HIGH AFFINITY ANTIBODIES TO HUMAN IL-6 RECEPTOR

Statement of Related Art

[0001] Interleukin-6 (IL-6) is a pleiotropic cytokine produced by immune and non-immune cells that plays a crucial role in regulation of immune response, acute-phase reactions, and hematopoiesis. It binds to soluble and cell membrane bound IL-6R (α chain) forming a binary complex and this complex is able to interact with cell membrane bound gp130 (β chain), induces formation of signaling complex comprising two each of IL-6, IL-6R, and gp130.

[0002] Antibodies to hIL-6R are described in US 5,670,373, 5,795,965, 5,817,790, 6,410,691, and EP 409 607B1. Therapeutic methods are described in US 5,888,510 and 6,723,319.

BRIEF SUMMARY OF THE INVENTION

[0003] In a first aspect, the invention provides human antibodies, preferably recombinant human antibodies, that specifically bind human interleukin-6 receptor (hIL-6R). These antibodies are characterized by binding to hIL-6R with high affinity and slow dissociation kinetics and by the ability to neutralize IL-6 activity. The antibodies can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to effect functionality, e.g., to eliminate residual effector functions (Reddy et al. (2000) J. Immunol. 164:1925-1933). In a preferred embodiment, the invention provides an antibody or antigen-binding fragment thereof, which binds human IL-6 receptor (SEQ ID NO:1) with a K_D of about 500 pM or less, as measured by surface plasmon resonance. In a more specific embodiment, the antibody or antigen-binding fragment has a K_D of less than 300 pM, or less than 200 pM, or even less than 100 pM. In various embodiments, the antibody or antigen-binding fragment thereof blocks hIL-6 activity with an IC_{60} of 250 pM or less, as measured by luciferase bioassay. In more specific embodiments, the antibody or antigen-binding fragment thereof exhibits an IC_{50} of 150 pM or less.

[0004] In related aspects, the antibody or antigen-binding fragment of the invention binds hIL-6R with an affinity at least 2-fold higher than it binds monkey IL-6R. In more preferred embodiments, the antibody or antigen-binding fragment binds hIL-6R protein (SEQ ID NO:1) with an affinity that is up to about 3-fold higher relative to its binding to monkey IL-6R (*Macaca fascicularis* extracellular domain shown in SEQ ID NO:251).

[0005] In one embodiment, the antibody or antigen-binding portion of the antibody of the invention comprises a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:3, 227, 19, 231, 35, 51, 67, 83, 99, 115, 131, 147, 239, 241, 163, 179, 235, 195 and 211, or substantially similar sequence thereof. In a more specific embodiment, the antibody or antigen-binding fragment thereof further comprises a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO: 11, 229, 27, 233, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 237, 203 and 219, or a substantially similar sequence thereof. In specific

embodiments, the antibody or antigen-binding fragment thereof comprise HCVR/LCVR pairs selected from the group consisting of SEQ ID NO:3/11; 227/229; 19/27; 231/233; 35/43; 51/59; 67/75; 83/91; 99/107; 115/123; 131/139; 147/155; 239/155; 241/155; 163/171; 179/187; 235/237; 195/203; and 211/219, or substantially similar sequences thereof.

[0006] In a second aspect, the invention provides isolated nucleic acid molecules that encode an antibody or antigen-binding fragment of an antibody of the invention. In one embodiment, the nucleic acid molecule of the invention encodes an antibody or fragment thereof comprising an HCVR as described above. In specific embodiments, the nucleic acid molecule encoding the HCVR is selected from the group consisting of SEQ ID NO:2, 226, 18, 230, 34, 50, 66, 82, 98, 114, 130, 146, 238, 240, 162, 178, 234, 194 and 210, or a substantially identical sequence thereof. In a related aspect, the invention provides an isolated nucleic acid molecule encoding an LCVR as described above. In specific embodiments, the nucleic acid molecule encoding the LCVR is a nucleotide sequence selected from the group consisting of SEQ ID NO: 10, 228, 26, 232, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 236, 202 and 218, or a substantially identical sequence thereof.

[0007] In a third aspect, the invention features an antibody or antigen-binding fragment, comprising a heavy chain complementary determining region 3 (CDR3) domain and a light chain CDR3 domain, wherein

the heavy chain CDR3 domain comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12} - X^{13} - X^{14} - X^{15} - X^{16} - X^{17} - X^{18} - X^{19}$ (SEQ ID NO:247) wherein X^1 = Ala, X^2 = Lys, X^3 = Gly, X^4 = Arg, X^5 = Asp, X^6 = Ser or Ala, X^7 = Phe, X^8 = Asp; X^9 = Ile, X^{10} = Pro or absent, X^{11} = Phe or absent, X^{12} = Val or absent, X^{13} = Tyr or absent, X^{14} = Tyr or absent, X^{15} = Tyr or absent, X^{16} = Gly or absent, X^{17} = Met or absent, X^{18} = Asp or absent, and X^{19} = Val or absent; and

the light chain CDR3 domain comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9$ (SEQ ID NO:250) wherein X^1 = Gln, X^2 = Gln or His, X^3 = Ala, X^4 = Asn or Tyr, X^5 = Ser, X^6 = Phe, X^7 = Pro, X^8 = Pro, and X^9 = Thr.

[0008] In a more specific embodiment, the antibody or antigen-binding fragment further comprises

a heavy chain CDR1 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8$ (SEQ ID NO:245) wherein X^1 = Gly or Arg, X^2 = Phe, X^3 = Thr, X^4 = Phe, X^5 = Asp, X^6 = Asp, X^7 = Tyr, and X^8 = Ala;

a heavy chain CDR2 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8$ (SEQ ID NO:246) wherein X^1 = Ile or Val, X^2 = Ser, X^3 = Trp, X^4 = Asn, X^5 = Ser, X^6 = Gly, X^7 = Ser, and X^8 = Ile;

a light chain CDR1 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8$ (SEQ ID NO:248), wherein X^1 = Gln, X^2 = Gly, X^3 = Ile, X^4 = Ser, X^5 = Ser, and X^6 = Trp; and

a light chain CDR2 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3$ (SEQ ID NO:249), wherein X^1 = Gly or Ala, X^2 = Ala, and X^3 = Ser.

[0009] In a fourth aspect, the invention features an antibody or antigen-binding fragment, comprising:

a heavy chain CDR3 domain selected from the group consisting of SEQ ID NO: 25, 153, 9, 185, 41, 57, 73, 89, 105, 121, 137, 169, 201 and 217; and

a light chain CDR3 domain selected from the group consisting of SEQ ID NO:33, 161, 17, 193, 49, 65, 81, 97, 113, 129, 145, 177, 209 and 225.

[0010] In a more specific embodiment, the antibody or antigen-binding fragment further comprises:

a heavy chain CDR1 domain selected from the group consisting of SEQ ID NO: 21, 149, 5, 181, 37, 53, 69, 85, 101, 117, 133, 165, 197, and 213;

a heavy chain CDR2 domain selected from the group consisting of SEQ ID NO: 23, 151, 7, 183, 39, 55, 71, 87, 103, 119, 135, 167, 199 and 215;

a light chain CDR1 domain selected from the group consisting of SEQ ID NO: 29, 157, 13, 189, 45, 61, 77, 93, 109, 125, 141, 173, 205 and 221; and

a light chain CDR2 domain selected from the group consisting of SEQ ID NO: 31, 159, 15, 191, 47, 63, 79, 95, 111, 127, 143, 175, 207 and 223.**

[0011] In specific embodiments, the antigen or antigen-binding fragment comprises heavy chain CDR sequences SEQ ID NO:21, 23, 25 and light chain CDR sequences SEQ ID NO:29, 31, 33; heavy chain CDR sequences SEQ ID NO:149, 151, 153 and light chain CDR sequences SEQ ID NO:157, 159, 161; heavy chain CDR sequences SEQ ID NO:5, 7, 9 and light chain SEQ ID NO: 13, 15, 17; and heavy chain CDR sequences SEQ ID NO: 181. 183, 185 and light chain CDR sequences SEQ ID NO:189, 191, 193.

[0012] In a fifth aspect, the invention features isolated nucleic acid molecules encoding an antibody or antigen-binding fragments of the invention, wherein the antibody or fragment thereof comprises

a heavy chain CDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:24, 152, 8, 184, 40, 56, 72, 88, 104, 120, 136, 168, 200 and 216; and

a light chain CDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:32, 160, 16, 192, 48, 64, 80, 96, 112, 128, 144, 176, 208 and 224; as well as substantially identical nucleic acid sequences thereof.

[0013] In a more specific embodiment, isolated nucleic acid molecules are provided encoding an antibody or antigen-binding fragment of the invention, wherein the antibody or fragment thereof comprises

a heavy chain CDR1 encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 20, 148, 4, 180, 36, 52, 68, 84, 100, 116, 132, 164, 196 and 212;

a heavy chain CDR2 domain encoded by a nucleotide sequence selected from the group

consisting of SEQ ID NO: 22, 150, 6, 182, 38, 54, 70, 86, 102, 118, 134, 166, 198 and 214;

a light chain CDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:28, 156, 12, 188, 44, 60, 76, 92, 108, 124, 140, 172, 204 and 220; and

a light chain CDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:30, 158, 14, 190, 30, 46, 62, 78, 94, 110, 126, 142, 174, 206 and 222; as well as substantially identical nucleic acid sequences thereof.

[0014] The invention encompasses anti-hIL-6R antibodies or antigen-binding fragments thereof having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety on an oligosaccharide chain, for example, to increase antibody-dependent cellular cytotoxicity (ADCC) (see Shield et al. (2002) JBC 277:26733). In other applications, modification of a galactosylation can be made in order to modify complement-dependent cytotoxicity (CDC).

[0015] In further aspects, the invention provides recombinant expression vectors carrying the nucleic acid molecules of the invention, and host cells into which such vectors have been introduced, as are methods of making the antibodies or antigen-binding fragments of the invention obtained by culturing the host cells of the invention. The host cell may be a prokaryotic or eukaryotic cell, preferably the host cell is an *E. coli* cell or a mammalian cell, such as a CHO cell.

[0016] In a further aspect, the invention features a pharmaceutical composition comprising a human antibody or antigen-binding fragment of an antibody which specifically binds hIL-6R and a pharmaceutically acceptable carrier.

[0017] In further aspects, the invention features methods for inhibiting human IL-6 activity using an antibody, or antigen-binding portion thereof, of the invention. In one embodiment, the invention encompasses a therapeutic method comprising administering an antibody of the invention, or a fragment thereof, to a human subject suffering from a disorder which is treated or ameliorated by inhibition of IL-6 activity. The disorder can be, for example, arthritis, including chronic rheumatoid arthritis; inflammatory bowel diseases, including Crohn's disease and ulcerative colitis; systemic lupus erythematosus; and inflammatory diseases.

[0018] In further aspects, the invention provides the use of an antibody or antigen-binding fragment of an antibody as defined above in the manufacture of a medicament for use to attenuate or inhibit an IL-6-mediated disease or disorder in a human. In a related aspect, the invention provides an antibody or antigen-binding fragment of an antibody as defined above for use in the attenuation or inhibition of an IL-6-mediated disease or disorder in a human.

[0019] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0020] Before the present methods are described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and

conditions 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 be limiting, since the scope of the present invention will be limited only by the appended claims.

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

[0022] The term "human IL6R" (hIL-6R), as used herein, is intended to refer to a human cytokine receptor that specifically binds interleukin-6 (IL-6). The extracellular domain of hIL-6R is shown in SEQ ID NO:1.

[0023] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementary determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0024] The term "antigen-binding portion" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hIL-6R). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL1 and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al. (1989) Nature 241:544-546), which consists of a VH domain; and (vi) an isolated complementary determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single contiguous chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also

intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies, are also encompassed (see e.g., Holliger et al. (1993) Proc. Natl. Acad Sci. USA 90:6444-6448).

[0025] A "neutralizing" or "blocking" antibody, as used herein, is intended to refer to an antibody whose binding to hIL-6R results in inhibition of the biological activity of hIL-6. This inhibition of the biological activity of hIL-6 can be assessed by measuring one or more indicators of hIL-6 biological activity known to the art, such as hIL-6-induced cellular activation and hIL-6 binding to hIL-6R (see examples below).

[0026] A "CDR" or complementary determining region is a region of hypervariability interspersed within regions that are more conserved, termed "framework regions" (FR). In different embodiments of the anti-hIL-6R antibody or fragment of the invention, the FRs may be identical to the human germline sequences, or may be naturally or artificially modified. A group of CDRs may be defined as an amino acid consensus sequence; for example, in one embodiment, the anti-hIL-6R antibody or antigen-binding fragment of the invention may be described as comprising a heavy chain CDR3 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12} - X^{13} - X^{14} - X^{15} - X^{16} - X^{17} - X^{18} - X^{19}$ (SEQ ID NO:247) wherein X^1 = Ala, X^2 = Lys, X^3 = Gly, X^4 = Arg, X^5 = Asp, X^6 = Ser or Ala, X^7 = Phe, X^8 = Asp; X^9 = Ile, X^{10} = Pro or absent, X^{11} = Phe or absent, X^{12} = Val or absent, X^{13} = Tyr or absent, X^{14} = Tyr or absent, X^{15} = Tyr or absent, X^{16} = Gly or absent, X^{17} = Met or absent, X^{18} = Asp or absent, and X^{19} = Val or absent; and a light chain CDR3 domain comprising an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9$ (SEQ ID NO:250) wherein X^1 = Gln, X^2 = Gln or His, X^3 = Ala, X^4 = Asn or Tyr, X^5 = Ser, X^6 = Phe, X^7 = Pro, X^8 = Pro, and X^9 = Thr.

[0027] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Pharmacia Biosensor AB).

[0028] The term "epitope" is an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstances, an epitope may include moieties of saccharides, phosphoryl groups, or sufonyl groups on the antigen.

[0029] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%,

97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below.

[0030] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) Science 256: 1443 45. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0031] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database

containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn, using default parameters. See, e.g., Altschul et al. (1990) J. Mol. Biol. 215: 403 410 and Altschul et al. (1997) Nucleic Acids Res. 25:3389 402.

Preparation of Human Antibodies

[0032] Methods for generating human antibodies include, for example, VelocImmune™ (Regeneron Pharmaceuticals), XenoMouse™ technology (Green et al. (1994) Nature Genetics 7:13-21; Abgenix), the "minilocus" approach, and phage display (and see, for example, US 5,545,807, US 6,787,637). The VelocImmune™ technology (US 6, 596,541) encompasses a method of generating a high specificity fully human antibody to a select antigen. This technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody. In specific embodiment, the cell is a CHO cell.

[0033] Antibodies may be therapeutically useful in blocking a ligand-receptor interaction or inhibiting receptor component interaction, rather than by killing cells through fixation of complement (complement-dependent cytotoxicity)(CDC) and participation antibody-dependent cell-mediated cytotoxicity (ADCC) The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[0034] Human immunoglobulins can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via interchain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covantlently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification. The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. In fact, a single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) Molecular Immunology 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, CH2 or CH3 region which may be desirable, for example, in production, to improve the yield of the

desired antibody form.

[0035] Antibodies of the invention are preferably prepared with the use of VelocImmune™ technology. A transgenic mouse in which the endogenous immunoglobulin heavy and light chain variable regions are replaced with the corresponding human variable regions is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0036] In one embodiment, the transgenic mouse comprises up to 18 functional human variable heavy chain genes and 12 functional human variable kappa light chain genes. In another embodiment, the transgenic mouse comprises up to 39 human variable heavy chain genes and 30 human variable kappa light chain genes. In yet another embodiment, the transgenic mouse comprises up to 80 human variable heavy chain genes and 40 human variable kappa light chain genes.

[0037] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_Ds of from about 10^{-9} through about 10^{-12} M, when measured by binding to antigen either immobilized on solid phase or in solution phase.

[0038] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As described below, the antibodies are characterized and selected for desirable characteristics, including binding affinity to hIL-6R, ability to block hIL-6, and/or selectivity for the human protein. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG4 or IgG1 (for example, SEQ ID NO:242, 243, 244). While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Epitope Mapping and Related Technologies

[0039] To screen for antibodies which bind to a particular epitope, a routine cross-blocking assay such as that described in Antibodies: A Laboratory Manual 1988 Cold Spring Harbor Laboratory, Harlow and Lane, eds., can be performed. Other methods include alanine scanning mutants, peptide blots (Reineke (2004) Methods Mol Biol 248:443-63), or peptide cleavage analysis as described in the examples below. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000)

Protein Science: 9: 487-496).

[0040] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US Patent Application Publication No. 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with an epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones with desired characteristics. MAP may be used to sort the hIL-6R antibodies of the invention into groups of antibodies binding different epitopes.

[0041] Agents useful for altering the structure of the immobilized antigen are enzymes, such as, for example proteolytic enzymes and chemical agents. The antigen protein may be immobilized on either biosensor chip surfaces or polystyrene beads. The latter can be processed with, for example, an assay such as a multiplex Luminex™ detection assay (Luminex Corp., TX). Because of the capacity of Luminex™ to handle multiplex analysis with up to 100 different types of beads, Luminex™ provides almost unlimited antigen surfaces with various modifications, resulting in improved resolution in antibody epitope profiling over a biosensor assay.

Therapeutic Administration and Formulations

[0042] The administration of therapeutic entities in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

EXAMPLES

[0043] 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 methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to Human IL-6 Receptor.

[0044] Immunization of rodents can be done by any methods known in the art (see, for example, Harlow and Lane (1988) *supra*; Malik and Lillehoj, Antibody techniques: Academic Press, 1994, CA). In a preferred embodiment, hIL-6R antigen is administered directly to mice which comprise DNA loci encoding both human Ig heavy chain variable region and Kappa light chain variable region (VelocImmune™, Regeneron Pharmaceuticals, Inc.; US 6,596,541), with an adjuvant to stimulate the immune response. Such an adjuvant includes complete and incomplete Freund's adjuvant, MPL+TDM adjuvant system (Sigma), or RIBI (muramyl dipeptides) (see O'Hagan, Vaccine Adjuvant, by Human Press, 2000, NJ). Such an adjuvant can prevent rapid dispersal of polypeptide by sequestering the antigen in a local depot, and may contain factors that can stimulate host immune response. In one embodiment, hIL-6R is administered indirectly as DNA plasmid that contains hIL-6R gene and expresses hIL-6R using the host cellular protein expression machinery to produce antigen polypeptide *in vivo*. In both approaches, the immunization schedule requires several administrations spaced by a few weeks. The antibody immune response is monitored by standard antigen-specific immunoassay. When animals reached their maximum immune response, the antibody expressing B cells were harvested and fused with mouse myeloma cells to preserve their viability, forming hybridoma cells. To select functionally desirable monoclonal antibodies, conditioned media of the hybridoma cells or transfected cells were screened for specificity, antigen-binding affinity, and potency in blocking hIL-6 binding to hIL-6R (described below).

Example 2. Anti-hIL6R antibodies generated via direct isolation of splenocytes

[0045] DNA encoding VH and VL domains may be isolated directly from a single antigen positive B cell. Briefly, the hIL-6Rα immunized transgenic mouse was terminated and splenocytes were harvested. Red blood cells were removed by lysis followed by pelleting the harvested splenocytes. Resuspended splenocytes were first incubated with a cocktail of human IgG, FITC-anti-mFc, and biotin-IL6Ra for 1 hour. The stained cells were washed twice with PBS, then stained with a cocktail of human and rat IgG, APC-anti-mIgM, and SA-PE for one hour. The

stained cells were washed once with PBS and were analyzed by flow cytometry on a MoFlo (Cytomation). Each IgG positive, IgM negative, and antigen positive B cell was sorted and plated into a separate well on a 96-well plate. RT-PCR of antibody genes from these B cells was performed according to a method described by Wang et al. (2000) (J Immunol Methods 244:217–225). Briefly, cDNAs for each single B cell were synthesized via RT-PCR. Each resulting RT product was then split and transferred into two corresponding wells on two 96-well plates. One set of the resulting RT products was first amplified by PCR using a 5' degenerate primer specific for human IgG heavy chain variable region leader sequence and a 3' primer specific for mouse heavy chain constant region, to form an amplicon. The amplicon was then amplified again by PCR using a 5' degenerate primer set specific for framework 1 of human IgG heavy chain variable region sequence and a nested 3' primer specific for mouse heavy chain constant region. The other set of the resulting RT products was first amplified by PCR using a 5' degenerate primer specific for human kappa light chain variable region leader sequence and a 3' primer specific for mouse kappa light chain constant region to form an amplicon. The amplicon was then amplified again by PCR using a 5' degenerate primer set specific for framework 1 of human kappa light chain variable region sequence and a nested 3' primer specific for mouse kappa light chain constant region. The heavy chain and light chain PCR products were cloned into Sap I-linearized antibody vectors containing IgG1 heavy chain constant region and kappa light chain constant region, respectively. The heavy chain plasmid has a lox2272 site and a lox511 site flanking the heavy chain expression cassettes. In addition, immediately downstream of the lox2272 in the heavy chain plasmid there is a hygromycin-resistance gene that lacks a promoter and an initiating ATG. The hygromycin-resistance gene is also transcriptionally linked to a downstream eGFP gene via an IRES sequence. The light chain plasmid has a loxP site and lox2272 site flanking the light chain expression cassette. In addition, The light chain plasmid has a SV40 promoter immediately before an ATG at the lox2272 site, such that upon integration into an appropriate host cell the lox2272-proximal SV40 promoter and initiating ATG from the light chain plasmid is brought adjacent to the hygromycin-resistance gene in the heavy chain plasmid in the proper reading frame to allow transcription and translation of the hygromycin-resistance and eGFP genes. Purified recombinant plasmids having a heavy chain variable region sequence and plasmids having a light chain variable region sequence from the same B cell were then combined and transfected, together with a plasmid that expresses the Cre recombinase, into a modified CHO host cell line. The modified CHO host cell line contains, from 5' to 3', a loxP site, an eCFP, a lox2272 site, DsRed, and a lox511 site at a transcriptionally active locus. Consequently, the host CHO cell can be isolated by flow cytometry as a blue-positive, red-positive, and green-negative cell. When recombinant plasmids expressing heavy chain and light chain genes are transfected together with a plasmid expressing the Cre recombinase, site-specific recombination mediated by the Cre recombinase results in the integration of the antibody plasmids at the chromosomal locus containing the lox

sites and replacement of the eCFP and DsRed genes. Recombinants can then be isolated as blue-negative, red-negative, and green-positive cells by flow cytometry. Accordingly, CHO cells transfected with recombinant plasmids having a heavy chain variable region sequence and plasmids having a light chain variable region sequence from the same B cell were sorted by flow cytometry, and proper recombinants that show the blue-negative, red-negative, and green-positive phenotype were isolated, and stable recombinant antibody-expressing CHO cell lines were established from isolated clones.

Example 3. Antigen Binding Affinity Determination

[0046] The K_D of the antigen binding to the selected antibodies described above were determined by surface kinetics on a real-time biosensor surface plasmon resonance assay (BIAcore™). More specifically, the affinity of the antibodies for human IL-6R was measured using a BIAcore® 2000 or BIAcore® 3000. The antibody was captured on an anti-mouse IgG surface and exposed to various concentrations of recombinant hIL-6R protein either in monomeric or dimeric form. Kinetic analysis using BIAevaluation™ software was performed to obtain the association and dissociation rate constants.

[0047] Binding affinities of the antibodies to hIL-6R was also measured for either hybridoma-conditioned media or purified proteins by plate-based competition immunoassay. The antibody proteins were purified using Protein G affinity chromatography from hybridoma cell conditioning medium that was bovine IgG-depleted (Invitrogen). For the competition ELISA, briefly, constant amounts of antibody at different levels were premixed with serial dilutions of antigen protein, hIL-6R-hFc, ranging from 0 to 10 μg/ml, and incubated for two hours at room temperature to reach pseudo-binding equilibrium between the antibody and antigen. These solutions were then transferred to 96-well hIL-6R-hFc pre-coated plates to allow the free-antibody in the mixtures to bind to plate-coated hIL-6R-hFc. The plates were typically coated with 1 to 2 μg/ml hIL-6R-hFc protein in PBS solution overnight at 4°C followed by BSA nonspecific blocking. After washing off excess antibody in solution, plate-bound antibodies were detected with an HRP-conjugated goat anti-mouse IgG or IgA polyclonal antibody reagent and developed using either colorimetric or chemiluminescence substrates. The dependency of the signals on the concentrations of antigen in solution was analyzed with a 4-parameter fit analysis using Prism™ software (Graph Pad) and reported as IC_{50}. Competition immunoassay were also carried out using steady state solution phase Kinexa™ instrument (Sapidyne Inc.).

[0048] Results are shown in Table 1 (control: humanized monoclonal antibody to human IL-6R (U.S. Patent No. 5,817,790 SEQ ID NO:69 and 71). Antibody (HCVR and LCVR amino acid sequences): VQ8A9-6 (3, 11); VQ8F11-21 (19, 27); VV7G4-1 (35, 43); VV7G4-10 (51, 59) VV6C10-1 (67, 75); VV6C10-3 (83, 91); VV6C10-4 (99, 107); VV6F12-11 (115, 123); VV9A6-11 (131, 139); VV6A9-5 (147, 155), VV3D8-4 (163, 171); VV1G4-7 (179, 187); 248982-13-1-E5 (195, 203); 248982-13-2-A9 (211, 219). Monomer and dimer K_D determined by BIAcore™;

solution K_D by Kinexa™; IC_{50} by ELISA assays (n.d. = not determined).

Table 1. Antigen Binding Affinity

Antibody	K_D Monomer (nM)	K_D Dimer (nM)	Solution K_D Monomer (nM)	ELISA IC_{50} Dimer (nM)
VQ8A9-6	0.222	0.101	0.120	0.004
VQ8F11-21	0.067	0.023	0.009	0.008
VV3D8-4	2.410	0.172	1.910	0.013
VV6A9-5	0.097	0.146	0.032	0.005
VV1G4-7	0.225	0.070	0.197	0.041
VV6C10-1	0.267	0.032	2.050	0.010
VV6F12-11	n.d.	n.d	n.d	0.033
VV7G4-10	n.d.	n.d.	n.d.	1.980
VV9A6-11	n.d.	n.d.	n.d.	0.347
VV6C10-3	n.d.	n.d.	n.d.	0.009
248982-13-1-E5	0.987	0.785	n.d.	0.360
248982-13-2-A9	2.870	n.d.	n.d.	0.054
Control	1.790	n.d.	1.960	n.d.

Example 4. Neutralization of hIL-6 Activity

[0049] hIL-6 blocking activities of the anti-hIL-6R antibodies of the invention were screened by hIL-6 blocking immunoassays, *in vitro* hIL-6 dependent cell growth bioassays, and surface plasmon resonance (BIAcore™). The immunoassay was used to screen ability of the tested antibody to block hIL-6 binding to hIL-6R, and the *in vitro* bioassay was used to determine the potency of the antibodies in neutralizing hIL-6R-mediated cellular signal transduction.

[0050] For the immunoassay, hIL-6 recombinant protein was coated on a 96-well plate in PBS buffer overnight at 4°C. This plate was used to capture free hIL-6R-hFc from antibody sample solutions, and the amount of captured hIL-6R-hFc was quantified according to the standard curve. The sample solutions were composed of a constant amount of hIL-6R-hFc recombinant protein (100 pM) and varying amounts of antibody, either in crude hybridoma condition medium or as purified antibody protein, ranging from 0 to about 50 nM in serial dilutions. The antibody-antigen mixtures were incubated at room temperature for ~2 hours to allow antibody-antigen binding to reach equilibrium. The equilibrated sample solutions were then transferred to the hIL-6 coated plates for measurement of free hIL-6R-hFc. After 1 hour binding, the plate was washed and bound hIL-6R-hFc was detected using HRP-conjugated goat anti-hFc polyclonal antibodies (Jackson Immuno Research), and developed using TMB substrate (BD Pharmigen). IC_{50}s were determined as the amount of antibody required to reduce 50% of IL-6R-hFc detectable to plate bound hIL-6 ligand. Results are shown in the first column of Table 2.

[0051] Additionally, the ability of the test antibody to block hIL-6 binding to the hIL-6R receptor was determined using surface plasmon resonance. Purified antigen hIL-6R-hFc molecules were captured by goat anti-human IgG polyclonal antibodies immobilized on CM-5 surface through amine coupling to a density of 250 RU. hIL-6 solution (0.25ml, 50 nM) was injected over the receptor surface and bound hIL-6 recorded (first injection of IL-6). Bound hIL-6 was then removed with a pulse of 3 M $MgCl_2$ following by conditioning buffer. Anti-hIL6R antibody in hybridoma conditioned medium was injected over the captured receptor surface followed by second injection of hIL-6. The percent reduction in hL-6 binding resulting from preformed antibody and receptor complex was used as a score to define hIL-6 blockers from non-blockers (second column, Table 2).

Table 2. *Neutralization of hIL-6 Binding*

Antibody	hIL6R/hIL6 Binding Inhibition IC_{50} (nM)	hIL6/hIL6R Binding Inhibition (%)	XG-1 cell proliferation Inhibition IC_{50} (nM)	HepG2/Stat3 Luciferase activity IC_{50} (nM)
VQ8A9-6	0.39	68	0.40	0.097
VQ8F11-21	0.12	98	0.62	0.135
VV3D8-4	0.61	93	>100	n.d.
VV6A9-5	0.35	100	1.10	0.188
VV1G4-7	1.10	34	1.80	0.578
VV6C10-1	4.60	61	>6.90	n.d.
VV6F12-11	2.20	n.d.	n.d.	n.d.
VV7G4-10	13.00	n.d.	n.d.	n.d.
VV9A6-11	0.50	n.d.	n.d.	n.d.
VV6C10-3	0.06	n.d.	n.d.	n.d.
Control	2.20	91	1.50	0.854

[0052] The ability of hIL-6R antibodies to block hIL-6 activity *in vitro* was measured in the hIL-6-dependent myeloma line XG-1. XG-1 cells maintained in hIL-6-containing medium were washed twice with hIL-6-free media and cultured for ~24 hours in hIL-6-free medium to deplete residual hIL-6. The starved cells were then spun down and re-suspended in the medium at 4 x 10^5 cells per ml and plated 20,000 cells per well in a 96-well tissue culture plate. The purified antibody proteins were serially diluted in medium and added to the plated cells at concentrations ranging from 0 to 50 nM. Subsequently, recombinant hIL-6 was added to the wells to a final concentration of 8 pM. Cells were allowed to grow for ~72 hours at 37°C in a humidified 5% CO_2 incubator. At the end of growth period, live cells were measured using CCK-8 kit (Dojindo, Japan). IC_{50}s were determined as described above, and reported in the third column of Table 2.

[0053] The ability of hIL-6R antibodies to block hIL-6 activity was also measured *in vitro* in the

hIL-6-responsive human hepatoma cell line, HepG2. HepG2 cells were transfected with a reporter plasmid containing a STAT3 (Signal Transducer and activator of Transcription 3) response element linked to a luciferase gene. The transfected cells were trypsinized, spun down and re-suspended in the medium at approximately 2.5 x 10^5 cells per ml and plated at 20,000 cells per well in a 96-well tissue culture plate. The purified antibody proteins were serially diluted in medium and added to the plated cells at concentrations ranging from 0 to 100 nM. Subsequently, recombinant hIL-6 was added to the wells to a final concentration of 50 pM. The response was measured after incubating the cells for 6 hours at 37°C in a humidified 5% CO_2 incubator. Luciferase activity was measured with the Steady-Glo™ luciferase assay system (Promega). IC_{50}s were determined as described above, and reported in the fourth column of Table 2.

Example 5. Binding Epitope Diversity

[0054] An antibody binding competition immunoassay was performed using as a control humanized antibody to human IL-6R. Briefly, a 96-well immunosorbent plate was coated with 20 ng per well hIL-6R recombinant protein overnight at 4°C. After blocking non-specific binding with BSA, the hIL-6R binding sites on one half of the plate were saturated with binding of the control antibody by addition of 500 ng of the control per well, and to the other half of the plate was added binding buffer only. After three hours binding at room temperature, the purified antibodies were spiked in at a final concentration of 50 ng/ml with and without the preexisting control antibody in the well. After one hour of additional binding, the free antibody was washed away and the plate-bound antibody was detected with HRP-conjugated goat anti-mouse IgG or IgA, polyclonal antibody and the plate was developed using chromatic HRP substrates and absorbance at 450 nm was recorded. Percentage deductions of the binding of the anti-hIL6R antibodies by the presence of the control antibody are listed in Table 3 below. A similar experiment was conducted using surface plasmon resonance technology (Table 3). Both methods generated consistent results. Antibodies VQ8F11, VV3D8, VV6A9, VV6C10-1 bound epitopes overlapping with the control antibody; while antibodies VQ8A9, VV1G4, VV6F12, VV7G4, VV9A6, and VV6C10-3 appeared to bind distinct epitopes as antigen binding was not blocked by the control antibody. Partial competition may result from steric hindrance from the first antibody bound, even though epitopes may not be overlapping.

Table 3. Competition of Antigen Binding with Control Antibody

Antibody	BIAcore™ (% reduction)	Immunoassay (% reduction)
VQ8A9-6	26	3
VQ8F11-21	96	79
VV3D8-4	97	84

VV6A9-5	96	84
VV1G4-7	12	3
VV6C10-1	90	80
VV6F12-11	n.d.	3
VV7G4-10	n.d.	26
VV9A6-11	n.d.	18
VV6C10-3	n.d.	1

Example 6. Cross-species Binding Property

[0055] Four antibodies were tested for cross-reactivity to monkey IL-6R recombinant protein using BIAcore™ technology. Briefly, a biosensor chip on which goat anti-mouse Fc polyclonal antibody was immobilized was used to present anti-hIL-6R monoclonal antibodies to a density of about 75 RU. Recombinant human or monkey monomeric IL-6R protein (*Macaca fascicularis*, extracellular domain; SEQ ID NO:251), at a concentration range between 1.25 – 40 nM, was injected over the antibody surface. The binding of the receptor to the antibody and the dissociation of the bound complex were monitored in real-time. Both association rate constant (ka) and dissociate rate constant (kd) were obtained, and K_D calculated (Table 4).

Table 4. Comparison of Binding Affinity to Human and Monkey IL-6R

Antibody	Antigen	ka ($M^{-1}S^{-1}$)	kd (S^{-1})	K_D (nM)
Control	Human IL6R	1.74E+05	1.67E-04	0.963
	Monkey IL6R	1.44E+05	1.68E-04	1.170
VQ8F11-21	Human IL6R	8.51E+05	4.38E-05	0.051
	monkey IL6R	3.39E+05	4.86E-05	0.143
VV1G4-7	Human IL6R	2.57E+05	6.18E-05	0.240
	monkey IL6R	no binding		
VV6A9-5	Human IL6R	5.18E+05	8.41E-05	0.162
	monkey IL6R	5.00E+05	7.70E-05	0.154
VQ8A9-6	Human IL6R	7.32E+05	2.76E-04	0.377
	monkey IL6R	7.31E+05	4.16E-04	0.569

[0056] Among the four tested antibodies, VQ8F11, VV6A9, and VQ8A9 strongly reacted to monkey receptor with K_D values that differed by up to about 1.5- to about 3-fold from human receptor binding, respectively. VV1G4, which was not blocked by the control antibody (Table 3), showed no binding to monkey receptor despite strong binding to the human receptor with K_D of 241 pM.

Example 7. Effect of Constant Region on Binding Affinity

[0057] The binding affinity to monomeric hIL-6R of four antibodies having mouse IgG, human IgG1 or human IgG4 (wild-type and modified) were determined using BIAcore™ as described above except a goat anti-human Fc polyclonal antibody surface was used to capture hIgG antibodies. Monomeric hIL-6R was injected at concentrations of 12.5, 6.25, 3.12, and 1.56 nM. The ability of the antibodies to neutralize hIL-6-dependent HepG2/STAT3 signal transduction was also determined in a luciferase assay (IC_{50}). IC_{50}s for different IgG isotypes were similar, suggesting no effect of isotype on antibody affinity for antigen.

Table 5. Comparison of IgG Isotypes

Antibody	IgG	ka ($M^{-1}S^{-1}$)	kd (S^{-1})	K_D (nM)	IC_{50} (nM)
VQ8F11-21	hIgG1	6.22E+05	4.54E-05	0.073	0.150
	hIgG4	7.17E+05	5.22E-05	0.073	0.228
	mIgG2a	7.86E+05	5.27E-05	0.067	0.135
	modhIgG4	8.81E+05	4.705-05	0.053	0.249
VQ8A9-6	hIgG1	1.09E+06	2.60E-04	0.238	0.130
	hIgG4	1.17E+06	2.35E-04	0.201	0.185
	mIgG1	9.95E+05	2.21E-04	0.222	0.097
VV6A9-5	hIgG1	7.12E+05	8.87E-05	0.125	0.204
	hIgG4	5.67E+05	7.64E-05	0.135	0.343
	mIgG2a	7.72E+05	7.52E-05	0.097	0.188
VQ1G4-21	hIgG1	3.34E+05	7.92E-05	0.237	0.767
	hIgG4	2.73E+05	9.18E-05	0.336	0.528
	mIgG2a	3.41E+05	7.66E-05	0.225	0.578

CLAIMS

1. An antibody or antigen-binding fragment thereof, which specifically binds human interleukin-6 receptor (hIL-6R), comprising a heavy chain CDR1 domain comprising SEQ ID NO: 21, a heavy chain CDR2 domain comprising SEQ ID NO: 23, a heavy chain CDR3 domain comprising SEQ ID NO: 25, a light chain CDR1 domain comprising SEQ ID NO: 29, a light chain CDR2 domain comprising SEQ ID NO: 31, and a light chain CDR3 domain comprising SEQ ID NO:33.

2. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 1 and a pharmaceutically acceptable carrier.

3. The antibody or antigen-binding fragment of claim 1, comprising a heavy chain variable region (HCVR) of SEQ ID NO:19.

4. The antibody or antigen-binding fragment of claim 1, comprising a light chain variable region (LCVR) of SEQ ID NO: 27.

5. An antibody or antigen-binding fragment thereof, which specifically binds human interleukin-6 receptor (hIL-6R), comprising a heavy chain variable region (HCVR) comprising SEQ ID NO:19, and a light chain variable region (LCVR) comprising SEQ ID NO: 27.

6. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 5 and a pharmaceutically acceptable carrier.

7. An antibody or antigen-binding fragment thereof, which specifically binds human interleukin-6 receptor (hIL-6R), wherein the antibody or antigen-binding fragment comprises a heavy and a light chain, each comprising CDR1, CDR2 and CDR3 domains, and wherein the heavy chain comprises SEQ ID NO:19 and the light chain comprises SEQ ID NO:27.

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aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tatagtagct ggcctccgta cacttttggc 300
caggggacca agctggagat caaac 325

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<220>
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<400> 11
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1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30
Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ser Trp Pro Pro
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 12
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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 12
cagagtatta gcagcaac 18

<210> 13
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 13
Gln Ser Ile Ser Ser Asn
1 5

<210> 14
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 14
ggtgcatcc 9

<210> 15
<211> 3
<212> PRT
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<220>
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<400> 15
Gly Ala Ser
1

<210> 16
<211> 30
<212> DNA
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<220>
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<400> 16
cagcagtata gtagctggcc tccgtacact 30

<210> 17
<211> 10
<212> PRT
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<220>
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<400> 17
Gln Gln Tyr Ser Ser Trp Pro Pro Tyr Thr
1 5 10

<210> 18
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<212> DNA
<213> Artificial Sequence

<220>
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<400> 18
gaagtgcagc tggtggagtc tgggggaggc ttggttcagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctagatt tacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag aataggttat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccgagaa ctccctcttt 240
ctgcaaatga acggtctgag agcagaggac acggccttgt attactgtgc aaaaggccga 300
gattcttttg atatctgggg ccaagggaca atggtcaccg tctcttcag 349

<210> 19
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 19
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Asp Ser Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110
Thr Val Ser Ser
115

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<211> 24
<212> DNA
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<220>
<223> Synthetic

<400> 20
agatttacct ttgatgatta tgcc 24

<210> 21
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 21
Arg Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 22
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<212> DNA
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<220>
<223> Synthetic

<400> 22
attagttgga atagtggtag aata 24

<210> 23
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 23
Ile Ser Trp Asn Ser Gly Arg Ile
1 5

<210> 24
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 24
gcaaaaggcc gagattcttt tgatatc 27

<210> 25
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 25
Ala Lys Gly Arg Asp Ser Phe Asp Ile
1 5

<210> 26
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
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<400> 26
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gggaaagccc ctaagctcct gatctatggt gcatccagtt tggaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caagttatta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 27
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 27
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Ser Leu Glu 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 Gln Pro
65 70 75 80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 28
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 28
cagggtatta gcagctgg 18

<210> 29
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29
Gln Gly Ile Ser Ser Trp
1 5

<210> 30
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 30
ggtgcatcc 9

<210> 31
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31
Gly Ala Ser
1

<210> 32
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32
caacaggcta acagtttccc gtacact 27

<210> 33
<211> 9
<212> PRT
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<220>
<223> Synthetic

<400> 33
Gln Gln Ala Asn Ser Phe Pro Tyr Thr
1 5

<210> 34
<211> 370
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 34
caggttcagc tggtgcagtc tggagctgag ctgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacttttacc cattatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgatga cacaaactat 180
gcacagaagt tccaggggag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgttt attactgtgc gagagaagcg 300
cagctcgtcc tctactacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctcag 370

<210> 35
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

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

<210> 36
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36
ggttacactt ttacccatta tggt 24

<210> 37
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 37
Gly Tyr Thr Phe Thr His Tyr Gly
1 5

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38
atcagcgctt acaatgatga caca 24

<210> 39
<211> 8
<212> PRT
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<220>
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<400> 39
Ile Ser Ala Tyr Asn Asp Asp Thr
1 5

<210> 40
<211> 48
<212> DNA
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<220>
<223> Synthetic

<400> 40
gcgagagaag cgcagctcgt cctctactac tactacggta tggacgtc 48

<210> 41
<211> 16
<212> PRT
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<220>
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<400> 41
Ala Arg Glu Ala Gln Leu Val Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 42
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcttcttag cctggaacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgccagcag cgtaacaatt ggccgtacat ttttggccag 300
gggaccaagc tggagatcag ac 322

<210> 43
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Phe
20 25 30
Leu Ala Trp Asn Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Tyr
85 90 95
Ile Phe Gly Gln Gly Thr Lys Leu Glu Ile Arg
100 105

<210> 44
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44

cagagtgtta gcagcttc 18

<210> 45
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
Gln Ser Val Ser Ser Phe
1 5

<210> 46
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46
gatgcatcc 9

<210> 47
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
Asp Ala Ser
1

<210> 48
<211> 27
<212> DNA
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<220>
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<400> 48
cagcagcgta acaattggcc gtacatt 27

<210> 49
<211> 9
<212> PRT
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<220>
<223> Synthetic

<400> 49
Gln Gln Arg Asn Asn Trp Pro Tyr Ile
1 5

<210> 50

<211> 370
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50
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tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgatga cacaaactat 180
gcacagaagt tccaggggag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgttt attactgtgc gagagaagcg 300
cagctcgtcc tctactacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctcag 370

<210> 51
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Ala Tyr Asn Asp Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ala Gln Leu Val Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 52
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52
ggttacacct ttaccagtta tggt 24

<210> 53
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
Gly Tyr Thr Phe Thr Ser Tyr Gly

1 5

<210> 54
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54
atcagcgctt acaatgatga caca 24

<210> 55
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 55
Ile Ser Ala Tyr Asn Asp Asp Thr
1 5

<210> 56
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
gcgagagaag cgcagctcgt cctctactac tactacggta tggacgtc 48

<210> 57
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57
Ala Arg Glu Ala Gln Leu Val Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 58
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58
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ctctcctgca gggccagtca gagtgttagc agcttcttag cctggaacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgccagcag cgtagcaatt ggccgtacat ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 59
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Phe
20 25 30
Leu Ala Trp Asn Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Tyr
85 90 95
Ile Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 60
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 60
cagagtgtta gcagcttc 18

<210> 61
<211> 6
<212> PRT
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<220>
<223> Synthetic

<400> 61
Gln Ser Val Ser Ser Phe
1 5

<210> 62
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62
gatgcatcc 9

<210> 63

<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
Asp Ala Ser
1

<210> 64
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64
cagcagcgta gcaattggcc gtacatt 27

<210> 65
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
Gln Gln Arg Ser Asn Trp Pro Tyr Ile
1 5

<210> 66
<211> 349
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgccc tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt gttagttgga atggtggtag aataggctat 180
gcggactctg tgaaaggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
ctgcaaatga acagtctgag agttgaggac acggccttgt attattgtgc aaaaggccgg 300
gatgcttttg atatctgggg ccaagggaca ttggtcaccg tctcttcag 349

<210> 67
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr

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            20                  25                  30
Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Val Ser Trp Asn Gly Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser
        115
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<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
ggattcacct ttgatgatta tgcc 24

<210> 69
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69
Gly Phe Thr Phe Asp Asp Tyr Ala
 1   5

<210> 70
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 70
gttagttgga atggtggtag aata 24

<210> 71
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71
Val Ser Trp Asn Gly Gly Arg Ile
 1   5

<210> 72

<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 72
gcaaaaggcc gggatgcttt tgatatc 27

<210> 73
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73
Ala Lys Gly Arg Asp Ala Phe Asp Ile
1 5

<210> 74
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agttacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cattttatta ctgtcagcag cgtaacaacc ggcctccatt cactttcggc 300
cctgggacca aagtggatgt cagac 325

<210> 75
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 76
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76
cagagtgtta gcagttac 18

<210> 77
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
Gln Ser Val Ser Ser Tyr
1 5

<210> 78
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
gatgcatcc 9

<210> 79
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
Asp Ala Ser
1

<210> 80
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
cagcagcgta acaaccggcc tccattcact 30

<210> 81
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
Gln Gln Arg Asn Asn Arg Pro Pro Phe Thr
1 5 10

<210> 82
<211> 370
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82
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tcctgtaagg cttctggttt caacttcttt cattatggta tcacctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcactt acaatggtga cacaatctat 180
gcacagaagg tccagggcag agtcaccatg accacagaca cagccacgag cacggcctat 240
atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagatcggaa 300
cagcaggtgg actactactt ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtttcctcag 370

<210> 83
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Phe Phe His Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Thr Tyr Asn Gly Asp Thr Ile Tyr Ala Gln Lys Val
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ala Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Glu Gln Gln Val Asp Tyr Tyr Phe Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 84
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84
ggtttcaact tctttcatta tggt 24

<210> 85

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85
Gly Phe Asn Phe Phe His Tyr Gly
1 5

<210> 86
<211> 24
<212> DNA
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<220>
<223> Synthetic

<400> 86
atcagcactt acaatggtga caca 24

<210> 87
<211> 8
<212> PRT
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<220>
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<400> 87
Ile Ser Thr Tyr Asn Gly Asp Thr
1 5

<210> 88
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
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<400> 88
gcgagatcgg aacagcaggt ggactactac ttctacggta tggacgtc 48

<210> 89
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 89
Ala Arg Ser Glu Gln Gln Val Asp Tyr Tyr Phe Tyr Gly Met Asp Val
1 5 10 15

<210> 90
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
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<400> 90
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ctctcctgca gggccagtca gagtgttagc agttacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cattttatta ctgtcagcag cgtaacaacc ggcctccatt cactttcggc 300
cctgggacca aagtggatgt cagac 325

<210> 91
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 92
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92
cagagtgtta gcagttac 18

<210> 93
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93
Gln Ser Val Ser Ser Tyr
1 5

<210> 94
<211> 9
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94
gatgcatcc 9

<210> 95
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95
Asp Ala Ser
1

<210> 96
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96
cagcagcgta acaaccggcc tccattcact 30

<210> 97
<211> 10
<212> PRT
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<220>
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<400> 97
Gln Gln Arg Asn Asn Arg Pro Pro Phe Thr
1 5 10

<210> 98
<211> 370
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98
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tcctgtaagg cttctggttt caacttcttt cattatggta tcacctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcactt acaatggtga cacaatctat 180
gcacagaagg tccagggcag agtcaccatg accacagaca cagccacgag cacggcctat 240
atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagatcggaa 300
cagcaggtgg actactactt ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtttcctcag 370

<210> 99
<211> 123

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Phe Phe His Tyr
20 25 30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Thr Tyr Asn Gly Asp Thr Ile Tyr Ala Gln Lys Val
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ala Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Glu Gln Gln Val Asp Tyr Tyr Phe Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 100
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100
ggtttcaact tctttcatta tggt 24

<210> 101
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 101
Gly Phe Asn Phe Phe His Tyr Gly
1 5

<210> 102
<211> 24
<212> DNA
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<220>
<223> Synthetic

<400> 102
atcagcactt acaatggtga caca 24

<210> 103
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 103
Ile Ser Thr Tyr Asn Gly Asp Thr
1 5

<210> 104
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104
gcgagatcgg aacagcaggt ggactactac ttctacggta tggacgtc 48

<210> 105
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 105
Ala Arg Ser Glu Gln Gln Val Asp Tyr Tyr Phe Tyr Gly Met Asp Val
1 5 10 15

<210> 106
<211> 325
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 106
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ctctcctgca gggccagtca gagtgttagc agttacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cattttatta ctgtcagcag cgtaacaacc ggcctccatt cactttcggc 300
cctgggacca aagtggatgt cagac 325

<210> 107
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

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

<210> 108
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
cagagtgtta gcagttac 18

<210> 109
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
Gln Ser Val Ser Ser Tyr
1 5

<210> 110
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110
gatgcatcc 9

<210> 111
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 111
Asp Ala Ser
1

<210> 112
<211> 30
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 112
cagcagcgta acaaccggcc tccattcact 30

<210> 113
<211> 10
<212> PRT
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<220>
<223> Synthetic

<400> 113
Gln Gln Arg Asn Asn Arg Pro Pro Phe Thr
1 5 10

<210> 114
<211> 361
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114
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tcctgcaagg cttctggata caccttcacc tcttatgata tcatctgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccaa acagtggtga cagaggctat 180
acacagaacc tccagggcag agtcaccttg accagggaca cctccataag tacagtctac 240
atggaactga gcagcctgag atctgaggac acggccgtat attattgtgc gcgagactac 300
agtaaccact actacggttt ggacgtctgg ggccaaggga ccacggtcac tgtctcctca 360
g 361

<210> 115
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 116
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116
ggatacacct tcacctctta tgat 24

<210> 117
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117
Gly Tyr Thr Phe Thr Ser Tyr Asp
1 5

<210> 118
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 118
atgaacccaa acagtggtga caga 24

<210> 119
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119
Met Asn Pro Asn Ser Gly Asp Arg
1 5

<210> 120
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120
gcgcgagact acagtaacca ctactacggt ttggacgtc 39

<210> 121
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121
Ala Arg Asp Tyr Ser Asn His Tyr Tyr Gly Leu Asp Val
1 5 10

<210> 122
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122
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atcacttgct gggccagtca ggacattagc aattatttag cctggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctttgtt gcatccactt tgcagagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag tttaatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcag ac 322

<210> 123
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Phe Val Ala Ser Thr Leu Gln 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg
100 105

<210> 124
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124
caggacatta gcaattat 18

<210> 125
<211> 6
<212> PRT
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<220>

<223> Synthetic

<400> 125
Gln Asp Ile Ser Asn Tyr
1 5

<210> 126
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126
gttgcatcc 9

<210> 127
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127
Val Ala Ser
1

<210> 128
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128
caacagttta atagttaccc gctcactttc 30

<210> 129
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 129
Gln Gln Phe Asn Ser Tyr Pro Leu Thr
1 5

<210> 130
<211> 370
<212> DNA
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<220>
<223> Synthetic

<400> 130

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tcctgcaagg cttctggtta caccttacc agttatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgatga cacaaactat 180
gcacagaagt tccaggggag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgttt attactgtgc gagagaagcg 300
cagctcgtcc tctactacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctcag 370

<210> 131
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Ala Tyr Asn Asp Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Ala Gln Leu Val Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 132
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132
ggttacacct ttaccagtta tggt 24

<210> 133
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 133
Gly Tyr Thr Phe Thr Ser Tyr Gly
1 5

<210> 134
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 134
atcagcgctt acaatgatga caca 24

<210> 135
<211> 8
<212> PRT
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<220>
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<400> 135
Ile Ser Ala Tyr Asn Asp Asp Thr
1 5

<210> 136
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
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<400> 136
gcgagagaag cgcagctcgt cctctactac tactacggta tggacgtc 48

<210> 137
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 137
Ala Arg Glu Ala Gln Leu Val Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 138
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
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<400> 138
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ctctcctgca gggccagtca gagtgttagc agcttcttag cctggaacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgccagcag cgtagcaatt ggccgtacat ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 139
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Phe
20 25 30
Leu Ala Trp Asn Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Tyr
85 90 95
Ile Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 140
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 140
cagagtgtta gcagcttc 18

<210> 141
<211> 6
<212> PRT
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<220>
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<400> 141
Gln Ser Val Ser Ser Phe
1 5

<210> 142
<211> 9
<212> DNA
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<220>
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<400> 142
gatgcatcc 9

<210> 143
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143

Asp Ala Ser
1

<210> 144
<211> 27
<212> DNA
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<220>
<223> Synthetic

<400> 144
cagcagcgta gcaattggcc gtacatt 27

<210> 145
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 145
Gln Gln Arg Ser Asn Trp Pro Tyr Ile
1 5

<210> 146
<211> 349
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
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tcctgtgcag cctctggatt cacctttgat gattatgccc tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt gttagttgga atggtggtag aataggctat 180
gcggactctg tgaaaggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
ctgcaaatga acagtctgag agttgaggac acggccttgt attattgtgc aaaaggccgg 300
gatgcttttg atatctgggg ccaagggaca ttggtcaccg tctcttcag 349

<210> 147
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Val Ser Trp Asn Gly Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Leu Tyr Tyr Cys

85 90 95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 148
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148
ggattcacct ttgatgatta tgcc 24

<210> 149
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 149
Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 150
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150
gttagttgga atggtggtag aata 24

<210> 151
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151
Val Ser Trp Asn Gly Gly Arg Ile
1 5

<210> 152
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152

gcaaaaggcc gggatgcttt tgatatc 27

<210> 153
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 153
Ala Lys Gly Arg Asp Ala Phe Asp Ile
1 5

<210> 154
<211> 322
<212> DNA
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<220>
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<400> 154
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atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacat gcttacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 155
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 155
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln 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 Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ala Tyr Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 156
<211> 18
<212> DNA
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<220>
<223> Synthetic

<400> 156
cagggtatta gcagctgg 18

<210> 157
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157
Gln Gly Ile Ser Ser Trp
1 5

<210> 158
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 158
gctgcatcc 9

<210> 159
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159
Ala Ala Ser
1

<210> 160
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 160
caacatgctt acagtttccc gtacact 27

<210> 161
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 161
Gln His Ala Tyr Ser Phe Pro Tyr Thr
1 5

<210> 162
<211> 349
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcct tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga acagtggtag aataggctat 180
gcggactctg tgaagggccg attcaccatt tccagagaca acgccaagaa ctccctcttt 240
ctgcaaatga acagtctgag agctgaggac acggccttgt attattgtgc aaaaggccgg 300
gatgcttttg atatctgggg ccaagggaca ttggtcaccg tctcttcag 349

<210> 163
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 164
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164
ggattcacct ttgatgatta tgcc 24

<210> 165
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165
Gly Phe Thr Phe Asp Asp Tyr Ala

1 5

<210> 166
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166
attagttgga acagtggtag aata 24

<210> 167
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167
Ile Ser Trp Asn Ser Gly Arg Ile
1 5

<210> 168
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168
gcaaaaggcc gggatgcttt tgatatc 27

<210> 169
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169
Ala Lys Gly Arg Asp Ala Phe Asp Ile
1 5

<210> 170
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 170
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 171
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln 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 Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 172
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172
cagggtatta gcagctgg 18

<210> 173
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173
Gln Gly Ile Ser Ser Trp
1 5

<210> 174
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174
gctgcatcc 9

<210> 175

<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175
Ala Ala Ser
1

<210> 176
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 176
caacaggcta acagtttccc gtacact 27

<210> 177
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 177
Gln Gln Ala Asn Ser Phe Pro Tyr Thr
1 5

<210> 178
<211> 361
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178
caggtgcagc tggtgcagtc tggggctgag gtgaaagagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc tcttatgata tcatctgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccaa acagtggtaa cacaggctat 180
acacagaacc tccagggcag agtcaccttg accaggaaca cctccataac tacagtctac 240
atggaactga gcagcctgag ctctgaggac acggccgttt attactgtgc gcgagactac 300
agtagccact actacggttt ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360
a 361

<210> 179
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ala
1 5 10 15

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


<210> 180
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180
ggatacacct tcacctctta tgat                                          24

<210> 181
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181
Gly Tyr Thr Phe Thr Ser Tyr Asp
 1               5


<210> 182
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182
atgaacccaa acagtggtaa caca                                          24

<210> 183
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183
Met Asn Pro Asn Ser Gly Asn Thr
 1               5
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<210> 184
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184
gcgcgagact acagtagcca ctactacggt ttggacgtc 39

<210> 185
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185
Ala Arg Asp Tyr Ser Ser His Tyr Tyr Gly Leu Asp Val
1 5 10

<210> 186
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 186
gacatccagt tgacccagtc tccatccttc ctgtctacat ctataggaga cagagtcacc 60
atcacttgct gggccagtca ggacattagc aattatttag cctggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctttgtt gcatccactt tgcagagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
gaggattttg caacttatta ctgtcaacag tttaatagtt acccgctcac tttcggcgga 300
gggaccaagg tggaaatcaa ac 322

<210> 187
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Thr Ser Ile Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Phe Val Ala Ser Thr Leu Gln 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 188
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
caggacatta gcaattat 18

<210> 189
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
Gln Asp Ile Ser Asn Tyr
1 5

<210> 190
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
gttgcatcc 9

<210> 191
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191
Val Ala Ser
1

<210> 192
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 192
caacagttta atagttaccc gctcactttc 30

<210> 193
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 193
Gln Gln Phe Asn Ser Tyr Pro Leu Thr Phe
1 5 10

<210> 194
<211> 378
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194
caggtccagc tggtgcagtc tgggggagac ttggtacagc ccggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaaact 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggggc cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtac aaaagaagaa 300
gtgggagcta cggtggatta tttctacttc tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

<210> 195
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195
Gln Val Gln Leu Val Gln Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Ala Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Thr Lys Glu Glu Val Gly Ala Thr Val Asp Tyr Phe Tyr Phe Tyr Gly
100 105 110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 196
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196
ggattcacct ttgatgatta tgcc 24

<210> 197
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197
Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 198
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198
attagttgga atagtggggc cata 24

<210> 199
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199
Ile Ser Trp Asn Ser Gly Ala Ile
1 5

<210> 200
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200
acaaaagaag aagtgggagc tacggtggat tatttctact tctacggtat ggacgtc 57

<210> 201
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201
Thr Lys Glu Glu Val Gly Ala Thr Val Asp Tyr Phe Tyr Phe Tyr Gly
1 5 10 15
Met Asp Val

<210> 202

<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202
gaaattgtga tgactcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgct gggccagtca gagtgttagc aactacttag cctggtacca acagaaacct 120
ggccaggctc ccagactcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 203
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Trp Ala Ser Gln Ser Val Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
85 90 95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 204
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 204
cagagtgtta gcaactac 18

<210> 205
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205
Gln Ser Val Ser Asn Tyr
1 5

<210> 206
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206
gatgcatcc 9

<210> 207
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 207
Asp Ala Ser
1

<210> 208
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 208
cagcagcgta gcaactggcc tacg 24

<210> 209
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209
Gln Gln Arg Ser Asn Trp Pro Thr
1 5

<210> 210
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210
caagtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag ggtaggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtac aaaaggccgg 300
gatgcttttg atatctgggg ccaggggaca atggtcaccg tctcttca 348

<210> 211
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 212
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 212
ggattcacct ttgatgatta tgcc 24

<210> 213
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 213
Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 214
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214
attagttgga atagtggtag ggta 24

<210> 215

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215
Ile Ser Trp Asn Ser Gly Arg Val
1 5

<210> 216
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 216
acaaaaggcc gggatgcttt tgatatc 27

<210> 217
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 217
Thr Lys Gly Arg Asp Ala Phe Asp Ile
1 5

<210> 218
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 218
gatattgtga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 219
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 219
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp

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            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln 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 Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
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<210> 220
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 220
cagggtatta gcagctgg 18

<210> 221
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 221
Gln Gly Ile Ser Ser Trp
1 5

<210> 222
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 222
gctgcatcc 9

<210> 223
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 223
Ala Ala Ser
1

<210> 224
<211> 27
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 224
caacaggcta acagtttccc gtacact 27

<210> 225
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 225
Gln Gln Ala Asn Ser Phe Pro Tyr Thr
1 5

<210> 226
<211> 378
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 226
gaagtgcagc tggtggaatc tggaggagga ctggtgcagc ctggaagatc tctgagactg 60
tcttgtgctg cttctggatt tatctttgat gattatgcta tgcattgggt gagacaggct 120
cctggaaagg gactggaatg ggtgtctgga atctcttgga attctggatc tatcggatat 180
gctgattctg tgaagggaag atttacaatc tctagagata atgctaagaa ttctctgtat 240
ctgcagatga attctctgag agctgaagat acagctctgt attattgtgc taaggatgga 300
ggatcttctt ggctgccttt tgtgtattat tatggaatgg atgtgtgggg acagggaaca 360
acagtgacag tgtcttct 378

<210> 227
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 227
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Asp Gly Gly Ser Ser Trp Leu Pro Phe Val Tyr Tyr Tyr Gly
100 105 110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 228
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 228
gaaatcgtga tgacacagtc tcctgctaca ctgtctgtgt ctcctggaga aagagctaca 60
ctgtcttgta gagcttctca gtctatctct tctaatctgg cttggtatca gcagaagcct 120
ggacaggctc ctagactgct gatctatgga gcttctacaa gagctacagg aatccctgct 180
agattttctg gatctggatc tggaacagaa tttacactga caatctcttc tctgcagtct 240
gaagattttg ctgtgtatta ttgtcagcag tattcttctt ggcctcctta tacatttgga 300
cagggaacaa agctggaaat caag 324

<210> 229
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 229
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ser Trp Pro Pro
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 230
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 230
gaggtccagc tggtcgagtc aggaggaggc ctcgtccaac cagggcgcag ccttcgactc 60
tcctgtgccg ccagtaggtt tactttcgat gactatgcca tgcactgggt ccggcaggcc 120
cctggtaagg gcttggagtg ggtgtccggt atctcctgga actccggacg tatcggttac 180
gccgacagcg tgaagggaag gttcactatc tctcgtgaca acgccaagaa ctccttgtat 240
ctgcaaatga acagcctccg ggccgaagac accgccttgt attactgtgc caagggtagg 300
gatagtttcg atatctgggg tcaaggcacc atggtgactg tgtcttca 348

<210> 231
<211> 116
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 231
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Asp Ser Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110
Thr Val Ser Ser
115

<210> 232
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 232
gacatacaga tgacccaaag cccaagcagc gttagcgctt ccgtaggcga cagggtgaca 60
attacatgca gagcctctca gggaatttct tcatggctgg catggtatca gcagaagccc 120
ggaaaagctc ccaagctgct gatatatggt gcctcctctc tccaaagcgg agtcccatca 180
cgcttctccg ggagtggctc tggtacagat tttactttga caatctctag ccttcagcct 240
gaagactttg ctacatacta ctgtcagcag gccaacagtt ttccttacac cttcggtcag 300
ggaactaaac tggaaattaa g 321

<210> 233
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 233
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Ser Leu Glu 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 Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 234
<211> 360

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 234
caggtgcagc tggtgcagtc tggagctgaa gtgaagaagc ctggagcttc tgtgaaggtg 60
tcttgtaagg cttctggata tacatttaca tcttatgata tcatctgggt gagacaggct 120
acaggacagg gactggaatg gatgggatgg atgaatccta attctggaaa tacaggatat 180
gctcagaagt ttcagggaag agtgacaatg acaagaaata catctatctc tacagtgtat 240
atggaactgt cttctctgag atctgaagat acagctgtgt attattgtgc tagagattat 300
tcttctcatt attatggact ggatgtgtgg ggacagggaa caacagtgac agtgtcttct 360

<210> 235
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 235
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Ile Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Ser His Tyr Tyr Gly Leu Asp Val Trp Gly Gln
100 105 110
Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 236
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 236
gatatccagc tgacacagtc tccttctttt ctgtctgctt ctgtgggaga tagagtgaca 60
atcacatgta gagcttctca ggatatctct aattatctgg cttggtatca gcagaagcct 120
ggaaaggctc ctaagctgct gatctatgtg gcttctacac tgcagtctgg agtgccttct 180
agattttctg gatctggatc tggaacagaa tttacactga caatctcttc tctgcagcct 240
gaagattttg ctacatatta ttgtcagcag tttaattctt atcctctgac atttggagga 300
ggaacaaagg tggaaatcaa g 321

<210> 237
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 237
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Val Ala Ser Thr Leu Gln 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 238
<211> 349
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgccc tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt gttagttgga atggtggtag aataggctat 180
gcggactctg tgaaaggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
ctgcaaatga acagtctgag agttgaggac acggccttgt attattgtgc aaaaggccgg 300
gatgcttttg atatctgggg ccaagggaca ttggtcaccg tctcttcag 349

<210> 239
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 239
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Val Ser Trp Asn Gly Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110
Thr Val Ser Ser
115

<210> 240
<211> 348

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 240
gaagtgcagc tggtggaatc tggaggagga ctggtgcagc ctggaagatc tctgagactg 60
tcttgtgctg cttctggatt tacatttgat gattatgcta tgcattgggt gagacaggct 120
cctggaaagg gactggaatg ggtgtctgga gtgtcttgga atggaggaag aatcggatat 180
gctgattctg tgaagggaag atttacaatc tctagagata atgctaagaa ttctctgtat 240
ctgcagatga attctctgag agctgaagat acagctctgt attattgtgc taagggaaga 300
gatgcttttg atatctgggg acagggaaca atggtgacag tgtcttct 348

<210> 241
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 241
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Val Ser Trp Asn Gly Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110
Thr Val Ser Ser
115

<210> 242
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 242
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

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

<210> 243
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 243

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

```
        195                 200                 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320
Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 244
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 244

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1               5                  10                  15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
```

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320
Leu Ser Leu Ser Leu Gly Lys
325

<210> 245
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(8)
<223> Xaa = Any Amino Acid

<400> 245
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 246
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(8)
<223> Xaa = Any Amino Acid

<400> 246
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 247
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(19)
<223> Xaa = Any Amino Acid

<400> 247

```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5                  10                  15
Xaa Xaa Xaa
```

<210> 248
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(8)
<223> Xaa = Any Amino Acid

<400> 248
```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5
```

<210> 249
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(3)
<223> Xaa = Any Amino Acid

<400> 249
```
Xaa Xaa Xaa
 1
```

<210> 250
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(9)
<223> Xaa = Any Amino Acid

<400> 250
```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5
```

<210> 251
<211> 311
<212> PRT
<213> Macaca Fascicularis

<400> 251
Ala Pro Gly Gly Cys Pro Ala Gln Glu Val Ala Arg Gly Val Leu Thr
1 5 10 15
Ser Leu Pro Gly Asp Ser Val Thr Leu Thr Cys Pro Gly Gly Glu Pro
20 25 30
Glu Asp Asn Ala Thr Val His Trp Val Leu Arg Lys Pro Ala Val Gly
35 40 45
Ser His Leu Ser Arg Trp Ala Gly Val Gly Arg Arg Leu Leu Leu Arg
50 55 60
Ser Val Gln Leu His Asp Ser Gly Asn Tyr Ser Cys Tyr Arg Ala Gly
65 70 75 80
Arg Pro Ala Gly Thr Val His Leu Leu Val Asp Val Pro Pro Glu Glu
85 90 95
Pro Gln Leu Ser Cys Phe Arg Lys Ser Pro Leu Ser Asn Val Ala Cys
100 105 110
Glu Trp Gly Pro Arg Ser Thr Pro Ser Pro Thr Thr Lys Ala Val Leu
115 120 125
Leu Val Arg Lys Phe Gln Asn Ser Pro Ala Glu Asp Phe Gln Glu Pro
130 135 140
Cys Gln Tyr Ser Gln Glu Ser Gln Lys Phe Ser Cys Gln Leu Ala Val
145 150 155 160
Pro Glu Gly Asp Ser Ser Phe Tyr Ile Val Ser Met Cys Val Ala Ser
165 170 175
Ser Val Gly Ser Lys Leu Ser Lys Thr Gln Thr Phe Gln Gly Cys Gly
180 185 190
Ile Leu Gln Pro Asp Pro Pro Ala Asn Ile Thr Val Thr Ala Val Ala
195 200 205
Arg Asn Pro Arg Trp Leu Ser Val Thr Trp Gln Asp Pro His Ser Trp
210 215 220
Asn Ser Ser Phe Tyr Arg Leu Arg Phe Glu Leu Arg Tyr Arg Ala Glu
225 230 235 240
Arg Ser Lys Thr Phe Thr Thr Trp Met Val Lys Asp Leu Gln His His
245 250 255
Cys Val Ile His Asp Ala Trp Ser Gly Leu Arg His Val Val Gln Leu
260 265 270
Arg Ala Gln Glu Glu Phe Gly Gln Gly Glu Trp Ser Glu Trp Ser Pro
275 280 285
Glu Ala Met Gly Thr Pro Trp Thr Glu Ser Arg Ser Pro Pro Ala Glu
290 295 300
Asn Glu Val Ser Thr Pro Thr
305 310