 30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45
Gln Ser Val Asp Asp 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 Thr Tyr Tyr Cys
100 105 110
Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala
115 120

<210> SEQ ID NO 70
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 70

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 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
50 55 60
Trp Ile Gly Ile Ile Gly Phe Gly Thr Thr Tyr Ala Thr Trp
65 70 75 80
 Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Val Asp Leu
85 90 95
Arg Ile Thr Ser Pro 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

<210> SEQ ID NO 71
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 71

Gln Ala Ser Gln Ser Val Asp Asp Asn Asn Trp Leu Gly
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 72

Ser Ala Ser Thr Leu Ala Ser
1 5
<210> SEQ ID NO 73
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 73

 Ala Gly Gly Phe Ser Gly Asn Ile Phe Ala
1 5 10

<210> SEQ ID NO 74
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 74

Ser Tyr Ala Met Ser
1 5

<210> SEQ ID NO 75
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 75

Ile Ile Gly Gly Phe Gly Thr Thr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 76
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 76

Gly Gly Pro Gly Asn Gly Gly Asp Ile
1 5

<210> SEQ ID NO 77
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 77

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acatcggcc aagtgtgac ccagaactca tcagctgtgc ctgcagctgt ggagggcaca 120
gtaccacca actcgccagc capcagactgt gtacagatca acaactctggc aggtgtgat 180
cagcagaaac ggggccagcc tcccaagtcg tctatatt tctgctcoca ctctgcgtct 240
gggtctgcc catccgctca agggcagctga tctgggacac agttcactct caccatcag 300
gacctggagt tgcagagtc tcccaatcact tctgtgcag ggcgtattgg tggtaattc 360
ttttgt 366

<210> SEQ ID NO 78
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 78

atggacactg ggtgctgcctg gcctctccctg gtcgctgtgc tcasaaggtgt ccagtgtcag 60
<210> SEQ ID NO: 79
<211> LENGTH: 120
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 79

tcggtgggag agtccggggg tcgctctgc tgcgtggga caacccctgac aacctctgct
120
acagttcctgc gtttcctcct cagtagctat gcataagcgt gggtggcgc ggtctcaggg
180
aaggggctcg agtctgatgct gttttggtgt gtttttgta ccacatact caacgacctgg
240
gcgaaaggcc gattcactat ctccaaaccct tgcacccggg tggatctggag aatccacagt
300
cgcacaccc aggacacggc cacatatttc tgtgccagag gtggctcctgg taatgggtgt
360
gacatc
366

<210> SEQ ID NO: 80
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 80
cagggcagtc agaggtgtgga tgataacaac tggttaggc
39

<210> SEQ ID NO: 81
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 81
tetgtatcct aatggtgcact t
21

<210> SEQ ID NO: 82
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 82
gcacggcttg ttatggttaa tatctttgct
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<210> SEQ ID NO: 83
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 83
atcattgtgt gttttgtgtac cacatactac gcgaacctgg gcaagccg
48

<210> SEQ ID NO: 84
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 84
ggtgttgcttg tataattgtgg tgacatc
27

<210> SEQ ID NO: 85
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
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<400> SEQUENCE: 85

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

<210> SEQ ID NO: 86
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 86

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Leu Lys Gly
1     5      10     15
Val Gln Cys Gln Ser Val 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
Asp Tyr Ala Met Ser Thr Val Arg Glu Ala Pro Gly Lys Gly Leu Glu
50    55      60
Trp Ile Gly Ile Ile Tyr Ala Gly Ser Gly Ser Thr Thr 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 Glu Asp Thr Ala Thr Tyr Tyrol Cys
100   105     110
Ala Arg Asp Gly Tyr Asp Asp Gly Phe Asp Arg Leu Asp Leu
115   120     125

<210> SEQ ID NO: 87
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 87

Gln Ser Ser Gln Ser Val Tyr Asn Asn Phe Leu Ser
1     5      10

<210> SEQ ID NO: 98
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 98
Gln Ala Ser Lys Leu Ala Ser
1 5

<210> SEQ ID NO 89
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 89
Leu Gly Gly Tyr Asp Asp Ala Asp Aom Ala
1 5 10

<210> SEQ ID NO 90
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 90
Asp Tyr Ala Met Ser
1 5

<210> SEQ ID NO 91
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 91
Ile Ile Tyr Ala Gly Ser Gly Ser Thr Tyr Ala Ser Trp Ala Lye
1 5 10 15

Gly

<210> SEQ ID NO 92
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 92
Asp Gly Tyr Asp Asp Tyr Gly Asp Phe Asp Arg Leu Asp Leu
1 5 10

<210> SEQ ID NO 93
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 93
atggacacga gggccccccac tcagctgtgc gggctctgtgc tgctctgtgc cccaggtgcc 60
acatttgcag cgggtgtgcac ccagacacca tcgccccgtg cttcatctgt gggagggcaca 120
gtccacata agggccagtc cagtcagagt gttataata atttttttttt cgggtgtcag 180
cagaaaccag gcggcagctcc cagctctctg atctaccagc catcacaact ggcgtctggg 240
gtccacaga ggtctcgacg cagttggactc gggacacagt tcactctcacc tactacgcgc 300
gtgcctgtcg acatgtgtgc caccctatcc tgtctaggct gttattgatc tgtgtgtctgat 360
aattct

<210> SEQ ID NO 94
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 94
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tgctgaggg ctgcctgtgt acgcctggga cacccctgac gctctactgc 120
aagctctctg gatactgacct cagtgactat gcaatgacgt gggtcgccac ggtctcagg 180
aaggggctgg aatgcatcgg aatctatatt gcttggtact gtggcactgt gtagcgcag 240
tggggaag gcaagttctac cagctcagaa acctgcacca cgggtgtctt gaaaacctcc 300
agtcgcagaa cggagaac gcggctcact tttggtgcgca gagctggatc atgagactat 360
gctgtaattgc atcgaattgg tctc 384

<210> SEQ ID NO 95
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 95
cagtcagc agagtggtaa taataatttc ttatcg 36

<210> SEQ ID NO 96
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 96
cagggcatca aactgcgttc t 21

<210> SEQ ID NO 97
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 97
catggcagtt atgatgatga ttgatgataat gct 33

<210> SEQ ID NO 98
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 98
gactatgca tggc 15

<210> SEQ ID NO 99
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 99
atcatttatt cttgtggcgg tagcatacag tggaggaact ggcgaagagc g 51

<210> SEQ ID NO 100
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 100
gatgatacg atgactatgg tgatctgcgt tgtgattgtc tc 42
<210> SEQ ID NO 101
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Gryctologus cuniculus

<400> SEQUENCE: 101

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

<210> SEQ ID NO 102
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Gryctologus cuniculus

<400> SEQUENCE: 102

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Ser 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 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
95  90  95
Lys Met Thr Ser Leu Thr Ala Asp Thr Ala Thr Tyr Phe Cys Ala
100 105 110
Arg Asp Asp Ser Ser Asp Thr Ala Lys Phe Asn Leu
115 120 125

<210> SEQ ID NO 103
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Gryctologus cuniculus

<400> SEQUENCE: 103

Gln Ala Ser Gln Ser Ile Asn Asn Glu Leu Ser
1  5  10

<210> SEQ ID NO 104
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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 104

Arg Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 105
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 105

Gln Gln Gly Tyr Ser Leu Arg Asn Ile Asp Asn Ala
1  5  10

<210> SEQ ID NO 106
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 106

Asn Tyr Tyr Met Thr
1  5

<210> SEQ ID NO 107
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 107

Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Trp Ala Ile Gly
1  5  10  15

<210> SEQ ID NO 108
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 108

Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu
1  5  10

<210> SEQ ID NO 109
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 109

atgacacga ggccccocac tcaagtgcctg gggtcttcgtc tggctctgct cccaggtgcc
60
agatgtgcct atgtataagc cccagactca gctcgggtct ctgcagcttg gggaggcaca
120
gtacccatca aatgcaaggc cagtccagagcattaaccagt mttatccctg gtatccacag
180
aatcacggc aagctccaca gtcctgtgct tataggcct tccacttgcc aatctggtggct
240
tctcctgcgg taagctgggc从来aaagacttctccatca ccttccacct gagcgcctgt
300
gagttgtgcgg atgtgcccac ttaacctggt caacagggtg atagttgtgag gaatttggt
tgtctaggct
360
aagtct
366

<210> SEQ ID NO 110
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 110

atggagactg ggcgtgcgtg gctttccctg gtggtgtgtc ttcaggttgt ccagtgctag 60
tgcgctggag aagcgaggggg tgcgcgtgcgc aecgctggaga caacocctgac actaoactgc 120
acagctcttg gattctctcc cagtaactac tacatgacct gggcgcgcca ggcgccaggg 180
aaggggcttg aatgagatcgg aatgatttat ggtagtgatg aacacgcctaa ccgcaactgg 240
gcgatagcgc gattcaccat ctcacaaccct tgtcaccggc tgtacttgaa aatgaccagt 300
tgacagccgc cggcagcggc caccatatctc tgcgccagag atgataagtg taactgggt 360
gccaaatatta acttg 375

<210> SEQ ID NO 111
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 111

cagggcagtc aagcgattaa caatgaatta tcc 33

<210> SEQ ID NO 112
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 112

agggcatcga tctgggcatc t 21

<210> SEQ ID NO 113
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 113

caacaggttt atagtctgag gaatatgag aatgct 36

<210> SEQ ID NO 114
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 114

aactactaca tgacc 15

<210> SEQ ID NO 115
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 115

atgaatttag tgaatgtgga aacagcctac gcgaactggg cgatagcg 48

<210> SEQ ID NO 116
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 116
<210> SEQ ID NO 117
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 117

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 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 Ser 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 Ala Lys Phe Asn Leu
100 105

<210> SEQ ID NO 118
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 118

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 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 Ser 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 Ala Lys Phe Asn Leu
100 105

<210> SEQ ID NO 119
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 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
-continued

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 95 90 95
Ile Asp Asn Ala 100

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 120

Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile Gly
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 121

Met Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Asn Ser Ala Ile Gly
1 5 10 15

<210> SEQ ID NO 122
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 122

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 Val Gly Thr Val Thr Ile Ser Cys Gln Ser Ser
35 40 45
Gln Ser Val Gly 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
95 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 Ala Asp Asn Ala
115 120

<210> SEQ ID NO 123
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 123

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
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 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> SEQ ID NO 124
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 124
Gln Ser Ser Gln Ser Val Gly Asn Asn Gln Asp Leu Ser
 1     5     10

<210> SEQ ID NO 125
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 125
Glu Ile Ser Lys Leu Glu Ser
 1     5

<210> SEQ ID NO 126
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 126
Leu Gly Gly Tyr Asp Asp Ala Asp Asn Ala
 1     5     10

<210> SEQ ID NO 127
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 127
Ser Arg Thr Met Ser
 1     5

<210> SEQ ID NO 128
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 128
Tyr Ile Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
 1     5     10     15
<210> SEQ ID NO 129
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 129

Leu Gly Asp Thr Gly Gly His Ala Tyr Ala Thr Arg Leu Asn Leu
1     5     10     15

<210> SEQ ID NO 130
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 130

atggacaca gggcccccac tcaagtgtgct gggcctctgct tcctctgtgct cccaggtgcc 60
acatttcag cctgcttgac ccagacacca tcacccctgt ctgcagctgt gggagggcaaa 120
gtccacatac gtgcgtcgtg cacctccagct gttgcataa aaccagacct acctgagtttt 180
cagccagac cagggcagcc tcccaagctc tggatctcac gaaaatccaa aacctggacagct 240
gggttcctcc cagcgctctgag ggccagctga tctgggacac accttacactc caccatgac 300
ggcgtatcac tgtccacgtg ccgcaacttc taatgtctctg gcgcgttatga tgtgatgtct 360
gataatgcct 369

<210> SEQ ID NO 131
<211> LENGTH: 364
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 131

atggagacctg ggcgtcgtgct gcttcctctg tgtgctctgct tcacagagctg ccaggtcact 60
tcgggctgggg acgcgggctg tcgcttcgggt acccggtgga cacccctggac actcagactgc 120
acaagccgt ttgcttcct cagtgatgct caaatgtcct ggcgtcgccaa ggctccacgg 180
aagggctggg aggcgtagcgg atacagttgg agtgggtgta gcacatacta ccggcgctg 240
ggcgaaagcgc tggatccatct tcccaacaac ccgacgctgcgt ggtgtgtatc atggccgtgac 300
ggcacagct cggccagggc gactctatcct gttgctcagat gggccgatag tgcgggtcact 360
gttgatgct otgctgtttaa tctctctctctctct 364

<210> SEQ ID NO 132
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 132

cagctcagtc agaggtgtgg tataaaccag gacttattc 39

<210> SEQ ID NO 133
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 133

gaaatctca aactggaatct 21

<210> SEQ ID NO 134
ctggcgttt atgatgatga tgtgataat gct

agtcgtacaa tgtcc

tacatttgga tgtggtgtc cacataact gcgacctggg cgsaaggc

ttgggcgtata tgtggtgctc cgcttatgct actcgctttaa acttc

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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 Ala Asp Asp Ala
115 120
-continued

Met Glu Thr Gyl 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 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

<210> SEQ ID NO 140
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 140

Gln Ser Ser Gln Ser Val Tyr Ser Asn Lys Tyr Leu Ala
1 5 10

<210> SEQ ID NO 141
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 141

Trp Thr Ser Lys Leu Ala Ser
1 5

<210> SEQ ID NO 142
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 142

Leu Gly Ala Tyr Asp Asp Ala Asp Asn Ala
1 5 10

<210> SEQ ID NO 143
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 143

Gly Gly Tyr Met Thr
1 5

<210> SEQ ID NO 144
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 144
Ile Ser Tyr Asp Ser Gly Ser Thr Tyr Ala Ser Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 145
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 145
Ser Leu Lys Tyr Pro Thr Val Thr Ser Asp Asp Leu
1  5  10

<210> SEQ ID NO 146
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 146
atggacacga ggccgccaca tcagctgctg ggctctctgct tcacggtgct cccagctgcc 60
acattgctcg ccgtcgtgac cccagacaca tgcctcgtct ctcagctcgt gcggagggaca 120
gtcagcatca tggccgctgc cagtcagcat gttatagta ataaggtact acgctgtgt 180
cagcagaaac ccgggcaagc tcccaagctc otgtactact gcgacaccaa aatgtgacatct 240
ggggccccat cccagctcgg gcctggtggaa tccgctgccac aatccactct cccagcgcag 300
gcgcgtcagt gcgcgtcagtc tgcctacaa tatactgtcag gcggctgtga tgaggtgtcgt 360
gatagtctgct 369

<210> SEQ ID NO 147
<211> LENGTH: 379
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 147
atggagactct ggcctcgctgt gttctccctg tgcgctgctg ctaaaggtgt ccaagctcag 60
tcggtggagag actggcgggg gtcgggctgct aagctgacag aacccggtac actcaactgc 120
acagctcgctt gattctccct ggagggccgc tgtatgaccc cgggctggcag gcggcaggg 180
agggcggtctg aacgagctcg aatcagttat gatacttgtag gcaactctca cggagccagctg 240
gggaagcggc gatccgctact cttcaagcaca tctcggctgat gataatgacc 300
agctggtgca cccggagacac gcggcagctat ttctgctgctg gataactaaaa atatcactct 360
gttacctttct agatcgct 378

<210> SEQ ID NO 148
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 148
caatccgactc agagtgattta tagtataag tacctgacc 39

<210> SEQ ID NO 149
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 149
tggacatcca aactgggcctc t 21
SEQ ID NO 150
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 150
cתארטיות atatgatgta tgtgtataat gct

SEQ ID NO 151
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 151
ggccgtaca tgacc

SEQ ID NO 152
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 152
atcagtttag atatggttag cacatactac gcgagctggg cgaaagcc

SEQ ID NO 153
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 153
tcactaaat atctctagt taccttgtac gacctg

SEQ ID NO 154
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 154

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 Thr Val Thr Ile Ser Cys Glu Ser Ser
35    40    45
Gln Ser Val Tyr Asn Asn Asp Leu Ala Trp Tyr Gln Glu 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 Ala Asp Asn Ala
115   120

SEQ ID NO 155
<211> LENGTH: 129
<212> TYPE: PRT
Oryctolagus cuniculus

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

Leu

Gln Ser Ser Gln Ser Ser Val Tyr Aen Aen Aen Aep Leu Ala
1 5 10

Tyr Ala Ser Thr Leu Ala Ser
1 5

Leu Gly Gly Tyr Asp Aep Ala Aep Aep Ala
1 5 10

Ser Aen Thr Ile Aen
1 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 160

Tyr Ile Trp Ser Gly Gly Ser Tyr Tyr Ala Ser Trp Val Asn Gly
1  5 10  15

<210> SEQ ID NO 161
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 161

Gly Gly Tyr Ala Ser Gly Gly Tyr Pro Tyr Ala Thr Arg Leu Asp Leu
1  5 10  15

<210> SEQ ID NO 162
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 162

atgagacag gggccccac tcagctgtgc gggtctctgc tgctctggct cccaggtgcc  60
acatttcag cggctgtgac ccaagacaca tcacccgtgt ctcagctgtg gggaggacaa 120
gtccacatac gttccagcgt cagtcagctg gttataata ataatgactt agctgtgtat 180
cacagaaacc cgggtcagcc tctaaacttc tcttatctat atcgcatcacc tctggtact 240
ggggttccag cgcgctgtaa agggcatgga tctgggacac aagttcactct cccatcagc 300
gggtgtcag gttgagacag tcgcgattac tacgtctctg gcgggtatga tctggtact 360

gatattgtc 369

<210> SEQ ID NO 163
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 163

atgagacag gggctcgctg gttttccctg gttgctctgc tcagaggttc ccagctgtcg  60
tgctggtgag agtcggcggat cgcctgtctgc agcgctggga caaccctgac acactacctc 120
acagtacttg gattatccct ctagtacaa caataaact gggctcggac ggtccaggg 180
aaggggtcag aggtcgctgg atatacttgg agtggtggga ttacatac ataagctcagtg 240
gtatacttc gattacact ctctaaacct cgcctgctgg tgtatctgaa aataccacgt 300
cagcagagcc aggccagcgc cacatatttc tgtgctcagag ggggttaagc tatacttggtc 360
tacattatg caaacttgtgt ggtactc 387

<210> SEQ ID NO 164
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 164

cagctctgctc aagttgttta tataataacc gacttacg 39

<210> SEQ ID NO 165
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 165

tatgatcacta ctctggtacc t

<210> SEQ ID NO 166
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 166

cagggcggttt atgatgatga tcgtgtaaat gct

<210> SEQ ID NO 167
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 167

agcaatcattg aaac

<210> SEQ ID NO 168
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 168
	 tacattttgga gtgggttttag tacataactac gogagctggg tgsatggt

<210> SEQ ID NO 169
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 169

ggggggttacg ctatggttgg ttatcctttat gcacctggttt ggtgatctc

<210> SEQ ID NO 170
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 170

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Leu Trp
1   5    10   15
Leu Pro Gyl Ala Thr Phe Ala Ala Val Leu Thr Gln Thr Pro Ser Ser
20   25   30
Val Ser Ala Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
35   40
Gln Ser Val Tyr Asn Asn Asp Tyr Leu Ser Trp Tyr Gln Gln Arg Pro
45   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
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
95  100  105  110
Leu Gly Asp Tyr Asp Asp Ala Asp Asn Thr
115  120
<210> SEQ ID NO 171
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 171
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    35
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Leu Ser
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
90    95
Asp Leu Lys Met Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe
100   105   110
Cys Ala Arg Asn Tyr Gly Gly Asp Glu Ser Leu
115   120

<210> SEQ ID NO 172
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 172
Gln Ser Ser Gln Ser Val Tyr Asn Asp Tyr Leu Ser
1     5     10

<210> SEQ ID NO 173
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 173
Gly Ala Ser Lys Leu Ala Ser
1     5

<210> SEQ ID NO 174
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 174
Leu Gly Asp Tyr Asp Asp Ala Asp Asp Asn Thr
1     5     10

<210> SEQ ID NO 175
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 175
Thr Asn Tyr Tyr Leu Ser
1     5
<210> SEQ ID NO 176
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ: 176

Ile Ile Tyr Pro Ser Gly Asn Thr Tyr Cys Ala Lys Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 177
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ: 177

Asn Tyr Gly Gly Asp Glu Ser Leu
1  5

<210> SEQ ID NO 178
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ: 178

atgacacaga ggacacctca tcatcgtcgt ggcctcctgc tctcctgcct ccacggtccc  60
acatggcgc gctgctgac ccagacacca tctcctgcgt ctgcagctgt gggagacaca 120
gtcacacata attgccagcag cagtcagcgt gttataata accgctactt attcgtgat 180
cacaagagcc caagacacag tctcactactg gttcttccaa aatggcactct 240
ggcctgcct ggagcctcaca ggggagggga ttgagaacct ccacgtaaaag 300
ggcctgcct gtgcacctctg tcacactctg gcagcagctg ttacctcagct 360
gttactact 369

<210> SEQ ID NO 179
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ: 179

atgacacagt ggctgcgcgt gcttcctcctt gtgcgtgctgt ctaaaggtgt ccagtgctcg  60
tgtcctagagg agtcccgggg tgccttggttc acgcctggga cacccttgac aatcaacctg 120
acatgcctct gttcactactg cagtcacacac tcaactctgga gtcggtcagc ccaggtcctaa 180
gggagagggg tagatagatg cgaatcacttt tattctcgtg ttgatcataa ttggcgcaag 240
tgcgaggg cgcgattcag cattctccaa actcctgct gcacggtggg ttctgaaatg 300
accgctcaga cagccagaga cacagcaggc tacctcctgt ccagaaaaa ttgctcagtg 360
gaaagtttg 369

<210> SEQ ID NO 180
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ: 180

cagtcagctc agagtgccata taataacgac taatttccc 39
<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 181

gggtgttcac aacctgccatct 21

<210> SEQ ID NO 182
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 182
cctggtgtgatt atgatgatgc tcgtgataac 33

<210> SEQ ID NO 183
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 183
accacacact acctgagc 18

<210> SEQ ID NO 184
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 184
atcatctc tctagtgtaa cacatattgct gogaagctgg cgaagagc 48

<210> SEQ ID NO 185
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 185
aattattggt gtagtgaagacttg 24

<210> SEQ ID NO 186
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 186
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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

116
<210> SEQ ID NO 187
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 187
Met Glu Thr Gly Leu Arg Trp Leu Leu Val Val Leu Lys Gly
1    5    10   15
Val Glu Cys Gln Glu Glu Leu Val Glu Ser 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 Glu Ala Pro Gly Gly Gly
50   55   60
Leu Glu Trp Ile Ala Cys Ile Phe Thr Ile 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 Glu 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

126
<210> SEQ ID NO 188
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 188
Gln Ala Ser Glu Thr Ile Gly Asn Ala Leu Ala
1    5    10

127
<210> SEQ ID NO 189
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 189
Lys Ala Ser Lys Leu Ala Ser
1    5

128
<210> SEQ ID NO 190
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 190
Gln Trp Cys Tyr Phe Gly Asp Ser Val
1    5

129
<210> SEQ ID NO 191
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 191
Ser Gly Tyr Tyr Met Cys
1     5

<210> SEQ ID NO 192
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 192
Cys Ile Phe Thr Ile Thr Thr Asn Thr Tyr Ala Ser Trp Ala Lys Gly
1     5     10    15

<210> SEQ ID NO 193
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 193
Gly Ile Tyr Ser Asp Asn Asn Tyr Ty r Ala Lys
1     5     10

<210> SEQ ID NO 194
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 194
atgggacagc gggccccca ctcagctgtc gggtctctgc tgtctctgct cccagtggcc  60
agatgtcatg ttgtagctac ccaagactca gctctcgttg aggcagcttg gggaggacca 120
gtcaccatca agtgcacaggc cactgacacc atggcaatg cattgcctgy gatccagcag 180
aatccagggc agctccccct cgcctctgac tacaagctg ccaacagctgc atctgggggtc 240
cctgcgcttg tcaagccagc tggatctggg acagactgac ctctcaccat cagcgaacctg 300
gatgtgcctg atgtggccac ttaactctgt caagttggtt atttggggtg tagtgg 367

<210> SEQ ID NO 195
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 195
atgggactgt ggctgctctg ctcctccctg tggactgtgc tccaaggtgt ccagtgctag  60
gagcagccttg tggatcctgc gggaggctctg gttccagcttg ggctctgccg gacagcactcc 120
tgcaagccttg catctgctca cttcatgca gttctactc gttgctctgt ccgcccaggt 180
cggagggaggg gctctgtcgcat cttccagcttctacctactacte ccacacatctttg 240
ggagctggcg cgaagctctg atcactac tccaagacct cgcggacacc ggtgaccttg 300
cataagcaca gtcgtcagagc cggccagcag gcccctactc tctgtgagcg agggatttat 360
tctgatact attattattg ccgg 384

<210> SEQ ID NO 196
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 196
caggccagtg aggccacctgg caactgcatta gcc

<210> SEQ ID NO 197
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 197
aagggacacca aactggcactc t

<210> SEQ ID NO 198
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 198
caatgtgtg attttggtga tagttg

<210> SEQ ID NO 199
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 199
agcggactac acatgtgc

<210> SEQ ID NO 200
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 200
tgatatctca ctattactac taacacttcac tagcgagct ggggcagagc c

<210> SEQ ID NO 201
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 201
gggattatatt ctgataatc tcattatgcc ttg

<210> SEQ ID NO 202
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Thr Val Thr Ile Lys Cys Gln Ala Ser
35      40   45
Glu Ser Ile Gly Asn Ala Leu Ala Trp Tyr Gln Glu 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
Cys Tyr Phe Gly Asp Ser Val
  115

<210> SEQ ID NO 203
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 203

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

<210> SEQ ID NO 204
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 204

Gln Ala Ser Glu Ser Ile Gly Asn Ala Leu Ala
  1  5 10

<210> SEQ ID NO 205
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 205

Lys Ala Ser Thr Leu Ala Ser
  1  5

<210> SEQ ID NO 206
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 206

Gln Trp Cys Tyr Phe Gly Asp Ser Val
  1  5

<210> SEQ ID NO 207
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
-continued-

<400> SEQUENCE: 207

Ser Gly Tyr Tyr Met Cys
1 5

<210> SEQ ID NO: 208
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 208

Cys Ile Phe Thr Ile Thr Asp Aen Thr Tyr Ala Aen Trp Ala Lys
1 5 10 15

Gly

<210> SEQ ID NO: 209
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 209

Gly Ile Tyr Ser Thr Asp Aen Tyr Ala Leu
1 5 10

<210> SEQ ID NO: 210
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 210

atggacaaca gggccccaca tcagcgtctg gggtcctctgc tggctctcctt cccag ggcttgc
60
agatgtgatg ttggtgagct ccaagcttcc caaagcgtt gaagcagcag tggagcagc aacaaggaca
120
gtccatcata ggtgcagctg ccagagcact gatgtgctgt tattgctgt gatgtgctgt gatgtgctgt
180
aaccaggg ccagcctccaa ggtttcctcgt tccacgtcgt cttaaagcgt caacagtctt atctgggggtc
240
caggtgctg tggagcagctg ccagagcact gatgtgctgt tattgctgt gatgtgctgt gatgtgctgt
300
catgtgctgt atgtgtctgtg ctatacgtgt caaatgtgctg attttggtgta tagctgt
357

<210> SEQ ID NO: 211
<211> LENGTH: 364
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 211

atggagactg ggtgctctcgct gcttccccgt tgcgtgtgc tccagcgtgt cccgtgtcag
60
cagcagctgg tggagcagctg ggaggtcaggt gcttaagccc gggtcactgc gacactaagcc
120
tgcaagactg cttgtccacgc tctcagcttc cgtttagcag gcgtcgctgt cggcaggtct
180
cagggagag gcgtgagctg gtcacgtcgt atttttcct cttaagagag gcacgttacat
240
ggcaagaggg cccagagagct gcaccctaca tgcctgcctgc gcgtggtctgc gcgtggtctgc
300
caatgcaca gtcgtacagc gcgcagacgg gcaccctatt tgcgtgcatg ggggatctct
360
tcatctgtt atattatatgt cttg
384

<210> SEQ ID NO: 212
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 212

```
caggccagtgc agagcattgg caatgcatta gcc
```

33

<210> SEQ ID NO 213
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 213

```
aaggcatcaca cctggcatc t
```

21

<210> SEQ ID NO 214
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 214

```
caatgtgtt attttgtgta tga tgggt
```

27

<210> SEQ ID NO 215
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 215

```
agcgctacct acatgtgc
```

18

<210> SEQ ID NO 216
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 216

```
tgcatatcata ctaacagcac tgcagacatgg caccagggc c
```

51

<210> SEQ ID NO 217
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 217

```
gggttatatt taactgtgat gttattagcc ttg
```

33

<210> SEQ ID NO 218
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Gln Ala Ala Val Gly Thr Val Thr Ile Lys Cys Gln Ala Ser 35 40 46
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 Ser Gly Thr Glu Phe Thr Leu Thr
95 96 97 98 99 100
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Cys Gln Cys
100 101 102 103 104 105
Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala
115 116 117

<210> SEQ ID NO 219
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 219

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Glu Ser Val 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 Glu 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
95 96 97 98 99 100
Leu Lys Ile Tyr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
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

<210> SEQ ID NO 220
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 220

Gln Ala Ser Gln Ser Val Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 221

Arg Ala Ser Thr Leu Glu Ser
1 5

<210> SEQ ID NO 222
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 222

Gln Cys Thr Tyr Gly Thr Ser Ser Ser Tyr Gly Ala Ala
1 5 10
<210> SEQ ID NO 223
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 223
Ser Asn Ala Ile Ser
1  5

<210> SEQ ID NO 224
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 224
Ile Ile Ser Tyr Ser Gly Thr Thr Tyr Ala Ser Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 225
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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> SEQ ID NO 226
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 226
atgsgaagca gggcccccaac tcagctgtcg ggtctctgcg tgcctctgct cccaggtgcc
60
agatgtggag tttgtgatcg cccagctgac gcctctgctt gggagcgtcg gggagcaca
120
gtacaccatca agtgcggagcc cagctgagcg tctagagctgt acttactcgt gttctgagcag
180
aacaacgggc agctctcaaca gctcttggtc tacagccgct ccactcctgag atctgagggctc
240
ccacgcggt tcaccagcag tggatctgca accacgttca ctctcaccct cagcaggttg
300
gggtgtgctg atgtctgccg ttcactgtct ccctgactctg ttaggtactgattgtagttat
360
ggtgtgctg
369

<210> SEQ ID NO 227
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 227
atgsgaagagt ggtctctgctg tctgctcttg tctgttggtc agtgcggag ccgcccctgac aaccagcagt
60
tggatctgag tttgtgatcg cccagctgac gcctctgctt gggagcgtcg gggagcaca
120
gtacaccatca agtgcggagcc cagctgagcg tctagagctgt acttactcgt gttctgagcag
180
aacaacgggc agctctcaaca gctcttggtc tacagccgct ccactcctgag atctgagggctc
240
ccacgcggt tcaccagcag tggatctgca accacgttca ctctcaccct cagcaggttg
300
gggtgtgctg atgtctgccg ttcactgtct ccctgactctg ttaggtactgattgtagttat
360
ggtgtgctg
369
atgctatgt tgaatacttt tggagccgag atggacttc

<210> SEQ ID NO 228
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 228

cagggcagtc agagcgttag tagctactta aac 33

<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 229

agggcatcca cttcggatct t 21

<210> SEQ ID NO 230
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 230

caatgtactt atggtactag tagtagttat ggtgtgct 39

<210> SEQ ID NO 231
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 231

agcagtgcac taagc 15

<210> SEQ ID NO 232
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 232

atcattagtt atagtggtac cacatactac gcgagctggg cgsaagggc 48

<210> SEQ ID NO 233
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 233

gatgactctc cggacatgttag atacctttgt gggagcgctg cat ggacttc 57

<210> SEQ ID NO 234
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Tyr Ser Trp Tyr Gln Gly Gly 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> SEQ ID NO 235
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 235
Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15
Val Gln Cys Gln Ser Leu 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 Glu Ala Pro Gly Lys Gly Leu Glu
50  55  60
Trp Ile Ala Cys Ile Val Thr Gly Asn Gly Asn Thr Tyr Ala Asn
65  70  75  80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr 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> SEQ ID NO 236
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 236
Gln Ala Ser Gln Ser Val Tyr Lys Asn Asn Tyr Leu Ser
1  5  10

<210> SEQ ID NO 237
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 237
Ser Ala Ser Thr Leu Asp Ser
1  5

<210> SEQ ID NO 238
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Tyr Ala
1    5    10

Ser Tyr Trp Met Cys
1    5

Cys Ile Val Thr Gly Asn Gly Thr Tyr Tyr Ala Asn Trp Ala Lye
1    5    10    15

Gly

Ala Tyr Asp Leu
1

atggacacga gggcccccag ccagccatg gggcctgcag tgggtcagct gggggtgcac 60
acattgccg ccagccggtg cccgcttggc ctggtcgcag gggcgcacccc 120
gtcacagaat gtcgacccag gggggtgctg ggcctgcttg ggcctgcttg 180
cagccagctg cctgccgctg cttggctgcc ggcctgcttg ggcctgcttg 240
ggggtgctac tggccgggag cacccctgctg cccgggctgc 300
gagctgcagc aagccgggag cacccctgctg cccgggctgc 360
ggatgtgtgt tgtgcttgctg ccctgctgctg cccgggctgc 375

atggacaagc gggcctgctg gggcctgctg gggcctgctg gggcctgctg 60
tcctgtgagc cctgctgctg gggcctgctg gggcctgctg gggcctgctg 120
aaggggcttg agtgcctcgc atgcattggt actgctaagt ctacactta ctacgcgaac 240
tggggaagaag ggcctacac catctctcaaa acctctgctga ccacctgtac tctgcaatgt 300
aaccagttga cagcagctga caggcacaac tatttttttg tggagaagct taaccttg 357

<210> SEQ ID NO 244
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 244
cagggcccagc agagtgtgta taagacacaac tctatatcc 39

<210> SEQ ID NO 245
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 245
tctgcatcga cttcgatctc t 21

<210> SEQ ID NO 246
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 246
catggragt atgattgtag taagctgat tagttatatct 39

<210> SEQ ID NO 247
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 247
agctactgga tgtgc 15

<210> SEQ ID NO 248
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 248
tgcatgtaa cttgaattgg taacacttac tagcgaacact ggaggagaag c 51

<210> SEQ ID NO 249
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 249
gcctgtgact tg 12

<210> SEQ ID NO 250
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 250
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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
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 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 Gln Thr Gln Phe Thr
85 90 95
Leu Thr Ile Thr Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Cys
100 105 110
Ala Gly Val Phe Asn Asp Ser Asp Asp Ala
115 120

<210> SEQ ID NO 251
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 251
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Pro 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 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 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

<210> SEQ ID NO 252
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 252
Gln Ala Ser Gln Ser Val Tyr Asp Asn Tyr Leu Ser
1 5 10

<210> SEQ ID NO 253
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 253
Gly Ala Ser Thr Leu Ala Ser
1 5

<210> SEQ ID NO 254
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 254

Ala Gly Val Phe Asn Asp Ser Asp Asp Ala
1   5   10

<210> SEQ ID NO 255
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 255

Ala Tyr Tyr Met Ser
1   5

<210> SEQ ID NO 256
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 256

Phe Ile Thr Leu Asp His Ile Ser Tyr Ala Arg Trp Ala Lys Gly
1   5   10   15

<210> SEQ ID NO 257
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 257

Ser Arg Gly Trp Gly Ala Met Gly Arg Leu Asp Leu
1   5   10

<210> SEQ ID NO 258
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 258

atgagacacg gggccccac tcgtcgtcg ggtgtctgct tctgtctgct cccaggtccc 60
acatttgcgc ccacatgcc ccagatccac tcgctgctg aagagagaca 120
gtcagcataa ggtgcacagc cagcagatgc gtttgacga acaactatttt accttggtat 180
cagcagacac cagagcagct ccacagctc ccatactcag gtcagctcag cctggaaac ggtctactct cccatcaca 240
gggttcccat cgccgagca cggcagggga tctggagac aagtgccatc 300
gacgtcagct gtagagcagc ccacaccttc tatggcagcg ggttttttaa ttaggtgtct 360
gatgatgcc 369

<210> SEQ ID NO 259
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 259

atgagacagct ggtgcgtgctg gccgtcctgtg cccagaggtgt ccagtgctcag 60
tctgtgaggg aagtcggaggt ctcgtggtgc acggtgagga ccacgctcag ccttttcgtg 120
acaactctcg gattcctctc cgcagcatac tatagtgagct ggtgcgtgca ggtgtcagg 180
aaggggctgg aatggtcagg attctattact ctagtggtac atatatcta cgcgaggtggg 240
gcgaagaagcc gatcatcact tcccaaaaaacc tgcacacgaggtgacatgaa aattgacaccag 300
cgacacccg agggacagcgg cactctatggc tgtgcttgagggatggtgtggg tgggtggaatg 360
ggctggttgg atctc 375

<210> SEQ ID NO 260
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 260

cagggccagtc agagttggta tgcacaagac tatatatcc 39

<210> SEQ ID NO 261
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 261
ggtgcatacct ctccttgccate t 21

<210> SEQ ID NO 262
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 262
gcaggggttt ttaatgtgaga taaggtgatcc gc 33

<210> SEQ ID NO 263
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 263
gcatactata tgcag 15

<210> SEQ ID NO 264
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 264
ttcattactc tgaagtgatca tatatatctac gcaggggtggc gcggacgggc 48

<210> SEQ ID NO 265
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 265
agtcgtggtct ggggtgaatt ggtcgttggtg atctc 36

<210> SEQ ID NO 266
<211> LENGTH: 123
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 266
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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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 Thr Tyr Tyr Cys
100   105   110
Leu Gly Val Phe Asp Asp Ala Thr Asp Ala Val Ala
115   120

<210> SEQ ID NO 267
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 267

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

<210> SEQ ID NO 268
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 268

Gln Ala Ser Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala
 1     5     10

<210> SEQ ID NO 269
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 269

Trp Ala Ser Thr Leu Ala Ser
 1     5
<210> SEQ ID NO 270
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 270
Leu Gly Val Phe Asp Asp Ala Asp Ala Ala
1 5 10

<210> SEQ ID NO 271
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 271
Ser Tyr Ser Met Thr
1 5

<210> SEQ ID NO 272
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 272
Val Ile Gly Thr Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 273
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 273
Ser Leu Ser Ser Ile Thr Phe Leu
1 5

<210> SEQ ID NO 274
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 274
atggacacga gggccccca tcagctgtcg ggctctctgc ttgcttctgt cccaggtgcc 60
acacctgca cgcgtgcgtc ccagcacca tcggccgtgt ctgggtctgt gggaggcaca 120
gtccatctca ggctggcgcg cagtcagtttt gtttataaca acaaaaaat ggctggcata 180
cagcagaaat cagccgagc tcccaagctc ctgatctact gggcattccac ttgggtctct 240
gggtgtctct cgcggttcag gcggcaggca attcactctt caccgtcacc 300
gggcgtcagt tgaaggtgcg tcggctttrac tacgtgtcag gcgttttttga tgtgtgtcgt 360
gataagct 369

<210> SEQ ID NO 275
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 275
atggagacct ggcgtgcgtgc gctctctctt gtcgggttgc gccaggtgtc ccagagtcag 60
-continued-

tcggtggagg agtcggggg aggctgtgac acgcctgaa ccacccctgac actaacttcg 120
cagcggctg gatctcctc cgatagtcct ttcagagcct tcggcagccc ggtgctccagg 180
aagggctgg aataatatgg agtcattgg gtactagtgta gcacatactac ggcacacttg 240
gcgaagggcc gattcaccatt cccgagacct tgcacacagg tgtgctcgaa aatcaccagt 300
cgcacaggg aggacaggg cacatatttc tgcgtcagga gtctttcttc tattacttc 360
ttg 363

<210> SEQ ID NO 276
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 276

caggcctgct agagtttta taacaacaa aaatttagcc 39

<210> SEQ ID NO 277
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 277

tgggcatcaa ctctgggcac t 21

<210> SEQ ID NO 278
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 278

cagggcttt ttgatgatga tgctgataat gct 33

<210> SEQ ID NO 279
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 279

agtcacctca tgacc 15

<210> SEQ ID NO 280
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 280

gttcatggga ctagtgtgtag cacatactac gcgaacctggg cgaaagggc 48

<210> SEQ ID NO 281
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 281

agcttttttt ctattacttt cttg 24

<210> SEQ ID NO 282
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 282

Gln Ala Ser Gln Asn Ile Tyr Arg Tyr Leu Ala 1 15

<210> SEQ ID NO 284
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Ornithologus cuniculus

<400> SEQUENCE: 284

Gln Ala Ser Gln Asn Ile Tyr Arg Tyr Leu Ala 1 15

<210> SEQ ID NO 285
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Ornithologus cuniculus

<400> SEQUENCE: 285
Leu Ala Ser Thr Leu Ala Ser
1     5

Gln Ser Tyr Tyr Ser Ser Asn Ser Val Ala
1     5     10

Ser Gly Tyr Trp Ile Cys
1     5

Cys Ile Tyr Thr Gly Ser Ser Gly Ser Thr Phe Tyr Ala Ser Trp Ala
1     5     10     15

Lys Gly

Gly Tyr Ser Gly Phe Gly Tyr Phe Lys Leu
1     5     10

atggaacag gccggcccac tcagctgtgc gggtctcttg tgcctctgtgc ccacaggtgcc 60
agaggtgcat tgaatcag cccgactcga gctcgttcgg aagcagctgt ggaggccaca 120
gtccacacat atgtccaggg cacagcagac atatagat acctaggcctg gtacctcagac 180
aaacaggcc agctctcaca gtctcgacg tatactgtgc atcagtgggg gcc 240
ccatcgcgt ttasaggccag tcgatcctgg aagcagtcac ctcctcact ccgcagcctg 300
gagtgctgccc atgtgccac ttacctctgt ccaagtttact agatgtaa tagtgctgct 360
...continued...

gacgactg ggtggtcgtc gttccttcg tgcgtctgc tcaaggtgtc ccaatgtcag 60
gacgactg tggagctcgg gggagacagt gtcacagctg agggacctc gacactcacc 120
tgcacagtt ctgtaatca cttcagtagc ggtaactgga tatactttgg tgcgcaatttt 180
caggggaaag ggtggagagt gatggtattc atttatattg ttagataaggt tagcactttt 240
tacgagatt gggcgaaggg cgtattcacc atctccaaaa ctctgctgac cacggtgact 300
cgtcaatgta caagttgtgac agcggcggac agcgccacct attcttgctgc gagggtttat 360
agtgggtttg gttaactttaa gttg 384

<210> SEQ ID NO 292
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 292
cagggcaga tgaacattta tagatactta goc 33

<210> SEQ ID NO 293
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 293
cagggcacta cttcgacact t 21

<210> SEQ ID NO 294
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 294
caaagttatt atagtagtaa tagtgctgct 30

<210> SEQ ID NO 295
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 295
agcggctact ggtatagc 10

<210> SEQ ID NO 296
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 296
tgcattttata ctggtagtga tgtatgact ttttaacgga gtggggcagaa aggc 54

<210> SEQ ID NO 297
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 297
gttatatagt gcttttgtta cttaaagttg 30

<210> SEQ ID NO 298
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 298

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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> SEQ ID NO 299
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Tyr 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

<210> SEQ ID NO 300
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 300

Gln Ala Ser Glu Asp Ile Tyr Arg Leu Leu Ala
1  5  10

<210> SEQ ID NO 301
<211> LENGTH: 7
<212> TYPE: PRT
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 301

Asp Ser Ser Asp Leu Ala Ser
1  5

<210> SEQ ID NO 302
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 302

Gln Gln Ala Trp Ser Tyr Ser Asp Ile Asp Asn Ala
1  5  10

<210> SEQ ID NO 303
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 303

Ser Tyr Tyr Met Ser
1  5

<210> SEQ ID NO 304
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 304

Ile Ile Thr Thr Ser Gly Asn Thr Phe Tyr Ala Ser Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 305
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 305

Thr Ser Asp Ile Phe Tyr Tyr Arg Asn Leu
1  5  10

<210> SEQ ID NO 306
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 306

atggaacacag gggccccaca tcagctgctg gggtcctgcg tgcctctgct cccaggtgcc 60
agatgtgacct atgataagct ccagactccta gctctctgctg aggtcctgctt gggagggcaca 120
gtcaacatca agctccaggg gagtgaggag attattaggt tatttgccctg gtatcaaacag 180
aaccacgggg agcgctcccaac gctctctgatc ttagattct catcgacctgg gcctctgggtc 240
cagctgccat tcaaaagcgag tggatctggg acagagttca cttcgctcag cagcgctgtg 300
cagctgccgt atgctgccac ttaagcttcat ccagagctct gcagatttag ttagattgat 360
aatgctt 366

<210> SEQ ID NO 307
<211> LENGTH: 369
<212> TYPE: DNA
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<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 307

atggaactg ggtgctgctg gttctctctg gtcgctgtgc tcgaaggtgt ccagagtcag 60
tcgctgagc agtcgggag ctcgctggtc acggcggtga cacccttgac actcaactgc 120
acagtctctg gattctcctt cagtagctac tacagtgcgt ggtgctgcaca ggtctcaggg 180
aaggggtctg aatgcatcgag aacatgctgtg ataactatttta cgcgagcttg 240
gcgaagggc ggtcaccat ctcgagacc tgcaccacgg tgggatctgaa aatcaccagt 300
cgcacaaccg aggacacggc cacctattcg tgtgccagaa cttctgtatat tttttatatt 360
cgtaacctg 369

<210> SEQ ID NO 308
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 308
cagggacagt agggcactta taggttatag gcct 33

<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 309
gatccatcctg atctgaccct t 21

<210> SEQ ID NO 310
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 310
cacaggtctt ggaagttacag tgcattgatg aatgct 36

<210> SEQ ID NO 311
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 311
agctactacag tggacg 15

<210> SEQ ID NO 312
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 312
atcattcactactgtgtaa tacattttac gcggagctggg gcgsagggc 48

<210> SEQ ID NO 313
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 313
actctgtata tttttatta tcgtaacctg 30
<210> SEQ ID NO 314
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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<212> TYPE: PRT
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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 317

Ser Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 318
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 318

Leu Gly Ala Phe Asp Asp Ala Asp Asp Ala Thr
1  5  10

<210> SEQ ID NO 319
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 319

Arg His Ala Ile Thr
1  5

<210> SEQ ID NO 320
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 320

Cys Ile Trp Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 321
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 321

Val Ile Gly Asp Thr Ala Gly Tyr Ala Tyr Phe Thr Gly Leu Asp Leu
1  5  10  15

<210> SEQ ID NO 322
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 322

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aagttgcag cgggtcgtgc ccagactgca tcacccggtc tgccgcctgc gggagccaca 120
gtcaatact actcgcaagt cagtcgggtg gtcttatacg acaagggactt agctgtgttt 180
cagcagacaac cagggcaggt tcccaagttc ctagtcattt cttgcactccac tctggtcatt 240
ggggtccag cggcagttcg aagtcagcag tgggagccag agtttcactt cagcactgac 300
ggggtcagc gtgacagagc tgcacaactc tachtctag ggcgttttta tgatcgagct 360
gataatct 369
<210> SEQ ID NO 323
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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aacgctctcg gactctccct cactagcat gcataacact ggctccgocac ggctccagg 180
aaggggtcctt atcgatgctg atgacattttg agtgggttga gcacataact cgcagacactg 240
ggacaaagcc gattcaccct ctcacaacc tgcacccagg tggatcttccg aactaccagt 300
cogacaacgg aggacaaggg ccactacctt ctctgcaagag tcaatgggga taatgctgt 360
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<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 324
cagtcaccgc agaagtctttta taatgacagt gacctagcc 39

<210> SEQ ID NO 325
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 325
tctgcaatca ctgggcact t 21

<210> SEQ ID NO 326
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 326
cagaaggcttt ttgatgtga tgcctataat act 33

<210> SEQ ID NO 327
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 327
agccatgcaaa taacc 15

<210> SEQ ID NO 328
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 328
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<210> SEQ ID NO 329
<211> LENGTH: 46
<212> TYPE: DNA

<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 329

gcattggcg atactgotgg ttatgottat tttaggggc ttgacctg 48

<210> SEQ ID NO: 330
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 330

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

<210> SEQ ID NO: 331
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 331

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 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 Gly Ser Thr Tyr Thr 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
130

<210> SEQ ID NO: 332
<211> LENGTH: 11
<212> TYPE: PRT
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<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 332

GLn Ala Ser Gin Ser Val Tyr Asn Trp Leu Ser
1  5  10

<210> SEQ ID NO 333
<211> LENGTH: 7
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 333

Thr Ala Ser Ser Leu Ala Ser
1  5

<210> SEQ ID NO 334
<211> LENGTH: 11
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 334

GLn Gin Gly Tyr Thr Ser Asp Val Asp Asn Val
1  5  10

<210> SEQ ID NO 335
<211> LENGTH: 5
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 335

Ser Tyr Ala Met Gly
1  5

<210> SEQ ID NO 336
<211> LENGTH: 16
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 336

Ile Ile Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 337
<211> LENGTH: 16
<212> TYPE: PPT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 337

Gly Gly Ala Gly Ser Gly Gly Val Trp Leu Leu Asp Gly Phe Asp Pro
1  5  10  15

<210> SEQ ID NO 338
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 338

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agatgtgct atgatagac cccacactca gctctcttgg aggtacttgct gggaggcaca 120
gtcacacata aacgccgagg cagtcagagt gttttaaa ggtattctgg gttacagcag 180
aaaccaggcg aagctccccc gctctctggt tatactgcat cccagctggc acctgggggc 240
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catcgccgt tcagtgccag tggtatcggg acagagttca ctctcaccat cagcggcgtg 300
ggttgctcg agtggtcacc taactactgt caacaggttt atactagtga tgggtataat
360
gtt
363

<210> SEQ ID NO 339
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 339
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tcgctggag aggccggggt tcggcgtggtc aagccctggga caccctgac actcaacctgc 120
acaggtctgg gaatcgacct cagtagttat gcatttgccgt ggtccggcga ggcccgaggg 180
aagggggtcg aatacattcg aatcattagt agtatgtgta gcacactcta cctcagctgg 240
gcggaaagcc gtacctcagc atctcagccc tctgcagcag ccgtggatct gaaattacc 300
agtctgcacaa cggaggactc gcgcacatat tcctgtgcga caggggtgtgc tgggtagtt 360
gtggtggtgc tgtctgtgatg tgtgtctcc 390

<210> SEQ ID NO 340
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 340
cagcccagtc agatgttta taattgtta tcc 33

<210> SEQ ID NO 341
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 341
actgcattca gctggtggatc t 21

<210> SEQ ID NO 342
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 342
cacagggttt atactagtga tgggtataat gtt 33

<210> SEQ ID NO 343
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 343
agctatgcac tgggcc 15

<210> SEQ ID NO 344
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 344
<210> SEQ ID NO 345
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 345

atcattgta gtagtggtg cacatacag gcgacotggc cgaasggc
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<210> SEQ ID NO 346
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 346

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu 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
Ser Val Ser Ala Ala Val Gly Thr Val Thr Ile Asn Cys Gln Ala
30  35  40  45
Ser Glu Asn Ile Tyr Asn Trp Leu Ala 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 Phe Thr Leu
90  95
Thr Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Cys Gln
105 110
Gln Gly Tyr Ser Ser Ser Tyr Val Asp Asn Val
115  120

<210> SEQ ID NO 347
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 347

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Leu Gly
1  5  10  15
Val Gln Cys Gin Glu Gln Leu Gln Ser Gly Gln Gly Arg Leu Val Thr
20  25
Pro Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu
30  35  40  45
Asn Asp Tyr Ala Val Gly Trp Phe Arg Gin Ala Pro Gly Lys Gly Leu
50  55  60
Glu Trp Ile Gly Tyr Ile Arg Ser Ser Gly Thr Thr Ala Tyr Ala
65  70  75  80
Trp Ala Lys Gly Arg Phe Thr Ile Ser Ala Thr Ser Thr Thr Val Asp
90  95
Leu Lys Ile Thr Ser Pro Thr Glu Asp Thr Ala Thr Tyr Phe Cys
105 110
Ala Arg Gly Gly Ala Gly Ser Val Trp 1le Leu Asp Gly Phe
115  120  125
Ala Pro
<210> SEQ ID NO 348
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 348

Gln Ala Ser Glu Asn Ile Tyr Asn Trp Leu Ala
  1   5   10

<210> SEQ ID NO 349
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 349

Thr Val Gly Asp Leu Ala Ser
  1   5

<210> SEQ ID NO 350
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 350

Gln Glu Gly Tyr Ser Ser Ser Tyr Val Asp Asn Val
  1   5   10

<210> SEQ ID NO 351
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 351

Asp Tyr Ala Val Gly
  1   5

<210> SEQ ID NO 352
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 352

Tyr Ile Arg Ser Ser Gly Thr Thr Ala Tyr Ala Thr Trp Ala Lys Gly
  1   5   10   15

<210> SEQ ID NO 353
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 353

Gly Gly Ala Gly Ser Ser Gly Val Ile Leu Asp Gly Phe Ala Pro
  1   5   10   15

<210> SEQ ID NO 354
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 354

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aaggagactg ggtgcggctg gcttcctcctg gtcgcttgctg tcgaaggtgt ccagtgctcag 60
ggcagctga aggsctcgog gggtcgctctg gtcaagcctctg ggacacctct gccagctcacc 120
tgcacagtct cttgattcct ccctaatgcct ctagcgctgg gtctgctcct gcaggctcaca 180
gggagggggt cgggatggt gctgaattct gatgattgtct gttgggacag ctacgacacc 240
tggcagaag gcccagcgtt ccattgctct cgtgagcttc cctcagcacc acgccagggct 300
agctgcgaca cccggagcac gcgcacatct ttcggtgcct gaggaggctgc tggtagattg 360
gggatgtgga tcccttctag ctttgctccc 390

<210> SEQ ID NO 356
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 356
caggccaggtg agaacattta taatgtgtta gcc 33

<210> SEQ ID NO 357
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 357
actgtgaggc atcgccactc t 21

<210> SEQ ID NO 358
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 358
cacagggttt atatgtagat ttaggtgact aatgttt 36

<210> SEQ ID NO 359
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 359
gactagcag tgggc 15

<210> SEQ ID NO 360
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<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 360

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<210> SEQ ID NO 361
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 361

gggggtcgtg gtagtggtg tgggtggatt cttgatggtt ttgctccc 48

<210> SEQ ID NO 362
<211> LENGTH: 121
<212> TYPE: PRO
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 362

Met Asp Thr Arg Ala Pro Thr Glu Leu Leu Leu Gly Leu Leu Leu Leu Thr
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 Thr Val Thr Ile Asn Cys Gln Ala Ser
35  40  45
Gln Ser Val Tyr Gln Asn Asn Tyr Leu Ser Thr 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 Thr Gly Thr 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> SEQ ID NO 363
<211> LENGTH: 130
<212> TYPE: PRO
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 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
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
Tyr Phe Cys Ala Lyn Trp Asp Tyr Gly Gly Asn Val Gly Trp Gly Tyr
115

Asp Leu
130

<210> SEQ ID NO 364
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 364

Gln Ala Ser Gln Ser Val Tyr Gln Asn Asn Tyr Leu Ser
1    5

<210> SEQ ID NO 365
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 365

Gly Ala Ala Thr Leu Ala Ser
1    5

<210> SEQ ID NO 366
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 366

Ala Gly Ala Tyr Arg Asp Val Asp Ser
1    5

<210> SEQ ID NO 367
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 367

Ser Thr Tyr Tyr Ile Tyr
1    5

<210> SEQ ID NO 368
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 368

Cys Ile Asp Ala Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Thr Trp Val
1    5    10    15

Asn Gly

<210> SEQ ID NO 369
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 369

Trp Asp Tyr Gly Gly Asn Val Gly Trp Gly Tyr Asp Leu
1    5
<210> SEQ ID NO 370
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 370
atggaacgca ggcccocca tcagctgctg ggtctctgtc tgcctctgct cccaggtgcc  60
aacatactgc aagtctgac ccacactccca tcctcctgtg ctgctagctg gggagggcaca 120
gtcaccata attgccaggg cagtcagagt gtttatcaga acaactaatt atctggtttt 180
cagcagaaac cagggcagcc tccaaagctc ctgatctatg gtggcggccac tcttgacatct 240
ggggtcccat cgccgctcaca aggcagttga tctgggacac agttcactct cacaattaga 300
gacttgagct gtgaagtgcg tcgcacttacc tcctgtcag ggccttatag ggatgtggat 360
tot
363

<210> SEQ ID NO 371
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 371
atggagactg ggtgctgctg gctttctctg gtcttgctgac tccaaaggtg tccaagtgtcg  60
tgctctggag aagctgggag agaactgtggt gcttcctgcac actaactggtgc 120
acagcctctg gttctctctc tatagtacct tactacacct actgggctcgc ccagccgtaa 180
ggggaggggc tgagttggtat cgcagttagt gatgtggtgat gtgtggagtag gcaattatc 240
ggggctgctg tgaatggcag attoacattc tccaaaacct gttgcaacag ggtgactcgtg 300
casattgacc gcctgacagt cgcggcagcc gcacattttact tccttgccgac atggatttat 360
ggttgaatct tgggtcggggt ttgctactg 390

<210> SEQ ID NO 372
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 372
cagggcagtc aagtgtttaa tccagaacaat tacttatcc 39

<210> SEQ ID NO 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 373
ggtgctgggca ccctggcatact 21

<210> SEQ ID NO 374
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 374
gccggcctt agaggtatgt ggttct 27

<210> SEQ ID NO 375
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 375
agtaacct acatetac

<210> SEQ ID NO 376
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 376
tgtattgtg tgtatgtgt tgtatcgact tactacgca cctggtgatgag tggc

<210> SEQ ID NO 377
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 377
tggctattata tgtattgtgt tgtgtgttgt tgtgacttg

<210> SEQ ID NO 378
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 378
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly 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 Thr Val Thr Ile Lys Cys Gln Ala Ser
35  40  45
Gln Ser Ile Ser Ser Tyr Leu Ala 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 Cys Gln Ser
100 105 110
Tyr Tyr Asp Ser Val Ser Asn Pro
115 120

<210> SEQ ID NO 379
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 379
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 Ser Gly Gly Asp Leu Val Lys Pro
20  25  30
Glu Gly Ser Leu Thr Leu Thr Cys 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
<210> SEQ ID NO 386
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 386
atggacacga gggcggcggc tcagctgtgc ggtctagtgc tgcgcagcttc cgcaggtgcc 60
aggtggtcat ttggaattgg ccagacttcc tacccggtcg gggcaggttg gccaggtgcc 120
gtcaccatca aggtggtcagg cgattgctac aaccagagtc gatcaggtgc gatcagctag 180
ccgcaagggc aggccttccca atcgtctcttc ccagcgggtt gctcgtggttc 240
ccaagggc atcaggtgcc gacaggtgcc gttcggcttc gcctgaatcc gcctgctagc 300
gagttgcctcg atgtgctgct tacagcagct ccagctgtgc atgtgctgct ttcagagct 360

<210> SEQ ID NO 387
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 387
atggagactgc ggtctgctgtc gctctctcttg gtctgctgtg tcctaggtgt ccaggtctag 60
tcgtctcttg cggcagggc agacgtctct gcgtctctgt gcctgtgtgc cggcaggtgc 120
aaagcgcttg gcgtctgtgt ccagcggttc gctggtgtgc ggtctggtgt gcctgtgtgc 180
ggcaagcggc tggcgaggttt cggtctgtgc gcgtctgtgc gcgtctgtgc gcgtctgtgc 240
gccagcggc agctctgctgg atctcgtcag tccaaacacct ccagcggttc gcgtctgtgc 300
cagcagctgc cggcaggtgc gcggcggcgc gtctgtgtgc gcgtctgtgc gcgtctgtgc 360
gtttaagtt attttaagtt g 381

<210> SEQ ID NO 388
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 388
caggccagtc aggcatcattc tagttactta gcc 33

<210> SEQ ID NO 389
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 389
agggcgtcca ctctgggcatc t 21

<210> SEQ ID NO 390
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 390
cagagtctg atgtagtctg ttcagagct 30
<210> SEQ ID NO: 391
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 391

acctactgtgtcatgtgc

<210> SEQ ID NO: 392
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 392
tgtatattata ctgtgtagtag tggtttccact ttctacgca gctggttgas tggc

<210> SEQ ID NO: 393
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 393
ggatatagtg gttatgtta ttttaagtg

<210> SEQ ID NO: 394
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 394

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

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gln Gln Gly Thr Ser Phe Thr
95    90    95

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
100   105   110

Ala Gln Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
115   120

<210> SEQ ID NO: 395
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 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 Glu Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Ile Ala Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Thr Ala
65 70 75 80
Ser Trp Ala Lys Gly Arg Phe Thr Ser Lys Thr Ser Ser Thr Thr
85 90 95
Val Thr Leu Glu Met Thr Ser Leu Thr Ala Ala Asp Thr Ala Thr Tyr
100 105 110
Phe Cys Ala Arg Glu Trp Ala Tyr Ser Glu Gly Tyr Phe Gly Ala Phe
115 120 125
Asp Leu
130

<210> SEQ ID NO 396
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 396
Gln Ala Ser Glu Ser Val Tyr Lys Asn Asn Glu Leu Ser
1 5 10

<210> SEQ ID NO 397
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 397
Gly Ala Ser Ala Leu Ala Ser
1 5

<210> SEQ ID NO 398
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 398
Ala Gly Ala Ile Thr Gly Ser Ile Asp Thr Asp Gly
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 399
Ser Ser Tyr Phe Ile Cys
1 5

<210> SEQ ID NO 400
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 400
Cys Ile Tyr Gly Gly Asp Gly Ser Thr Tyr Thr Ala Ser Trp Ala Lys
1 5 10 15
Gly
-continued

<210> SEQ ID NO 401
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 401

Glu Trp Ala Tyr Ser Gln Gly Tyr Phe Gly Ala Phe Asp Leu
1 5 10

<210> SEQ ID NO 402
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 402

atgpcacagc ggccccccac tcagctgctg ggctctctgc tgctcttgct gcacaggtgc 60
acatttgca tcgaatgac ccagagtcca tttctctggt gtgcagctgt ggaggagcaca 120
gtctagatca gttgcacggc cagtcagagt gtttataaga acaaccaatt atcctggtat 180
cagcagaaat cagggcagcc tcccaagctc otgatctatg gtgcatcggc tctggtcatct 240
gggtgcccat ggccgttcac aagcagtgga tctgggcacg agttcaacct cacccctcgc 300
gacctgcagc tgtccagctc tgcacattac tactgtgcag ggcctattac tgtgcagatt 360
gtaoagggtg t
372

<210> SEQ ID NO 403
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 403

atgpcagactg ggctgcgctg gctctctctg gtgcagctgc tccaaaggtgc ccaggtcaag 60
tgatggagc gcctcggggg aagccggtgc aagccgtggg catcctcgac actcaactgc 120
acactctctg gattctctct cagtagcagc taactctatt gctgggtccg ccaggctccs 180
gggaagggc tggacgtggat cgcctcatct tggggtcttg atgccagacg acatacgcg 240
agctcgccga aagggcgcat cactatacct aaaaacctcg gacacaaagt gcgctggcaaa 300
atgacacgct cgacacgccc gcacacgggc acctatatt ctgtgcagaga atgggcatat 360
agncaaggtt attttgggtgc ttttgctctc 390

<210> SEQ ID NO 404
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 404

cagggcagtc agaatggtta taagaacac caattaycc 39

<210> SEQ ID NO 405
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 405

gtgtcatcgg ctctgggtatc t 21

<210> SEQ ID NO 406
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 406

gcagggctcta ttaactggtgtag tatgatacg gatggt 36

<210> SEQ ID NO 407
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 407

agcagctact tcaattgc 18

<210> SEQ ID NO 408
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 409
tgcatattag gtggtgatgg cagcacatac tacgcgagct ggccgaagg c 51

<210> SEQ ID NO 409
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 409
gaatgggcat atagtcaagg ttattttggt gcttttgatc tc 42

<210> SEQ ID NO 410
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 410

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

<210> SEQ ID NO 411
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 411
-continued

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 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 Thr Val Arg Glu Ala Pro Gly 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> SEQ ID NO 412
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 412

Gln Ala Ser Glu Asp Ile Ser Ser Tyr Leu Ala
 1 5 10

<210> SEQ ID NO 413
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 413

Ala Ala Ser Asn Leu Glu Ser
 1 5

<210> SEQ ID NO 414
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 414

Gln Cys Thr Tyr Gly Thr Ile Ser Ile Ser Asp Gly Asn Ala
 1 5 10

<210> SEQ ID NO 415
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 415

Ser Tyr Phe Met Thr
 1 5

<210> SEQ ID NO 416
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 416

Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Val Lys Gly
Val Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
1  5 10

<210> SEQ ID NO 418
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 418
atggacacga gggcccacc tcagctgctg gggctctgct tgccttgctg cccaggtgcc 60
agatgtgtag tttgatgagc cccagctcga ggcgctgctg aggccagctg gggaggcaca 120
gtcaccatca agttggccgg ccaggtggaat ctttctctta cactcagctg gttccagcg 180
aagttcgggc acgctccccga ggcgccctcct tggctgctct ccaacttggca atctgaggtgc 240
tcttctcag tcttctcag ttcgccctcct cccagctggct acagactcag cccagctcctg 300
gagttgctgctg atggccgctg cctattctctt caaatgtact atgctactat ttcatttgtg 360
gttgctgctg ct
372

<210> SEQ ID NO 419
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 419
atggacactg ggtctgctgct gctctctctct gcgtctccttg cctcagctgc ccaatgtcag 60
tcggtggagg agtcgggggg tgcgtctggtc aegctggggg aacccctgcac aacctctgct 120
acagctctctg gatccccctgt ccagctgtcct tgcgtctctg ggtcgcccaca ggtcgccagg 180
gaggggcctg aatatccattg attoattctt atcggttggta gogtcaacta ogcagacctg 240
gtggagggtc gatccccggct tatctcgtct cctcgagcct cggctttttc ctgctgctgt gccttctct 300
cgcagacattg gaggcagcagc aaccatatttc ttcgcgctgg ttcgtggtgc ttcttttgaa 360
gcctttacac tc
372

<210> SEQ ID NO 420
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 420
caggcagctg assatatagg tagcactta gccc
33

<210> SEQ ID NO 421
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 421
gctgcacca atctgsgaatc t
21
<210> SEQ ID NO 422
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 422
caatgtacct atggtacct ttctattagt gatgtaatg ct

<210> SEQ ID NO 423
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 423
agctactca tgcac

<210> SEQ ID NO 424
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 424
tttctaatgt ctggtgtcag cgttacct cggagctggg tgaagggc

<210> SEQ ID NO 425
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 425
gttctgattg ttctttatgg agcttttac atc

<210> SEQ ID NO 426
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

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

<210> SEQ ID NO 427
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 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 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
  95  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 Tyr Gly Ala Phe Asn Ile
 115 120

<210> SEQ ID NO: 428
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 428
Gln Ala Ser Glu Asp Ile Glu Ser Tyr Leu Ala
  1  5  10

<210> SEQ ID NO: 429
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 429
Gly Ala Ser Asn Leu Glu Ser
  1  5

<210> SEQ ID NO: 430
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 430
Gln Cys Thr Tyr Gly Ile Ile Ser Ile Ser Asp Gly Asn Ala
  1  5  10

<210> SEQ ID NO: 431
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 431
Ser Tyr Phe Met Thr
  1  5

<210> SEQ ID NO: 432
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 432

Phe Met Asn Thr Gly Asp Arg Ala Tyr Ala Ser Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 433
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

Val Leu Val Val Ala Tyr Gly Ala Phe Arg Ile
1  5  10

<210> SEQ ID NO 434
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 434

atggacagcg ggccccac cc tcagctgcgt ggctcttcgc tgcatgctgct ggacaggtgc cccaggggcc 60
agatgtattg ttttgtattc ccagacgcca gctcttcgcgt ggcaggtgc 120
gtaccatac agtgcaaggg cagtgagctgg attgaagagc ttcagcctgt gcctcagcag 180
aaactcaggg agcctcgcct cctctttcgc tttaattgcg ccaattcgg ccttcgggttc 240
tcatgtctgc cttaaacaggg tggattctgg gacaggttca tttgtcctcact cagcagctc 300
gatggtcgcg atgcgctgct gaaattcattctc aaagctgtcct taatcattagc 360
gatgttaag ct 372

<210> SEQ ID NO 435
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 435

atggagactag ggctgcgggg ggttctcccc gtgcgagctgc tcaaggggtgc ccaagtcgcag 60
tcgtagggag tgcgggggggt gcgcggctgtc aagctggtgg cccaggctgac aatcagctgc 120
acagtattcg gactctccct cagtagctac tttcatgcatt ggcggcgcct ggtctcagg 180
gaggggtgag aatacagggg atctggtggt aagctagtaa aagcataaca ggcgcagttg 240
gccactagcc gattcaccatt ctccccacct tgggagccgt tggatctgga aatcagctac 300
cggacacagcg aggcagccgc cctcatattc tgtgacgagg tttgtggttg tgttattgga 360
gctttataac tc 372

<210> SEQ ID NO 436
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 436
cagcccagtg aggcaggtga aagctatcta gcc 33

<210> SEQ ID NO 437
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 437
<210> SEQ ID NO 418
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 438

ggtgcataca atctgggaatc t 21

<210> SEQ ID NO 439
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 439

caatgcacct atgttaatt ttagttagtg gtagtaac ot 42

<210> SEQ ID NO 440
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 440

agctacttca tgtacc 15

ttcgatgataa ctgctactac gcggactggg cggaagggc 48

<210> SEQ ID NO 441
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 441

gttcttgttg tgtcctatttg agctttaac atc 33

<210> SEQ ID NO 442
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 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 Thr Val Ser Ile Ser Cys Glu Ser Ser 35 40 45
Lys Ser Val Met Asn Asn Tyr Leu Ala Trp Tyr Gln Glu 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
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr 95 100 105 110
Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys 115

Gln Gly Gly Tyr Thr Gln Gly Thr Ser Asp His Gly Thr 120

<210> SEQ ID NO 443
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 443

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1      5      10     15
Val Glu 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 Thr Val Arg Glu Ala Pro Gly Lys Gly Leu Glu
50     55     60
Trp Ile Gly Phe Ile Asn Thr 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

<210> SEQ ID NO 444
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 444

Gln Ser Ser Lys Ser Val Met Asn Asn Tyr Leu Ala
1      5      10

<210> SEQ ID NO 445
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 445

Gly Ala Ser Asn Leu Ala Ser
1      5

<210> SEQ ID NO 446
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 446

Gln Gly Gly Tyr Thr Gly Tyr Ser Asp His Gly Thr
1      5      10

<210> SEQ ID NO 447
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 447

Ser Tyr Pro Met Asn
1      5

<210> SEQ ID NO 448
<211> LENGTH: 16
Phe Ile Ann Thr Gly Gly Thr Ile Val Tyr Ala Ser Trp Ala Lys Gly
1  5          10     15

Gly Ser Tyr Val Ser Ser Gly Tyr Ala Tyr Tyr Phe Asn Val
1  5          10

atgagcaacg gggcccccac tcagctgtcg ggctctctgc tgcctctgtct cccaggtgccg 60
acatgtgccg cggtgtgac ccagactca ttcctcgttg cagatactgt ggggaggcaca 120
gtgcacaatt gcctgctgag cagtaagagt gtatgatata acaactactt agcttggtat 180
cacgcaaaac caggccagcc tcccaagctc cagatctatg gtcacatcaca tacccggctacet 240
gggctcctcat ccagctgtcg ggcacagtga tgcctggtc cagtcactct caccatcagc 300
gagctgtagt gtgacagtgc tgcacattc tacgtcagc gcggtttatac tggttatagt 360
gattacgttgc tctg 372

atgagcaacg gggcccccac tcagctgtcg ggctctctgc tgcctctgtct cccaggtgccg 60
tcgctgaggg agtcgcgctgc tcgctctgtc agctgcgctc aaccctgac actacaatctgc 120
acatgtgccg cggtgtgac ccagactca ttcctcgttg cagatactgt ggggaggcaca 180
gtgcacaatt gcctgctgag cagtaagagt gtatgatata acaactactt agcttggtat 240
gcasaacgcg cattccacat ctcacacaccc tgcacccagc ggagcttgtg aatggacagt 300
cacgcaaaac caggccagcc tcccaagctc cagatctatg gtcacatcaca tacccggctacet 360
tatgagcaacg gggcccccac tcagctgtcg ggctctctgc tgcctctgtct cccaggtgccg 381

cagtagttga gataacacac ttcatttagcgttgc 39
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**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 453**

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<th>ggtgcateca atgtgcate t</th>
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**<210> SEQ ID NO 454**

**<211> LENGTH: 36**

**<212> TYPE: DNA**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 454**

| caaggcggtt atactggtta tagtgatcat gggact | 36 |

**<210> SEQ ID NO 455**

**<211> LENGTH: 15**

**<212> TYPE: DNA**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 455**

| agctatccas tgac | 15 |

**<210> SEQ ID NO 456**

**<211> LENGTH: 48**

**<212> TYPE: DNA**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 456**

| ttcatataa otggtggtac catagtctac gogagctgg caaaaggc | 48 |

**<210> SEQ ID NO 457**

**<211> LENGTH: 42**

**<212> TYPE: DNA**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 457**

| ggcagttatg ttctcatctg ttatgcctac tatatatatg tc | 42 |

**<210> SEQ ID NO 458**

**<211> LENGTH: 121**

**<212> TYPE: PRT**

**<213> ORGANISM: Oryctolagus cuniculus**

**<400> SEQUENCE: 458**

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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
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<210> SEQ ID NO 459
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 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 Thr 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
85
Ala Lys Gly Arg Phe Thr Val Ser Lys Thr Ser Thr Thr Val Asp Leu
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

<210> SEQ ID NO 460
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 460

Gln Ser Ser Gln Ser Val Tyr Asn Asn Trp Leu Ser
1  5  10

<210> SEQ ID NO 461
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 461

Lys Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 462
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 462

Ala Gly Gly Tyr Leu Asp Ser Val Ile
1  5

<210> SEQ ID NO 463
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 463

Thr Tyr Ser Ile Asn
1  5
<210> SEQ ID NO 464
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ ID NO: 464
Ile Ile Ala Asn Ser Gly Thr Thr Phe Tyr Ala Asn Trp Ala Lys Gly
1  5  10  15

<210> SEQ ID NO 465
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ ID NO: 465
Glu Ser Gly Met Tyr Asn Glu Tyr Gly Lys Phe Asn Ile
1  5  10

<210> SEQ ID NO 466
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ ID NO: 466
atggacaag gggccccaa ctcagctgtg ggctccctg atccaggtcc 60
acatttgccg ccgtctgagc ccagactcca tctccctgtc ctgcaagcgt gggagacaa 120
gtcagacca gttgcaagct cgctcaagat gttatatata cacaacaggtt atcctggttt 180
cagcagacac cagggcagcc tcctcagctc ctcagactca aggcactccac tctggctaatt 240
ggcttcgcat cgcgggtcagc aggcagtgga tgtggcagcc aagttcaactt caccatcagc 300
gagctgcaagt tgcacagctg tgtgcacttc tacgtgaggg ggcgtaatct tgcagcgttt 360
att  363

<210> SEQ ID NO 467
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ ID NO: 467
atggsagactg gggctgcgtg gttccctctg gtgaatggg gggccggttg ccaggtcag 60
tcggttgag ggccgggagc tctggctggc aagcgtgga caccctcttgac actagctgca 120
acagttcctc gatttcacct cagtaacct tcaataaact gggtcgcgca gggtccaggg 180
gagggccctag aatgtgacgt aatagtgga cccacattctca cgcgacagtgg 240
ggcgacagcc gattccacagct tcctcaaaacc tcgaaccaggg tggaatgga aactaccaagt 300
cgcacaacgg aggacacggc caccaatcttcc tgtgccacag agagtggaat gtacactgaa 360
tgtgttaaatt ttaacacatc 378

<210> SEQ ID NO 468
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQ ID NO: 468
cagtcacagt cagagttta taataacaac tggttaccc 39
<210> SEQ ID NO: 469
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 469
aaggcaatca ctctggcatc t

<210> SEQ ID NO: 470
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 470
gcggcgggt atcttgatag tggatt

<210> SEQ ID NO: 471
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 471
acctttcga taasa

<210> SEQ ID NO: 472
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 472
atcattgcta atagtggtac cacatttac gogaactgg cgaaaggc

<210> SEQ ID NO: 473
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 473
gagagtggaa tgtacaatga ataggttaaa tttaacatc

<210> SEQ ID NO: 474
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 474
Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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 Ala Ala Thr Tyr Cys Gln Gln
100 105 110
Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
115
120

<210> SEQ ID NO 475
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 475

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Val Leu Lys Gly
1      5    10   15
Val Gln Cys Gln Ser Leu Glu Glu Ser Gly Arg Leu Val Thr Pro
20    25
Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
35   40
Ala Tyr Ala Met Ile Trp Val Arg Glu 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
90  95
Lys Ile Thr Ser Pro Thr Gly Asp Thr Ala Tyr Thr 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

<210> SEQ ID NO 476
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 476

Gln Ala Ser Glu Asn Ile Tyr Ser Phe Leu Ala
1    5    10

<210> SEQ ID NO 477
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 477

Lys Ala Ser Thr Leu Ala Ser
1    5

<210> SEQ ID NO 478
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 478

Gln Gln Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
1    5    10

<210> SEQ ID NO 479
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 479
Ala Tyr Ala Met Ile
1 5

<210> SEQ ID NO 480
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 480

Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 481
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 481

Asp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
1 5 10 15

<210> SEQ ID NO 482
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 482

atggacacga gggcccccag tccagctgctg gggctctggtc tggctggtgcc cccaggtgcc 60
agatgtgctt cagtaatgac ccaagacctta tctcctgtgt ctctcagctgt gggagcgca 120
gttcccatca aatggcagag cagtgagaaac acaaattgctat tttggctgtg gtctcagcag 180
aasaccggg cagctccccaa gccctcgatg tccaaagcttg ccacctctggc atctgagggtc 240
tcctcggtct ccaacgggct tcggatcctgg cacaggttca ctctcaccat cagagacagc 300
gctgggtcag atgctgcaac ttcacatgtg caacagggtct cactgtgtgta tgaattgat 360
aataat 366

<210> SEQ ID NO 483
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 483

atggagactg ggtgtcgttg gttctctctg gttgctggtcg ccagagttggt ccaaggtcag 60
tcggcttgag cagctcgggag tcggctggtgc aagccctggga ccccccagac aactcactcg 120
acagggctgt gatctgagct cagtgctcttg gcaatgtcat ggacctgcca gggctcagggtg 190
gaggggcttg attggatcac aatcatttat cccataagta tcagataacta cgccgagatgg 240
ggcsacggcg gatctgcctct cccaaaccct gcaggcagcata ctgacagttga aatccaccgtg 300
cctgacaccag cagcagcagc cactctttttc tggtccagag atgcaagaga tagtaagat 360
gotattgagg gtcacattttaa ccgct 384

<210> SEQ ID NO 484
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 484
<210> SEQ ID NO 485
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 485

agggcagt agaacattta tagcttttttg gcc

<210> SEQ ID NO 486
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 486

aggggtcct ctctgggcatact

<210> SEQ ID NO 487
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 487

cacaaggtga ctaactgtga tgtatgtag ataatt

<210> SEQ ID NO 488
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 488

gccatgcaat g tgtac

<210> SEQ ID NO 489
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 489

atcattatc ctaactgtat cacatactac gagaactggg cgaaggc

<210> SEQ ID NO 490
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 490

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 Thr Val Thr Ile Asn Cys Gln Ala Ser
35 40 45
Glu Asn Ile Tyr Ser Phe Leu Ala Trp Tyr Gin 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 Gin Phe Thr Leu Thr
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> SEQ ID NO: 491
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 491
Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1   5  10  15
Val Gln Cys Gln Ser Leu Glu Glu Ser 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 Glu 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 Tyr Phe Cys Ala
100 105 110
Arg Asp Ala GluSer Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val
115 120 125

<210> SEQ ID NO: 492
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 492
Gln Ala Ser Glu Asn Ile Tyr Ser Phe Leu Ala
1   5  10

<210> SEQ ID NO: 493
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 493
Arg Ala Ser Thr Leu Ala Ser
1   5

<210> SEQ ID NO: 494
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 494
Gln Gln Gly Ala Thr Val Tyr Asp Ile Asp Asn Asn
1   5  10

<210> SEQ ID NO: 495
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 495

Ala Tyr Ala Met Ile  
1    5

<210> SEQ ID NO 496  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 496

Ile Ile Tyr Pro Asn Gly Ile Thr Tyr Ala Asn Trp Ala Lys Gly  
1    5    10    15

<210> SEQ ID NO 497  
<211> LENGTH: 15  
<212> TYPE: PRT  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 497

Amp Ala Glu Ser Ser Lys Asn Ala Tyr Trp Gly Tyr Phe Asn Val  
1    5    10    15

<210> SEQ ID NO 498  
<211> LENGTH: 366  
<212> TYPE: DNA  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 498

atgagacaga gggcccccac tcaagctgctg gggtctctgc tgtcttggtc ccaggtgcc 60
agatgtgtct tgtatagac ccaagactcca tctctccgtg ctagctggtg gggagagca 120
gtcacatca attgcaaggc cagtgagaac atttatacgt ttttgcttct gtacagagcg 180
aaaccagggc agcctccccaa gctctctgat ttcaggttcct ccaacctggtgc attcgaggtc 240	
tcatctcttg tcaagggcag tggatctggg acaagggcca ctctccacat cagcgacttg 300
gagttgatcg atgctgaccac ttaaactcgt ccaaggggtc tcaactgtga ttgatattgat 360
taat 366

<210> SEQ ID NO 499  
<211> LENGTH: 364  
<212> TYPE: DNA  
<213> ORGANISM: Oryctolagus cuniculus  

<400> SEQUENCE: 499

atggagacag ggtctctctgt gctttctcctg gttgtctgtgc tcaaggggtc ccagtgcatc 60
tcgctgaggg agtccccgggg tctgctctgc agctctggga caaaccctgac actcactgc 120
acagtttcat gaactgaac tcaagctgat gcaatgactc gggctcgca ggtccaggg 180
gagggctgg aagtgaacac aatactttat ctaaatgtgta tcaactata ctgggaacttg 240
gcacaagagc gatctccgct ctctaaacc ctcaccgcgc tggatctgaa aatcaccagt 300
cggccacccag aggacccggc caccatatc tctgctcagag attgcgaaga tagtaagat 360
gttatggc gtataatgct 384
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<400> SEQUENCE: 500
cagggcaagt agaacattta tagtttttg gcc
33

<210> SEQ ID NO 501
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 501
agggcttca ctctgggcatct
21

<210> SEQ ID NO 502
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 502
cacaggtgctacttgtgat tgaatggtgaaataat
36

<210> SEQ ID NO 503
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 503
gcctatgcaatgatc
15

<210> SEQ ID NO 504
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 504
atcattttac ctaatggtat cacatactac cggaactggc cgaagggc
48

<210> SEQ ID NO 505
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 505
gatgcagaa gtagaagaa tgctatgag ggctactttgacgto
45

<210> SEQ ID NO 506
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 506
Met Asp Thr Arg Ala Pro Thr Glu Leu Leu Gly Leu 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 Glu Thr Val Thr Ile Asn Cys Glu Ala Ser 35 40 46
Glu Ser Val Phe Thr Asn 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 Glu Phe Thr Leu
95 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> SEQ ID NO 507
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 507
Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15
Val Gln Cys Glu Ser Leu 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 Glu Ala Pro Gly Gly Glu 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 Cys Ala
100 105 110
Arg Gly His Pro Gly Leu Gly Ser Gly Asn Ile
115 120

<210> SEQ ID NO 508
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 508
Gln Ala Ser Glu Ser Val Phe Asn Asn Met Leu Ser
1 5 10

<210> SEQ ID NO 509
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 509
Asp Ala Ser Asp Leu Ala Ser
1 5

<210> SEQ ID NO 510
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 510
Ala Gly Tyr Lys Ser Asp Ser Asn Asp Gly Asp Asn Val
1 5 10

<210> SEQ ID NO 511
-continued

<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 511

Arg Asn Ser Ile Thr
1 5

<210> SEQ ID NO 512
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 512

Ile Ile Thr Gly Ser Gly Arg Thr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> SEQ ID NO 513
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 513

Gly His Pro Gly Leu Gly Ser Gly Asn Ile
1 5 10

<210> SEQ ID NO 514
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 514

atggagacag gggccccac tcagctgtgc ggctcctgct tgctcttgct cccaggtgcc 60
acatttgcca ttagaatgac ccaagactca tccccgggt gctggcctgt gggaggcaca 120
gtcatcacata atggccagcc atggagagt ttttaata atatgttatctcttgatcag 180
cagaaacacg ggcacgcttc taagtccttg atctatgtag ccattcctgct ggcctctgggg 240
gtcccaatgc ggtgcaaaag cagctagatt gggacacagt tcaactctcac catcagtggc 300
gtggaggttg cagatgcctgc caacctatct tgtgcaggtgt ataaagtgta tagtaatgt 360
ggcgataatg tt 372

<210> SEQ ID NO 515
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 515

atggagacagt ggctcgctgtg gtttcttcttg gttgcggac tcaagaggttg ccaatgtgcag 60
tgctggaggg atgcggggga tcgcctggtc acgcctggga caacactgac actacactgc 120
acagtctctg gattcctcgt ccaacggatt tcaataacct gggctccgaga ggctcagggg 180
gaggggtctt aatctgatcg gaaatcttat atggagagt gtgatgtgta gacgtgtata ccgcaactgg 240
gccaaactgc gattcactat ctcctaaacc tggggccggt tgggtaagatt aatgacacag 300
cgtacacgc gggcactgtgc cacatatttc tgtgcagag gcccctctgg tcttggtagt 360
ggtacatc 369

<210> SEQ ID NO 516

...
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 516

cagggcagtg agagtttttt taatatgtg ttatcc 36

<210> SEQ ID NO 517
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 517

gatgcattc acctggtac t 21

<210> SEQ ID NO 518
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 518

gcaggtgata aagtgatag taatggtgc gataatgtt 39

<210> SEQ ID NO 519
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 519

agaatccaa taacc 15

<210> SEQ ID NO 520
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 520

atcattactg gtaatggtag aacgtactac gcaacctggg caaaaaggc 48

<210> SEQ ID NO 521
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 521

ggcacatcg gttttgtag tgtaacatc 30

<210> SEQ ID NO 522
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 522

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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 Cys Gln
100 105 110
Gly Tyr Tyr Ser Gly Pro Ile Ile Thr
115 120

<210> SEQ ID NO 523
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 523
Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1   5   10   15
Val Gln Cys Glu Ser Leu 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 Ser Ala Tyr Tyr Ala Thr Trp
65  70  75  80
Ala Asn Gly Arg Phe Thr Ile Ala Lys Thr Ser Ser Thr Ser 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

<210> SEQ ID NO 524
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 524
Gln Ser Ser Glu Ser Val Tyr Asn Asn Tyr Leu Ser
1   5   10

<210> SEQ ID NO 525
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 525
Thr Ala Ser Ser Leu Ala Ser
1   5

<210> SEQ ID NO 526
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 526
Gln Gly Tyr Tyr Ser Gly Pro Ile Ile Thr
1   5   10
<210> SEQ ID NO 527
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 527

Asn Tyr Tyr Ile Gln
1  5

<210> SEQ ID NO 528
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 528

Ile Ile Tyr Ala Gly Gly Ser Ala Tyr Tyr Ala Thr Trp Ala Asn Gly
1  5  10  15

<210> SEQ ID NO 529
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 529

Gly Thr Phe Asp Gly Tyr Glu Leu
1  5

<210> SEQ ID NO 530
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 530

atgagacgc ggcgcgcgcc tcagctgtgc ggtctctgct gctctctgct cccagctgcc 60
acatttgcc aagtgctgac ccagactgca tcgctctgtg tcgactgtgc gggagcaca 120
gtcaacatca atggcagatg ccagctagat gttataata actatattac ctagatatag 180
cagaaacag ggccagctcc caagctcttg atctatactg catccagctg ggcactctggg 240
gtccccctcg cggctcaaaag cagctggagt gggacacat tcactctcctc catcagcga 300
gtccagtgct agctgtgtgc cacttactac tcgaaggtg attataagtg tcctataaatt 360
act 363

<210> SEQ ID NO 531
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 531

atggaagactg ggtgtagcgtg gttctctctg tggctgtggtc tcagagcggt gcaatgtcag 60
tgcgcgggag atccgcgggg tccgctgtgc cagcctggga cacccctgca actctcactgc 120
acagctctctg gattgctct tctactacact tacatacact gggctccgca ggcctccagg 180
agagagctct atagatgcct gatctctatatt gttggtgtgta ggcctacta cgggtacctgg 240
gcaacgcgc gattcacaatt ccgagcacac tcgtaaccca cgggtggtcgt gcagagac 300
agcttgacaa ccgagcaca gcggcagctt ttcttggtcct caggggacct tgaaggtttat 360
gagttg 366
<210> SEQ ID NO 532
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 532

cagtcagtc agagtgtta taataactac t tatcc 36

<210> SEQ ID NO 533
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 533

acctgcatca gcotggcactc t 21

<210> SEQ ID NO 534
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 534

caaggtcatt atagtggtcc tataattact 30

<210> SEQ ID NO 535
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 535

aactactaca taca 15

<210> SEQ ID NO 536
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 536

atcatttattg otggtgtag cgcatactac ggcacggtgg c a a a c g g c 48

<210> SEQ ID NO 537
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 537

gggacatttg atggttatga gt gg 24

Met Asp Thr Arg Ala Pro Thr Glu Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe Ala Glu 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
-continued

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 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> SEQ ID NO 539
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 539
Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1   5 10 15
Val Gln Cys Glu Ser Val 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 Glu Ala Pro Gly Glu Gly Leu Glu
50  55  60
Tyr Ile Gly Phe Ile Asn Pro Gly Ser Ala Tyr Tyr Ala Ser Trp
65  70  75  80
Ala Ser Gly Arg Leu Thr Ile Ser Lys Thr Ser 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

<210> SEQ ID NO 540
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 540
Gln Ser Ser Glu Ser Val Tyr Ser Asn Asn Leu Leu Ser
1   5 10

<210> SEQ ID NO 541
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 541
Arg Ala Ser Asn Leu Ala Ser
1   5

<210> SEQ ID NO 542
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 542
Gln Gly Tyr Tyr Ser Gly Val Ile Asn Ser
1  5  10

<210> SEQ ID NO 543
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus
<400> SEQUENCE: 543
Ser Tyr Phe Met Ser
1  5

<210> SEQ ID NO 544
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus
<400> SEQUENCE: 544
Phe Ile Asn Pro Gly Gly Ser Ala Tyr Tyr Ala Ser Trp Ala Ser Gly
1  5  10  15

<210> SEQ ID NO 545
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Orectolagus cuniculus
<400> SEQUENCE: 545
Ile Leu Ile Val Ser Tyr Gly Ala Phe Thr Ile
1  5  10

<210> SEQ ID NO 546
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Orectolagus cuniculus
<400> SEQUENCE: 546
atggacacga ggcccccaca tcaagctcgtg ggcgtctcct gcggatcgcgtcc  60
acatgtggcc aagttgctga ccaagcttca cccctgctgt cgtgccccct ctggagacaca  120
gtcaacatca gttggcgatt cagtgagag ccgtttatag ataacccttt atctctgtat  180
cagcagaacc cagggccgac tcccaagctc cgtatctaca gggcatccca ctcggcatct  240
ggtgcttcct ccgggtgctg gatggctgta ctgggagac ccggccgac ccatcttacgc  300
gggggcagtc gttgctgact gcggccttac tctgtcagag gccattttag tgtggctcatt  360
aattgat              366

<210> SEQ ID NO 547
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Orectolagus cuniculus
<400> SEQUENCE: 547
atgggacgtg ggtgctgatc gttttccctg gttgctgatg tcaaggttgct gcagtgctcag  60
tgcgtggaggt aagggagccg cgcctggtc gcggatcgggt aacccctggca cactcccttgcc  120
aagttgctgtg gattttctct cagttgtagc tctgcagatc ggtggccggt ggttcaggg  180
gaggggctgg aatatcagct acatacctata ccttgtgctgt ggcctataaa cgcggagcttg  240
ggggggtgccc ggtgctcctc ctggcctacc gcggcgccgg tagtgctgg aatcaccagt  300
cggacaacg aggaacgc cacotatttc tgtgccagga ttctttgtg ttcttttgga  360
 gccttatca tc  372

<210> SEQ ID NO 548
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 548

cagtcctagc agagcgttta tagtataac ctcattaccc  39

<210> SEQ ID NO 549
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 549

agggcctaca atctggcgac t  21

<210> SEQ ID NO 550
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 550

cagagctatt atagtggtgt cattatagt  30

<210> SEQ ID NO 551
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 551

agctatcca tgagc  15

<210> SEQ ID NO 552
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 552

ttcattaatc ctgtggtgtc gcgacatcc gcgacgaggg cggagtggc  48

<210> SEQ ID NO 553
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 553

atctctattg ttcttttattg agcctttatcc atc  33

<210> SEQ ID NO 554
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 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 Aam 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
95  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> SEQ ID NO 555
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 555

Met Glu Thr Gly Leu Arg Trp Leu Leu Val Ala Val Leu Lys Gly
1  5  10  15

Val Glu Cys Gln Ser Leu 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 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 Gly 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

<210> SEQ ID NO 556
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 556

Gln Ala Thr Glu Ser Ile Gly Aam Glu Leu Ser
1  5  10

<210> SEQ ID NO 557
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 557

Ser Ala Ser Thr Leu Ala Ser
1  5

<210> SEQ ID NO 558
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 558

Gln Gln Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
1  5

<210> SEQ ID NO 559
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 559

Lys Tyr Tyr Met Ser
1  5

<210> SEQ ID NO 560
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 560

Tyr Ile Asp Ser Thr Thr Val Asn Thr Tyr Tyr Ala Thr Trp Ala Arg
1  5  10

Gly

<210> SEQ ID NO 561
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 561

Gly Ser Thr Tyr Phe Thr Asp Gly Gly His Arg Leu Asp Leu
1  5  10

<210> SEQ ID NO 562
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 562

atggaacaca ggcctccccac tcagctgtcg tggctctgtgc tgctctgtgc cccaggtgcc 60
agatgtgtct atgtatatgc ccgaactcca gctctgtgag ggtgactgtg ggagggcaaa 120
gtcaacacta agtgccagcc cactgagac attgcaaatg agttacctcg gtatccag 180
aaaccagggc agctcctccaa gctctgtgat tatttgcata ccaacctgga atctggggtc 240
catcgcgtc ttcaaggcgc tggatctgag acaagttcca ctctcacaoct caccggtgctg 300
agatgtgtag atgctgcccac ttaactactg caaacggttt atagtagtgcc taatattgt 360
aatgtct 366

<210> SEQ ID NO 563
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 563

atggaagactg ggtctgctgtc gctctctctg gtcgcgttgc tcaaggtgtc ccaagtgcacag 60
tgctctggag agtcgcgagg tgtctctgtgc aatcttggtag aaccccgtgac aaactcactcg 120
acgctctcgt gattctccc gcaagaagtc tacatgagct ggtcgcgca aagttgcaag 180
aaggggctga aatcatacg gatatgtgat atactactgt ttaatacata ctacgogacc 240
tgggpgag ggcaggtcac catctccaa actcagacca ccggttgatct gaagatcacc 300
agtcgacacg tggagcacgg ggcacacttt tctgtgccag gagaagtgct tattattact 360
gatggaggc atcggttggaca ttc 384

<210> SEQ ID NO 564
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 564
caggccactcg agacaactgg caatgagtt ctc 33

<210> SEQ ID NO 565
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 565
tctgcatcca tctgggcact t 21

<210> SEQ ID NO 566
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 566
cacaaggttt atagtaggcc taatattgat aatgct 36

<210> SEQ ID NO 567
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 567
aagtactaca tgcagc 15

<210> SEQ ID NO 568
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 568
tacatgtgata tataactatgtat atacatac atacgacgct tgggagaggg c 51

<210> SEQ ID NO 569
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 569
ggaagtaact tattttactga tggagcccg tgggttggatctq 42

<210> SEQ ID NO 570
<211> LENGTH: 122
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus
<400> SEQUENCE: 570
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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu 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 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
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Ile Thr Gly Val Glu Cys Asp Arg Ala Ala Thr Tyr Tyr Cys Gln Gln
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Gly Tyr Ser Ser Ala Asn Ile Asp Asn Ala
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  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 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 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

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<212> TYPE: PRT
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Arg Glu Ala Lys Val Gln Trp Lys Val Asp Aen Ala Leu Gln Ser Gly
35 40 45
Aen Ser Glu Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
50 55 60
Ser Leu Ser Ser Thr Leu Leu Ser Lys Ala Asp Tyr Glu Lys His
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<223> OTHER INFORMATION: Kappa constant domain of Abl

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35 40 45
Aen Ser Glu Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
50 55 60
Ser Leu Ser Ser Thr Leu Leu Ser Lys Ala Asp Tyr Glu Lys His
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100 105

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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45
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50 55 60
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65 70 75 80
Tyr Ile Cys Aen Val Aen His Pro Ser Aen 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
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Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu  
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Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu  
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His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Ann  
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Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Ann  
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Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Glu Gln Gly Ann  
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900
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<210> SEQ ID NO 591
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 591

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1      5      10      15

<210> SEQ ID NO 592
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Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser
1      5      10      15

<210> SEQ ID NO 593
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Pro His Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln
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<210> SEQ ID NO 595
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 1  5   10  15

Cys Arg Lys Ser Arg Met Cys Glu Ser Ser Lys Glu Ala Leu Ala
 1  5   10  15

Ser Arg Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Arg Asn
 1  5   10  15

Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Arg Asn Leu Arg Leu
 1  5   10  15

Ser Lys Glu Ala Leu Ala Glu Arg Asn Leu Arg Leu Pro Lys Met
 1  5   10  15

Ala Leu Ala Glu Arg Asn Leu Leu Pro Lys Met Ala Glu Lys
 1  5   10  15

Glu Asn Asl Leu Asn Leu Pro Lys Met Ala Glu Lys Asp Gly Cys
 1  5   10  15
Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr
1 5 10 15

Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr
1 5 10 15

Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr Leu Gln Asn
1 5 10 15

Leu Glu Phe Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu
1 5 10 15

Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu
1 5 10 15

Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gin Ala
1 5 10 15

Leu Gln Asn Arg Phe Glu Ser Ser Glu Gin Ala Arg Ala Val
1 5 10 15
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Ser Ser Glu Glu Gin Ala Arg Ala Val Gln Met Ser Thr Lys Val
1  5 10 15

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1  5 10 15

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1  5 10 15

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<400> SEQUENCE: 632
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1   5  10  15

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1   5  10  15

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 634
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1   5  10  15

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1   5  10  15

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1   5  10  15

Thr Lys Leu Gln Ala Gln Aem Gln Trp Leu Gln Asp Met Thr Thr
1   5  10  15

Gln Ala Gln Aem Gln Trp Leu Gln Asp Met Thr Thr His Leu Ile
1   5  10  15

Asn Gln Trp Leu Gln Asp Met Thr Thr His Leu Ile Leu Arg Ser
1   5  10  15

Leu Gln Asp Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu
1   5  10  15

Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln
1   5  10  15

His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu
1   5  10  15
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<213> ORGANISM: Homo sapiens

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1      5      10     15

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<212> TYPE: PRT
<213> ORGANISM: Orcytolagus cuniculus

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

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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1      5      10     15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Gly Ile Arg Asn Asp
20     25     30
Leu Gly Trp Tyr Gin Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35     40     45
Tyr Ala Ala Ser Ser Leu Gin Ser Gly Val Pro Ser Arg Phe Ser Gly
50     55     60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
65     70     75     80
Glu Asp Phe Ala Thr Tyr Tyr Cys
95
<210> SEQ ID NO 649  
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<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens  

<400> SEQUENCE: 649  

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

<210> SEQ ID NO 650  
<211> LENGTH: 88  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens  

<400> SEQUENCE: 650  

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 Arg Ala Ser Gin Gly Ile Ser Ser Trp
20  25  30
Leu Ala Trp Tyr Gln Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35  40  45
Tyr Lys Ala Ser Ser Leu Gin 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 Gin Pro
65  70  75  80
Asp Asp Phe Ala Thr Tyr Tyr Cys
85

<210> SEQ ID NO 651  
<211> LENGTH: 111  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<222> FEATURE:  
<223> OTHER INFORMATION: Humanized antibody  

<400> SEQUENCE: 651  

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5  10  15
Asp Arg Val Thr Ile Thr Cys Gin Ala Ser Gin Ser Ile Asn Asn Glu
20  25  30
Leu Ser Trp Tyr Gln Gin 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 Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
65  70  75  80
-continued

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn  
  85 90 95
Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg  
  100 105 110

<210> SEQ ID NO 652
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 652

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

<210> SEQ ID NO 653
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 653

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

<210> SEQ ID NO 654
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 654

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

<210> SEQ ID NO 655
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 655
Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Tyr Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys

<210> SEQ ID NO 656
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized antibody
<400> SEQUENCE: 656
Glu Val Gln Leu Val Glu Ser 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 Trp Ala Ile
50 55 60
Gly Arg Phe Thr Ile Ser Arg Asp 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 Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
<210> SEQ ID NO 657
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<222> OTHER INFORMATION: Humanized antibody

<400> SEQUENCE: 657

Glu Val Glu Val Val Glu Ser Gly Gly Leu Val Glu Val 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 Glu 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 Asp Thr Ala Val Tyr Tyr Cys Ala
  85 90  95
Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
 100 105 110
Gly Thr Leu Val Thr Val Val Ser Ser
  115 120

<210> SEQ ID NO 658
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 658

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
  1  5  10  15
Val Gln Cys Glu 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
Asn Tyr Tyr Val Thr Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu
  50 55  60
Trp Ile Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser
  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
Arg Asp Asp Ser Ser Asp Trp Ala Lys Phe Asn Leu Trp Gly Gln
 115 120 125
Gly Thr Leu Val Thr Val Ser Ala Ser Thr Thr Lys Gly Pro Ser Val
 130 135 140
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 145 150 155 160
Leu Gly Cys Leu Val Lys
  165
138. A nucleic acid or nucleic acids, which nucleic acid or nucleic acids separately or in combination encode for the variable heavy (VH) and the variable light (VL) regions of an antibody or antibody fragment specifically binds human IL-6, wherein said antibody or antibody fragment specifically binds to an epitope on an intact human IL-6 polypeptide, which epitope when ascertained by epitopic mapping using overlapping linear peptide 15-mer fragments which span the full length of the native human IL-6 polypeptide includes one or more residues comprised in each of the following IL-6 fragments (i) a fragment consisting of amino acid residues 37-51 of human IL-6, (ii) a fragment consisting of amino acid residues 70-84 of human IL-6, (iii) a fragment consisting of amino acid residues 169-183 of human IL-6, (iv) a fragment consisting of amino acid residues 31-45 of human IL-6 and (v) a fragment consisting of amino acid residues 58-72 of human IL-6 and which antibody or antibody fragment further competes with an antibody comprising the variable light and heavy regions in SEQ ID NO:2 and 3 for binding to human IL-6.

139. The nucleic acid or acids of claim 138, wherein the antibody fragment is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks) and Fab, Fab\' and F(ab\')2 fragments.

140. The nucleic acid or acids of claim 138, wherein the encoded antibody or antibody fragment contains a mutation or mutations that eliminate or modify glycosylation.

141. The nucleic acid or acids of claim 138, wherein the nucleic acid or acids further encode human constant domains.

142. The nucleic acid or acids of claim 141, wherein said-human constant domains are IgG1, IgG2, IgG3 or IgG4 constant domains.

143. The nucleic acid or acids of claim 141, wherein said-human constant domains are IgG1 constant domains.

144. The nucleic acid or acids of claim 138, wherein the nucleic acid or nucleic acids further encode an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

145. The nucleic acid or acids of claim 138, wherein the nucleic acid or nucleic acids which encode a humanized antibody or humanized antibody fragment.

146. The nucleic acid or acids of claim 138, wherein the nucleic acid or nucleic acids encode for a human, humanized, single chain or chimeric antibody.

147. A vector containing the nucleic acid or nucleic acids of claim 138.

148. A recombinant cell or virus containing the nucleic acid or nucleic acids of claim 138.

149. A method of making an anti-IL-6 antibody or antibody fragment specifically binds human IL-6, wherein said antibody or antibody fragment that specifically binds to an epitope on an intact human IL-6 polypeptide, which epitope when ascertained by epitopic mapping using overlapping linear peptide 15-mer fragments which span the full length of the native human IL-6 polypeptide includes one or more residues comprised in each of the following IL-6 fragments (i) a fragment consisting of amino acid residues 37-51 of human IL-6, (ii) a fragment consisting of amino acid residues 70-84 of human IL-6, (iii) a fragment consisting of amino acid residues 169-183 of human IL-6, (iv) a fragment consisting of amino acid residues 31-45 of human IL-6 and (v) a fragment consisting of amino acid residues 58-72 of human IL-6 and which antibody or antibody fragment further competes with an antibody comprising the variable light and heavy regions in SEQ ID NO:2 and 3 for binding to human IL-6, which method comprises:

(i) culturing a cell according to claim 148 under conditions that result in the expression of said antibody or antibody fragment and

(ii) isolating said antibody or antibody fragment from the cell culture.

* * * * *