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- (73) Patenthaver: **Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA**
- (72) Opfinder: **REINHARDT, Joel, C., 63 Moore Avenue, Mount Kisco, NY 10549, USA**
MORRA, Marc, R., 108 Foxton Court, Beacon Falls, CT 06403, USA
MARTIN, Joel, H., 244 Church Road, Putnam Valley, NY 10579, USA
MACDONALD, Lynn, 16 Gedney Way, White Plains, NY 10605, USA
TORRES, Richard, 344 West 72nd Street, Apt. 7h, New York, NY 10023, USA
- (74) Fuldmægtig i Danmark: **JESPER LEVIN A/S, Vedbæk Strandvej 341, 2950 Vedbæk, Danmark**
- (54) Benævnelse: **HØJAFFINE HUMANE ANTISTOFFER TIL HUMAN NERVEVÆKSTFAKTOR**
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Fortsættes ...

Description**Field of the invention**

- 5 **[0001]** The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind human nerve growth factor (NGF), and therapeutic methods of using those antibodies.

Statement of Related Art

- 10 **[0002]** Nerve growth factor (NGF) was the first neurotrophin to be identified, and its role in the development and survival of both peripheral and central neurons has been well characterized. NGF has been shown to be a critical survival and maintenance factor in the development of peripheral sympathetic and embryonic sensory neurons and of basal forebrain cholinergic neurons (Smeyne et al. (1994) Nature 368:246-249; Crowley et al. (1994) Cell 76:1001-1011). NGF upregulates expression of neuropeptides in sensory neurons (Lindsay et al. (1989) Nature 337:362-364) and its activity is
 15 mediated through two different membrane-bound receptors, the TrkA receptor and the p75 common neurotrophin receptor.
[0003] NGF is elevated in synovial fluid in patients suffering from rheumatoid arthritis and other types of arthritis. NGF antagonists have been shown to prevent hyperalgesia and allodynia in animal models of neuropathic and chronic inflammatory pain.
 20 **[0004]** Anti-NGF antibodies are described in, for example, WO 01/78698, WO 02/096458, WO 2004/032870, US patent publications 2005/0074821, 2004/0237124, and 2004/0219144.

BRIEF SUMMARY OF THE INVENTION

- 25 **[0005]** The invention relates to fully human antibodies and antigen-binding fragments thereof that specifically bind human nerve growth factor (NGF) with a K_D of 1 pM or less and do not cross-react with neurotrophin-3 (NT-3). These antibodies are characterized by binding to NGF with high affinity, high specificity and by the ability to neutralize NGF activity. In preferred embodiments, the antibody or fragment thereof binds human NGF about 2-10 fold higher than rat NGF and/or mouse NGF.
 30 **[0006]** 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 (Glu which eliminates residual effector functions (Reddy et al. (2000) J. Immunol. 164:1925-1933).
[0007] The invention therefore provides a human antibody or antigen-binding fragment of an antibody that specifically
 35 binds human nerve growth factor (NGF) with a K_D of 1 pM or less, as measured by surface plasmon resonance, wherein the antibody or antibody fragment comprises (a) a heavy chain complementarity determining region 3 (HCDR3) and a light chain CDR3 (LCDR3), wherein the HCDR3 and LCDR3 comprise the amino acid sequences set forth in SEQ ID NO:90 and 98, respectively, and (b) a HCDR1, HCDR2, LCDR1 and LCDR2, wherein the HCDR1 is SEQ ID NO:86, HCDR2 is SEQ ID NO:88, LCDR1 is SEQ ID NO:94 and LCDR2 is SEQ ID NO:96.
 40 **[0008]** In specific embodiments, the antibody or fragment thereof comprises a HCVR and LCVR (HCVR/LCVR) sequence pair of SEQ ID NO:108/110.
[0009] The invention also provides nucleic acid molecules encoding said anti-NGF antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the
 45 host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.
[0010] The invention features a fully human antibody or antibody fragment which blocks NGF activity with an IC_{50} of less than about 10 nM, as measured in *in vitro* PC12 cell-based assay (described below). In a preferred embodiment, the antibody of the invention exhibits an IC_{50} of about 500 pM or less; even more preferably, an IC_{50} of about 100 pM or less; about 50 pM or less; or about 25 pM or less.
 50 **[0011]** The invention provides an isolated human antibody, or an antigen-binding portion thereof, that binds NGF with a K_D of less than about 1 pM, as determined by surface plasmon resonance (BIAcore™). In a preferred embodiment, the anti-NGF human antibody or antibody fragment of the invention binds human NGF with a K_D of about 0.5 pM or less. The antibody or fragment thereof also preferably binds human NGF with about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold or 10-fold higher affinity than rat NGF and about 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold,
 55 9-fold, or 10-fold higher than mouse NGF.
[0012] In a preferred embodiment, the antibody or fragment thereof exhibits high specificity for human NGF, for example, does not cross-react with closely related neurotrophin-3 (NT-3). Thus, in a preferred embodiment, the high affinity and high selectivity antibody or fragment thereof exhibits a K_D for human NGF of 1.0 pM or less, inhibits binding of NGF to

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receptors TrkA and p75, and does not cross-react with human NT-3, as measured by surface plasmon resonance. NT-3 plays a critical role in such physiological processes as, for example, muscle motor neuron coordination, and thus, antibodies or antibody fragments that do not cross-react with NT-3 provide an unexpected clinical and therapeutic advantage over prior art antibodies. NT-3 has been shown to prevent the development of thermal hyperalgesia in the CCI model of neuropathic pain (see, for example, Wilson-Gerwing et al. (2005) J Neuroscience 25:758-767). More recently, exogenous NT-3 has been shown to significantly decrease expression of two sodium channels which appear to play a role in the generation of neuropathic pain (Wilson-Gerwing & Verge (2006) Neuroscience 141:2075-2085). These data suggest a beneficial role of NT-3 in neuropathic pain.

[0013] The invention encompasses anti-NGF antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0014] The invention features a composition comprising a recombinant human antibody or fragment thereof that specifically binds NGF and an acceptable carrier. In a related aspect, the invention features a composition that is a combination of an NGF inhibitor and a second therapeutic agent. In one embodiment, the NGF inhibitor is an antibody or fragment thereof. In a preferred embodiment, the second therapeutic agent is any suitable therapeutic agent that is advantageously combined with an NGF inhibitor.

[0015] The invention relates to inhibiting human NGF activity using the anti-NGF antibody or antigen-binding portion of the antibody of the invention. The disorder treated is any disease or condition that is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of NGF activity. More specifically, the invention relates to treating an NGF-mediated condition or disease such as inflammatory pain, post-operative incision pain, complex regional pain syndrome, primary or metastatic bone cancer pain, neuropathic pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pains associated with sickle cell crises, and other nociceptive pains, as well as hepatocellular carcinoma, breast cancer, and liver cirrhosis, by administering an NGF inhibitor, such as the antibody or antibody fragment of the invention, as a single agent, or with a second therapeutic agent. In preferred embodiments of neuropathic pain, referred trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, reflex sympathetic dystrophy and neurogenic pain conditions are preferably treated. The second therapeutic agent may be an interleukin-1 (IL-1) inhibitor, for example, a fusion protein such as that described in U.S. 6,927,044; or an antiepileptic drug, such as gabapentin, pregabalin, topiramate; or a tricyclic antidepressant, such as amitriptyline; celecoxib; a cytokine antagonist, such as an antagonist protein or antibody against IL-1, IL-6, IL-6R, IL-18 or IL-18R. The second therapeutic agent may be a neurotrophin, for example, NT-3.

[0016] The invention also provides an antibody or antigen-binding fragment as described above for use to attenuate or inhibit a NGF-mediated disease or condition in a human. The NGF-mediated condition or disease is inhibited without significant impairment of motor coordination, and is one of inflammatory pain, post-operative incision pain, neuropathic pain, fracture pain, gout joint pain, post-herpetic neuralgia, pain resulting from burns, cancer pain, osteoarthritis or rheumatoid arthritis pain, sciatica, pain associated with sickle cell crises, or post-herpetic neuralgia.

[0017] In a related aspect, the invention provides use of an antibody or antigen-binding fragment of an antibody as described above in the manufacture of a medicament for use to attenuate or inhibit an NGF-mediated disease or condition in a human as listed above.

[0018] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0019] 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.

[0020] 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.

Definitions

[0021] The term "human nerve growth factor" or "NGF", as used herein, refers to human NGF having the nucleic acid sequence shown in SEQ ID NO:1 and the amino acid sequence of SEQ ID NO:2, or a biologically active fragment thereof.

[0022] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypep-

ptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity 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.

[0023] 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., NGF). 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, CL 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 complementarity 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 protein 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. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak et al. (1994) Structure 2:1121-1123).

[0024] Still further, an antibody or antigen-binding portion thereof may be part of larger immunoadhesion molecules, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov et al. (1995) Human Antibodies and Hybridomas 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov et al. (1994) Mol. Immunol. 31:1047-1058). Antibody portions, such as Fab and F(ab')₂ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, antibodies, antibody portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques, as described herein.

[0025] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0026] The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0027] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds NGF is substantially free of antibodies that specifically bind antigens other than NGF). An isolated antibody that specifically binds NGF may, however, have cross-reactivity to other antigens, such as NGF molecules from other species. Moreover, an isolated

antibody may be substantially free of other cellular material and/or chemicals.

[0028] A "neutralizing antibody", as used herein (or an "antibody that neutralizes NGF activity"), is intended to refer to an antibody whose binding to NGF results in inhibition of the biological activity of NGF. This inhibition of the biological activity of NGF can be assessed by measuring one or more indicators of NGF biological activity, such as NGF-induced cellular activation and NGF binding to NGF receptor. These indicators of NGF biological activity can be assessed by one or more of several standard *in vitro* or *in vivo* assays known in the art (see examples below).

[0029] A "CDR" or complementarity determining region is a region of hypervariability interspersed with regions that are more conserved, termed "framework regions". A group of CDRs may be defined as an amino acid consensus sequence.

[0030] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[0031] The term " K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0032] The term "isolated nucleic acid molecule", as used herein in reference to nucleic acids encoding antibodies or antibody portions (e.g., VH, VL, CDR3) that bind NGF is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than NGF, which other sequences may naturally flank the nucleic acid in human genomic DNA. Thus, for example, an isolated nucleic acid of the invention encoding a VH region of an anti-NGF antibody contains no other sequences encoding other VH regions that bind antigens other than human NGF.

[0033] The term "epitope" includes any determinant, preferably a polypeptide determinant, capable of specific binding to an immunoglobulin or T-cell receptor. In certain embodiments, epitope determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. An epitope is a region of an antigen that is bound by an antibody. In certain embodiments, an antibody is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In preferred embodiments, an antibody is said to specifically bind an antigen when the equilibrium dissociation constant is less than or equal to 10^{-8} M, more preferably when the equilibrium dissociation constant is less than or equal to 10^{-9} M, and most preferably when the dissociation constant is less than or equal to 10^{-10} M.

[0034] 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 90%, and more preferably at least about 95%, 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.

[0035] 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 90% sequence identity, even more preferably at least 95%, 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 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: 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.

[0036] Sequence similarity for polypeptides 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

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using FASTA with 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

[0037] Methods for generating human antibodies include, for example, VELOCIMMUNE™, XENOMOUSE™ technology (Green et al. (1994) Nature Genetics 7:13-21), the "minilocus" approach, and phage display. The VELOCIMMUNE™ technology (US 6,596,541, Regeneron Pharmaceuticals) 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.

[0038] 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 and participation in complement-dependent cytotoxicity (CDC), or killing cells through antibody-dependent cell-mediated cytotoxicity (ADCC). The constant region of an antibody is thus 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.

[0039] 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 inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[0040] 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. 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.

[0041] 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.

[0042] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_D of from about 10^{-10} through about 10^{-12} M or higher, for example, at least 10^{-10} M, at least 10^{-11} M or at least 10^{-12} M, when measured by binding to antigen either immobilized on solid phase or in solution phase.

[0043] 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 affinity, selectivity, epitope, etc. 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 IgG1 or IgG4 (for example, SEQ ID NO:541, 542 or 543). 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

[0044] To screen for antibodies that bind to a particular epitope (e.g., those which block binding of IgE to its high affinity

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receptor), a routine cross-blocking assay such as that described in Harlow and Lane (1990) *supra* can be performed. Other methods include alanine scanning mutants, peptide blots (Reineke (2004) *Methods Mol Biol* 248:443-63), or peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) *Protein Science* 9: 487-496).

[0045] The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0046] 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 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with 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 that produce mAbs having the desired characteristics. MAP may be used to sort the anti-NGF antibodies of the invention into groups of antibodies binding different epitopes.

Immunoconjugates

[0047] The invention encompasses a human anti-NGF monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxin agents include any agent that is detrimental to cells. Examples of suitable cytotoxin agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081).

Bispecifics

[0048] The antibodies of the present invention may be monospecific, bispecific, or multispecific. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al. (1991) *J. Immunol.* 147:60-69. The human anti-NGF antibodies can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity.

Therapeutic Administration and Formulations

[0049] The invention provides therapeutic compositions comprising the anti-NGF antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions 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, Mack Publishing Company, Easton, PA. 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. See also Powell et al. "Compendium of excipients for parenteral formulations" *PDA* (1998) *J Pharm Sci Technol* 52:238-311.

[0050] The dose may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating various conditions and diseases associated with NGF, including inflammatory pain, neuropathic and/or nociceptive pain, hepatocellular carcinoma, breast cancer, liver cirrhosis, and the like, in an adult patient, it is advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight, preferably about 0.1 to about 10 mg/kg body weight, and more preferably about 0.1 to about 5 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted.

[0051] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) *J. Biol. Chem.* 262:4429-4432). Methods of

introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0052] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533; Treat et al. (1989) in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez Berestein and Fidler (eds.), Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*

[0053] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton (1987) CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974). In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138, 1984). Other controlled release systems are discussed in the review by Langer (1990) Science 249:1527-1533.

[0054] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0055] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the antibody contained is generally about 5 to 500 mg per dosage form in a unit dose; in the form of injection, it is preferred that the antibody is contained in about 5 to 100 mg and in about 10 to 250 mg for the other dosage forms.

[0056] Single and combination therapies. The invention provides therapeutic methods in which the antibody or antibody fragment of the invention is useful to treat pain associated with a variety of conditions involving NGF. The anti-NGF antibodies or antibody fragments of the invention are particularly useful for the treatment of pain resulting from any condition associated with neurogenic, neuropathic or nociceptive pain. In preferred embodiments of neuropathic pain, referred trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, reflex sympathetic dystrophy and neurogenic pain conditions are preferably treated. In other preferred embodiments, cancer pain, particularly, bone cancer pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, post-operative incision pain, fracture pain, osteoporotic fracture pain, osteoporosis, gout joint pain, diabetic neuropathy, sciatica, pains associated with sickle cell crises, migraine, and other neuropathic and/or nociceptive pain are preferably treated.

[0057] Other indications include, for example, treatment for breast cancer (Adriaenssens et al. (2008) Cancer Res 68:346-51). In specific embodiments of the therapeutic methods of the invention, a subject suffering from joint pain associated with gout is treated with a combination of an antibody or antibody fragment of the invention and optionally with a second therapeutic agent. In one embodiment, the second therapeutic agent is preferably an interleukin-1 (IL-1) antagonist such as rilonacept ("IL-1 trap"; Regeneron). Suitable second therapeutic agents may be one or more agents selected from the group consisting of rilonacept, anakinra (KINERET®, Amgen), a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (IL1Ra), an anti-IL-18 drug such as IL-18BP or a derivative, an IL-18 Trap, or an antibody such as an anti-IL-18, anti-IL-18R1, anti-IL-18Racp, anti-IL-6 and/or anti-IL6Ra antibody. Other co-therapies which may be combined with an NGF antibody or antigen-binding fragment thereof, alone or in combination with an IL-1 antagonist, include low dose colchicine, aspirin or other NSAIDs, steroids such as prednisolone, methotrexate, low dose cyclosporine A, TNF inhibitors such as ENBREL®, or HUMIRA®, other inflammatory inhibitors such as inhibitors of caspase-1, p38, IKK1/2, CTLA-4Ig, etc., and/or co-therapies such as uric acid synthesis inhibitors to inhibit the accumulation of uric acid in the body, for example, allopurinol, uric acid excretion promoters to accelerate the rapid excretion of uric acid accumulated in the body, for example, probenecid, sulfipyrazone and/or benzbromarone are examples of uric acid excretion promoters; corticosteroids; non-steroidal antiinflammatory drugs (NSAIDs), anti-epileptic drugs such as topiramate; gabapentin, pregabalin; celecoxib; or a neurotrophin, such as NT-3.

EXAMPLES

[0058] 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. The statistical analyses were conducted according to mixed Factorial ANOVA with Bonferroni post hoc or Turkey HSD post hoc tests.

Example 1. Immunization and Antibody Generation

[0059] Immunization of rodents can be done by any methods known in the art (see, for example, Harlow and Lane, Antibodies: A Laboratory Manual: Cold Spring Harbor Press, New York; Malik and Lillehoj, Antibody techniques: Academic Press, San Diego). In a preferred embodiment, human NGF protein is administered directly to mice which have DNA loci encoding both human Ig heavy chain variable region and Kappa light chain variable region (VELOCIMMUNE™, Regeneron; 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, Human Press, 2000, Totawa, 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, NGF is administered indirectly as a DNA plasmid that contains NGF gene and expresses NGF using the host cellular protein expression machinery to produce antigen polypeptide *in vivo*. In both approaches, to obtain optimal anti-antigen responses, mice are given boost injections every 3~4 weeks and serum samples are collected 10 days after each injection. The antibody immune response is monitored using standard antigen direct binding ELISA methods. Post-boost serum samples diluted in 3-fold serial dilutions are applied to NGF coated plates. Serum titer is defined as the dilution of serum sample that yielded two-fold over background signal in the assay. Animals with optimal responses receive a final boost via intravenous and intra-peritoneal injections without an adjuvant 3~4 days prior to sacrifice. The harvested splenocytes are processed as described below in order to obtain antigen specific monoclonal antibodies.

Example 2. Monoclonal Antibody Isolation

[0060] In one embodiment, antibody-expressing B cells are fused with mouse myeloma cells to form hybridoma cells. The hybrid cells are plated in 96-well plates under HAT selection and allowed to grow for 10 to 20 days. The conditioned media from wells with growing hybridoma cells is screened for antigen binding and receptor blocking activities as described below. Hybridoma cells expressing antibodies of interest are single-cell sub-cloned using flow cytometry, and VH and VL genes from clonal hybridoma cells cloned and sequenced. Antibody proteins are also purified from cultures of antigen specific hybridomas using IgG depleted medium (Invitrogen) and characterized as described below.

[0061] In another embodiment, antigen specific antibodies are isolated directly from antigen positive B cells without being immortalized with specific myeloma cells, and a host CHO cell producing a stable recombinant antibody is generated, as described in USSN 11/809,482 (US patent Publication No. 2007/0280945).

Example 3. Primary Antigen Binding and Receptor Blocking Screening

[0062] To identify antigen specific antibody producing hybridomas, conditioned media was sampled from 96-well culture plates 10 to 20 days after fusion, and antigen binding specificity determined using high through-put direct binding ELISA. Briefly, the condition media at 1:10 and 1:100 fold dilution were allowed to bind to recombinant NGF protein coated MAXISORB™ plates (Nunc) at 100 ng/well. The plate-bound antibodies were detected using goat anti-mouse IgG Fcγ specific HRP conjugated polyclonal antibody (Jackson Immuno Lab). Plates were developed using TMB substrates (BD Pharmingen) and optical density at OD_{450nm} recorded. In parallel, samples at the same dilutions were applied to a streptavidin presented biotin-labeled NGF plates, and the plate bound antibodies detected. Wells showing binding activity to either plate were selected for cell culture expansion and cryo-preserved, and antibody containing supernatants were used for further analysis to obtain specificity, affinity, and functionality profile.

[0063] In addition to the direct antigen binding screening, functional screening was also utilized in order to identify clones secreting antibody with desirable properties. Maxisorb plates were coated with 100 ng/well recombinant human TrkA-hFc overnight at 4°C. Conditioned media at 1:2 and 1:10 fold dilutions were allowed to bind to 2 ng/ml biotin-NGF in solution for 1 hour prior to transfer to the TrkA-hFc coated plates for the measurement of plate-bound biotin-NGF. The plate-bound biotin-NGF was detected using HRP conjugated streptavidin (Pierce) and developed using TMB substrates (BD Pharmingen) and optical density recorded. Hybridomas in which culture media prevented binding of biotin-

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NGF to TrkA-hFc were identified as potential blockers and were further characterized.

[0064] Similar *in vitro* screens were applied to 96-well conditioned medium from CHO cells transfected with the fully human IgG containing V genes isolated directly from antigen positive B cells. In addition, samples were screened for NGF binding activity using antigen-coated LUMINEX™ beads, to which antigen specific bound antibody was detected using PE-conjugated goat anti-human IgG Fcγ-specific polyclonal antibodies. The antigen-binding antibodies were subjected to affinity measurement using BIACORE™. Briefly, antibodies from crude culture supernatants were captured on an amine coupled hFc specific polyclonal antibody surface. Antigen binding at a single concentration was monitored. A 1:1 bimolecular interaction model was used to fit the binding sensogram to determine the antigen-binding affinities (K_D) using the kinetic rate constants k_a and k_d for each antibody interaction under identical conditions. Specifically, goat anti-human IgG Fcγ-specific polyclonal antibodies were covalently coupled onto CM-5 chip surfaces, and antibody-containing CHO supernatants were injected at 1 μl/min for 5 minutes followed by a buffer wash. Human NGF (25 nM) was injected for 3 minutes to allow NGF to bind to the human antibody immobilized surface. Immediately following NGF injection, the surfaces were buffer injected at 100 μl/min for ~ 10 minutes and the decay of RU signal recorded. Surfaces were regenerated to remove bound antibody and NGF, and the cycle repeated with the next CHO supernatant sample.

Example 4. Antigen Binding Affinity Determination

[0065] Antigen binding affinities of the antibodies for human NGF were determined by surface kinetics using a real-time biosensor surface plasmon resonance assay (BIACORE™). Antibodies were captured on either a goat, anti-human or anti-mouse IgG polyclonal antibody surface created by direct amine coupling of the capture antibody to a BIACORE™ chip. Various concentrations of human NGF were injected over the captured antibody surfaces while the association of the antigen to the antibody and the dissociation of the bound complex were monitored in real time. Kinetic analysis was performed to obtain the equilibrium dissociation constant (K_D) and dissociation rate constant, and the latter was used to calculate the antigen/antibody complex dissociation $t_{1/2}$ (Table 1). A humanized anti-human NGF monoclonal antibody E3 ("RN624") (tanezumab; CAS Registry No. 880266-57-9; US patent publication 2004/0237124) was used as the control.

Table 1

Antibody	K_D (pM)	$t_{1/2}$
301272-1D07-B10	0.5	34.6 hr
301272-1H07-G9	60.1	32.8 min
301272-1H08-G8	0.2	55.6 hr
301272-3D08-C11	0.7	6.9 hr
301272-3F12-D7	190.0	13.2 min
301272-3G11-C1	1.1	14.6 hr
301272-3H10-A10	0.1	25.2 hr
301272-3H11-A3	23.8	4.3 hr
301272-6E07-D10	13.0	4.5 hr
301272-6G10-D7	7.7	44.3 min
301272-7A10-D7	75.0	11.6 min
301272-7C05-G1	162.0	10.1 min
301272-7E05-F6	0.4	40.0 hr
301272-7F11-A8	5.8	5.3 hr
301272-7G09-E4	17.0	4.3 hr
301272-7G10-E1	292.0	10.1 min
301272-7G11-F6	4.9	2.9 hr
301272-7H05-D4	77.6	1.0 hr
301272-7H07-C12	9.8	6.0 hr
VAT 8C10-8	102.0	14.7 min

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(continued)

Antibody	K _D (pM)	t _{1/2}
VAT 13F5-5	156.0	13.7 min
VAT 12A10-13	109.0	9.4 min
VAT 2C2-1	959.0	9.0 min
Control (RN624)	1.3	35.0 hr

[0066] Antigen binding affinities of selected purified antibodies for NGF were also determined by surface kinetics employing a real-time biosensor surface plasmon resonance assay (BIAcore™) as described above. For convenience, antibody 301272-3H10-A10 was renamed "REGN261" (HCVR/LCVR SEQ ID NOs:84/92 and hlgG1 SEQ ID NO:541); 301272-6E07-D10 was renamed "REGN263" (HCVR/LCVR SEQ ID NO:208/216 and hlgG1 SEQ ID NO:541). Derived antibodies tested included REGN472 (HCVR/LCVR SEQ ID NO:100/102 and hlgG1 SEQ ID NO:541), REGN474 (HCVR/LCVR SEQ ID NO:100/102 and mutant hlgG4 SEQ ID NO:543), REGN475 (HCVR/LCVR SEQ ID NO:108/110 and mutant hlgG4 SEQ ID NO:543), REGN476 (HCVR/LCVR SEQ ID NO:224/226 and mutant hlgG4 SEQ ID NO:543), and REGN477 (HCVR/LCVR SEQ ID NO:232/234 and mutant hlgG4 SEQ ID NO:543).

Table 2

Antibody	K _D (pM)	t _{1/2} (hr)
REGN472	0.41	30
REGN474	0.41	31
REGN475	0.18	57
REGN476	8.91	4
REGN477	7.98	4
Control (RN624)	1.25	35

Example 5. Cross-reactivity to Neurotrophin-3 (NT-3)

[0067] NGF and NT-3 belong to nerve growth factor family and are small, basic, secretory proteins that allow the survival of specific neuronal populations. Though these two neurotrophins share some amino acid identities, biological functions may vary (Barde et al. 1990 Prog Growth Factor Res 2(4):237-48).

[0068] The anti-NGF antibodies were examined for binding cross-reactivity with human NT-3. Briefly, goat anti-human IgG polyclonal antibody was chemically linked to a CM5 chip. Anti-NGF monoclonal antibodies were injected forming a surface of about 50 to 900 RU of immobilized antibody through the interaction with the chip coupled polyclonal antibodies. NGF or NT-3 protein at a concentration of 20 nM was injected over the surface, followed by a buffer wash to allow bound ligand to dissociate. Both association and dissociation phases were monitored and data were analyzed. Results are shown in Table 3 (NB = no binding activity observed). In contrast to the control antibody (RN624), all of the test antibodies showed no measurable binding to NT-3, thus indicating a higher degree of antigen specificity relative to the control antibody.

Table 3

Antibody	NGF K _D (pM)	NT-3 K _D (nM)
301272-1D07-B10	0.5	NB
301272-1H07-G9	60.1	NB
301272-1H08-G8	0.2	NB
301272-3D08-C11	0.7	NB
301272-3F12-D7	190.0	NB
301272-3G11-C1	1.1	NB

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(continued)

Antibody	NGF K_D (pM)	NT-3 K_D (nM)
301272-3H10-A10	0.1	NB
301272-3H11-A3	23.8	NB
301272-6E07-D10	4.3	NB
301272-6G10-D7	7.7	NB
301272-7A10-D7	75.0	NB
301272-7C05-G1	162.0	NB
301272-7E05-F6	0.1	NB
301272-7F11-A8	7.5	NB
301272-7G09-E4	5.5	NB
301272-7G10-E1	292.0	NB
301272-7G11-F6	4.9	NB
301272-7H05-D4	77.6	NB
301272-7H07-C12	9.8	NB
Control (RN624)	1.3	1.1

[0069] OCTET™-based solution competition assays were also employed to measure the ability of REGN475 and RN624 to compete in solution for the binding to NT-3, NGF or human brain derived neurotrophic factor (hBDNF). Briefly, antibody-antigen samples were prepared by pre-incubating control antibody RN624 (2.5 µg/ml) or REGN475 (2.5 µg/ml), with various concentrations of NT-3 (0 to 4 µM), hBDNF (0 to 4 µM) or NGF (0 to 0.2 µM) for 1 hour at 30°C. Streptavidin high binding FA sensors (HBS, ForteBio, Inc., CA) were incubated with biotin-NGF at 2 µg/ml for 10 min at 30°C. Biotin-NGF bound sensors were then incubated with the pre-incubated antigen-antibody samples for 10 min at 30°C. Changes in the thickness of the biological layer were measured after incubation. The binding was normalized as a percentage of binding relative to the binding of antibody in absence of competitor. As shown in Table 4, the binding between NGF and RN624 was blocked by NT-3 in a dose-dependent manner, whereas binding between REGN475 and NGF was not blocked by NT-3. The presence of hBDNF did not block the binding of either RN624 or REGN475 to NGF, whereas the presence of soluble NGF almost completely blocked the binding of both RN624 and REGN475 to immobilized NGF.

Table 4

Competitor	RN624 % Binding	REGN475 % Binding
NT-3 (4 µM)	17	102
NT-3 (2 µM)	26	102
NT-3 (1 µM)	38	98
NT-3 (0.5 µM)	52	93
NT-3 (0.25 µM)	72	101
NT-3 (0 µM)	100	100
BDNF (4 µM)	103	116
BDNF (2 µM)	104	115
BDNF (1 µM)	104	106
BDNF (0 µM)	100	100
NGF(0.2 µM)	1	3
NGF(0.1 µM)	-1	2
NGF(0.05 µM)	0	1

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(continued)

Competitor	RN624 % Binding	REGN475 % Binding
NGF(0 μ M)	100	100

[0070] The binding between selected purified human anti-NGF antibody REGN472, REGN474, REGN475, REGN476, REGN477, or control antibody RN624 and NT-3 was also evaluated using the BIAcore™ assay with NT-3 concentrations ranging from 1.25 nM to 40 nM. While control antibody (RN624) bound NT-3 with a K_D of 1.1 nM, none of the test antibodies exhibited measurable affinity for NT-3.

Example 6. Cross-reactivity to Murine and Rat NGF

[0071] Human NGF (NGF) is highly homologous in amino acid sequence to mouse NGF (mNGF) and rat NGF (rNGF) with about 90% identity. The binding affinities of the antibodies to both mNGF and rNGF were determined as described above. All antibodies showed cross-reactivity to both mNGF and rNGF. One group of antibodies bound NGF from all species strongly with a K_D value of less than 10 pM; a second group preferably bound NGF and exhibited K_D s > ~ 100 pM for mNGF and rNGF (control = RN624) (Table 5).

Table 5

Antibody	Human NGF K_D (pM)	mNGF K_D (pM)	rNGF K_D (pM)
301272-1D07-B10	0.5	3.0	6.6
301272-1H07-G9	60.1	2280.0	6330.0
301272-1H08-G8	0.2	1.7	0.7
301272-3D08-C11	0.7	5.0	8.5
301272-3F12-D7	190.0	3130.0	8710.0
301272-3G11-C1	1.1	6.1	5.9
301272-3H10-A10	0.1	0.2	0.6
301272-3H11-A3	23.8	619.0	800.0
301272-6E07-D10	13.0	362.0	360.0
301272-6G10-D7	7.7	94.7	157.0
301272-7A10-D7	75.0	2630.0	4900.0
301272-7C05-G1	162.0	2000.0	1790.0
301272-7E05-F6	0.4	4.1	1.6
301272-7F11-A8	5.8	320.0	459.0
301272-7G09-E4	16.8	379.0	425.0
301272-7G10-E1	292.0	7090.0	11800.0
301272-7G11-F6	4.9	157.0	160.0
301272-7H05-D4	77.6	5520.0	7090.0
301272-7H07-C12	9.8	1200.0	473.0
Control (RN624)	1.25	1.4	1.5

[0072] The binding affinity of selected purified anti-NGF antibodies to mNGF and rNGF were also determined (Table 6).

Table 6

Antibody	NGF K_D (pM)	mNGF K_D (pM)	rNGF K_D (pM)
REGN472	0.41	0.61	3.96

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(continued)

Antibody	NGF K_D (pM)	mNGF K_D (pM)	rNGF K_D (pM)
REGN474	0.41	0.43	3.42
REGN475	0.18	0.36	0.93
REGN476	8.91	115	155
REGN477	7.98	133	164
Control (RN624)	1.25	1.4	1.51

Example 7. Inhibition of NGF Binding to Receptors TrkA/hFc and p75/hFc

[0073] To identify blocking antibodies, a receptor blocking assay was designed using a BIACORE™ 3000 instrument. Recombinant human TrkA-hFc and human p75-hFc proteins were amine-coupled to a CM5 chip to a density of about 5000 - 6000 RU. Human NGF (10 nM to 25 nM) was bound to the TrkA and p75 surface to determine maximal RU for NGF binding. The surface was then regenerated and 10 nM to 25 nM NGF was mixed with excess molar concentrations of the individual antibodies or soluble receptorbodies, and the solution was injected over the regenerated chip surface to determine the remaining free NGF binding signals. Table 7 shows the percentage free NGF bound to TrkA and p75 in the presence of antibody or receptorbody. The maximal RU binding of human NGF in the absence of antibody was given a relative value of 100%. As positive controls, RN624, TrkA-hFc and p75-hFc in solution were used and, as a negative binding control, IgG1 control (AVASTIN®; Genentech, CA) was used.

Table 7

Antibody	% Binding TrkA-hFc	% Binding p75-hFc
NGF alone	100	100
301272-1D07-B10	2	4
301272-1H07-G9	20	25
301272-1H08-G8	1	3
301272-3D08-C11	1	2
301272-3F12-D7	25	23
301272-3G11-C1	1	1
301272-3H10-A10	1	2
301272-3H11-A3	18	20
301272-6E07-D10	4	6
301272-6G10-D7	2	2
301272-7A10-D7	31	26
301272-7C05-G1	1	1
301272-7E05-F6	1	1
301272-7F11-A8	4	3
301272-7G09-E4	8	16
301272-7G10-E1	62	62
301272-7G11-F6	1	1
301272-7H05-D4	14	20
301272-7H07-C12	42	81
VAT 8C10-8	4	395
VAT 13F5-5	4	5

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(continued)

Antibody	% Binding TrkA-hFc	% Binding p75-hFc
VAT 12A10-13	11	539
VAT 2C2-1	11	360
REGN472	4	7
REGN474	6	9
REGN475	6	10
REGN476	6	13
REGN477	9	13
Control mAb (RN624)	10	16
Control (TrkA-hFc)	10	15
Control (p75-hFc)	3	5
IgG1 Control	116	116

[0074] The ability of selected test antibodies, REGN472, REGN474, REGN475, REGN476 and REGN477, and control antibody RN624 to block human NGF binding to human TrkA and p75 receptors was also quantitatively measured with a competition sandwich ELISA, in which the presence of the antibody with a fixed concentration of NGF in solution prevented NGF from binding to TrkA-hFc or p75-hFc coated on a microtiter plate. The human NGF used in the assay was a recombinant protein produced in *E. coli* and the human TrkA-hFc and p75-hFc proteins were dimeric fusion proteins consisting of the extracellular domains of the respective receptors fused in-line with the Fc portion of human IgG1. Biotin-labeled NGF protein at a fixed concentration of 50 pM was titrated with various amounts of the antibody from 1.5 pM to 1.5 nM in solution for one hour at room temperature. The amount of unbound free biotin-NGF in the solution mixtures was then quantified by capturing the biotin-NGF on either hTrkA-hFc or hp75-hFc coated microtiter plates, followed by detection of plate bound biotinylated-NGF with Streptavidin-HRP. Specifically, the microtiter plates were prepared by coating the plates with 0.5 µg/ml hTrkA-hFc or 1 µg/ml hp75-hFc solution in PBS buffer overnight at 4°C, followed by blocking the plates with 0.5% BSA prior to use. To measure the unbound biotin-NGF, the pre-incubated antibody and biotin-NGF solutions were transferred to the receptor-coated plates followed by 1-hour incubation at room temperature. The plate-bound biotinylated-NGF was detected with Streptavidin-HRP and developed with a colorimetric TMB substrate, and OD_{450 nm} recorded. The dependence of the OD_{450 nm} values on REGN475 concentrations in the pre-binding solutions was analyzed using a sigmoidal dose-response model provided by PRISM™ (Graph Pad, CA). The predicted IC₅₀ value, which is defined as the antibody concentration required to block 50% of the binding of 50 pM biotinylated-NGF to the receptor coated plates, was used as an indicator of the potency of the antibody in blocking NGF binding to hTrkA-hFc or hp75-hFc. Table 8 shows IC₅₀ values of each antibody tested against hTrkA-hFc and hp75-hFc. Control mAb = RN624.

Table 8

	TrkA-hFc Blocking IC ₅₀ (pM)	p75-hFc Blocking IC ₅₀ (pM)
REGN472	12	12
REGN474	8.1	6.3
REGN475	20	22
REGN476	65	61
REGN477	65	62
Control (RN624)	48	72

Example 8. Inhibition of NT-3 Binding to Receptors TrkA-, TrkB-, TrkC- and p75-hFc

[0075] The binding of 20 nM human NT-3 to human TrkA-, TrkB-, TrkC- and p75-hFc surfaces, respectively, in the presence of 500 nM of REGN475, RN624 and AVASTIN® (IgG1 control), was also tested. Human TrkA-hFc (9300 RU),

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human TrkB-hFc(6000 RU), human TrkC-hFc (9100 RU) and human p75-hFc (7500 RU) were covalently coupled to BIACORE® CM5 chip surfaces by amine-coupling procedure. Twenty nM of human NT-3 was mixed with 500 nM of control (IgG1 control AVASTIN®), REGN475, RN624, hTrkA-hFc, TrkB-hFc, TrkC-hFc or p75-hFc in solution. The binding mixture was first incubated at room temperature to reach equilibrium (about 1 hr) and then was injected over the above TrkA-hFc, TrkB-hFc, TrkC-hFc and p75-hFc surfaces. The level of human NT-3 binding in each sample was measured. The binding RU from each sample mixture was normalized according to the RU value from the negative control sample (i.e., 20 nM human NT-3 with 500 nM AVASTIN®) and presented as % binding to Trk surfaces (Table 9). REGN475 showed almost no interference with NT-3 binding to the receptors, while the remaining samples showed significant blocking of NT-3 binding to the receptors.

Table 9

Antibody	TrkA-hFc	TrkB-hFc	TrkC-hFc	p75-hFc
IgG1 Control	100	100	100	100
RN624	7	8	8	19
REGN475	90	99	101	103
TrkA-hFc	21	5	3	7
TrkB-hFc	6	0	0	0
TrkC-hFc	11	0	0	0
P75-hFc	14	2	2	4

Example 9. Neutralization of NGF Biological Activity *In Vitro*

[0076] The ability of NGF antibodies to block NGF-dependent and TrkA receptor-mediated cell growth activity was carried out using MG87 cells stably transfected with a plasmid encoding human TrkA receptor. Briefly, the transfected cells were trypsinized and resuspended at approximately 2.5×10^5 cells per ml and plated at 5,000 cells per well in a 96-well tissue culture plate. The purified antibody proteins were serially diluted in defined medium plus 0.1 % BSA and added to the plated cells at concentrations ranging from 0 to 500 nM. Human NGF was added to the wells to a final concentration of 373 pM. The response was measured after incubating the cells for 3 days at 37°C in a humidified 5% CO₂ incubator. Cell growth activity was measured with a CCK8 kit (Dojindo) and OD_{450nm} recorded. The dependency of the signals on the concentrations of antibody was analyzed and IC₅₀ values reported (Table 10, column 2).

[0077] The ability of NGF antibodies to block NGF signaling p75 and TrkA receptor-mediated activity was also measured *in vitro* using a rat adrenal medulla cell line, PC12, which express both receptors endogenously (Urdiales et al. 1998 J. Neuroscience 18(17):6767-6775). Briefly, PC12 cells were stably transfected with a reporter plasmid containing a serum response element (SRE) linked to a luciferase gene. The transfected cells were resuspended at approximately 2.5×10^5 cells per ml and plated at 50,000 cells per well in a 96-well tissue culture plate in Opti-MEM media overnight. The purified antibody proteins were serially diluted in medium (DMEM plus 0.1% BSA) and added to the plated cells at concentrations ranging from 0 to 100 nM. Human NGF was added to the wells to a final concentration of 12.5 pM. Luciferase activity was measured after incubating the cells for 6 hours at 37°C in a humidified 7.5% CO₂ incubator using BRIGHT GLOW™ luciferase assay system (Promega). IC₅₀ values were determined as described above, and reported in Table 10, column 3. Control mAb = RN624.

Table 10

Antibody	MG87 IC ₅₀ (nM)	PC12 IC ₅₀ (nM)
301272-1D07-B10	< 0.186	0.011
301272-1H07-G9	2.000	0.261
301272-1H08-G8	< 0.186	0.006
301272-3D08-C11	0.576	0.005
301272-3F12-D7	< 0.186	--
301272-3G11-C1	< 0.186	0.019
301272-3H10-A10	< 0.186	0.009

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(continued)

Antibody	MG87 IC ₅₀ (nM)	PC12 IC ₅₀ (nM)
301272-3H11-A3	16.000	0.842
301272-6E07-D10	0.293	0.726
301272-6G10-D7	106.000	0.087
301272-7A10-D7	15.000	--
301272-7C05-G1	< 0.186	0.035
301272-7E05-F6	< 0.186	0.018
301272-7F11-A8	0.428	0.071
301272-7G09-E4	3.000	--
301272-7G10-E1	< 0.186	--
301272-7G 11-F6	9.000	0.088
301272-7H05-D4	3.000	--
301272-7H07-C12	0.383	0.183
VAT2C2-1	532.000	--
VAT8C10-8	41.000	--
VAT12A10-13	41.000	--
VAT13F5-5	5.000	--
Control (RN624)	< 0.186	0.021

[0078] The ability of selected purified anti-NGF antibodies, REGN472, REGN474, and REGN475, and control mAb RN624 to block NGF signaling through p75 and TrkA receptor-mediated activity in a PC12 cell line was also evaluated with the luciferase assay described above (Table 11).

Table 11

Antibody	IC ₅₀ (pM)
REGN472	4.5
REGN474	6.6
REGN475	9.6
Control (RN624)	4.9

[0079] The ability of anti-NGF antibody, REGN475, and control antibody to block NT-3 signaling through p75 and TrkA receptor-mediated activity in PC12 cell line was evaluated with the luciferase assay described above, modified by replacing 12.5 pM NGF with 75 nM NT-3. Results showed that the control mAb RN624 blocked NT-3 signaling with an IC₅₀ of about 104.8 nM, while REGN475 did not affect NT-3 signaling under the current experimental conditions.

[0080] Further, a bioassay was developed to determine the ability of anti-NGF antibodies, REGN475 and RN624, to neutralize NT-3 mediated cellular function through TrkC *in vitro*. An engineered HEK293 cell line expressing TrkC was transfected with a SRE-luciferase reporter plasmid. NT-3 drives luciferase expression in a 6-hour assay. The ability of REGN475 and RN624 to block NT-3 signaling through TrkC receptor-mediated activity in this engineered cell line was evaluated with the luciferase assay. The engineered HEK293 cell line was seeded onto 96-well plates at 1 x 10⁴ cells/well in serum-free media and incubated overnight at 37°C, 5% CO₂. REGN475 and RN624 at concentrations ranging from 1.6 μM to 28 pM were preincubated with 15 pM NT-3 for 1 hour and the mixture was added to the cells. The cells were then incubated at 37°C, 5% CO₂ for 6 hours. Luciferase activity was determined by adding an equal well volume of BRIGHT GLOW™ (Promega). The result showed that RN624 inhibited NT-3-mediated luciferase activity with an IC₅₀ of ~ 150-200 nM in the presence of a constant concentration of 15 pM NGF, whereas REGN475 did not inhibit NT-3 mediated luciferase activity.

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Example 10. Neutralization of NGF Biological Activity *In Vivo*

[0081] Complete Freund's Adjuvant (CFA) test of inflammatory pain. To determine if anti-NGF antibodies could relieve pain in a chronic peripheral inflammatory mouse model, complete Freund's adjuvant (CFA) was injected subcutaneously (s.c.) into the hind paw of C57BL/6 male mice, causing thermal hyperalgesia, which was measured using the Hargreaves' test (Torres et al. (2007) Pain 130:267-278). Control mice received the vehicle (i.e., PBS) only. After acclimating the mice to the Hargreaves' apparatus (model 336, IITC Life Science) for 2-3 hours per day for 3 days, they were tested in the apparatus with an active intensity setting of 17%. A cut-off time of 25 sec was used to avoid tissue damage. For each mouse, 3 readings were obtained during a period of 30 min per day and the median latency was used for analysis. After obtaining a baseline reading in the Hargreaves' apparatus, test anti-NGF antibodies, 301272-7E05-F6 (REGN268) and 301272-7G09-E4 (REGN270), and humanized anti-NGF antibody (RN624) as a positive control, were injected s.c. at 10 mg/kg or 25 mg/kg, 1 hr prior to injecting a 50% solution of CFA (10 mg/20 μ l) into the intraplantar hind paw. The Hargreaves' test was repeated daily for up to 4 days after CFA injection and % decrease from the baseline in paw withdrawal latency calculated (Tables 12 and 13, mean % change $\pm$ SEM). A significant decrease in thermal hyperalgesia was observed for at least one of the days examined for each of the antibodies tested, compared to control mice that received vehicle only ($p < 0.001-0.05$). There was no statistical difference between the tested antibodies and the control antibody. Table 12: $n=7$ for each group; all groups 10 mg/kg. Table 13: vehicle: $n=5$; control RN624: $n=5$, 10 mg/kg; both REGN269: $n=9$).

Table 12

Time after CFA injection	Vehicle	Control (RN624)	REGN268	REGN270
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Day 1	-73.8 $\pm$ 1.8	-58.3 $\pm$ 5.5	-68.3 $\pm$ 3.0	-55.8 $\pm$ 9.2
Day 2	-67.9 $\pm$ 2.1	-30.9 $\pm$ 5.2	-44.7 $\pm$ 9.5	-36.6 $\pm$ 9.9
Day 3	-54.4 $\pm$ 2.8	-20.7 $\pm$ 6.3	-28.9 $\pm$ 11.3	-38.1 $\pm$ 5.6

Table 13

Time after CFA injection	Vehicle	Control (RN624)	REGN269 10 mg/kg	REGN269 25 mg/kg
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Day 1	-82.6 $\pm$ 1.6	-61.7 $\pm$ 9.7	-79.8 $\pm$ 1.8	-80.4 $\pm$ 2.2
Day 2	-76.7 $\pm$ 3.6	-33.1 $\pm$ 17.9	-57.0 $\pm$ 8.2	-54.0 $\pm$ 5.2
Day 3	-60.8 $\pm$ 5.5	-9.6 $\pm$ 15.4	-23.9 $\pm$ 12.4	-41.1 $\pm$ 8.9
Day 4	-40.3 $\pm$ 5.0	-0.4 $\pm$ 18.5	-25.3 $\pm$ 6.6	-16.9 $\pm$ 12.6

[0082] Post-operative incision pain model. A rodent model of post-operative pain in which a hind paw plantar incision causes increased sensitivity to touch, guarding behavior, and thermal hyperalgesia, was used to study the efficacy of anti-NGF antibody therapy. For the plantar incision surgery, C57BL/6 mice under isoflurane received an incision through skin, fascia and then isolating the underlying flexor muscle and bisecting vertically. After suture and recovery, the mice were tested for thermal hyperalgesia in the Hargreaves' test and for guarding behavior in the weight bearing test (model 600, IITC Life Science) for 5 days. A single s.c. injection of vehicle ($n=7$), mAb REGN268 ($n=7$), or control mAb RN624 ($n=7$), at 10 mg/kg, was administered 1 hr prior to the incision (Table 14, mean percent change from Hargreaves baseline $\pm$ SEM). Table 15 shows results of the weight bearing test (mean percent weight distribution on affected limb $\pm$ SEM) ($n=7$ for each group, control RN624 and REGN268 each 10 mg/kg). In both tests, the pre-treatment with the test antibody or the control antibody significantly reduced the post-operative pain compared to the control mice that received vehicle only ($p < 0.001-0.05$).

Table 14

Time after surgery	Vehicle	Control (RN624)	REGN268
Baseline	0.00 $\pm$ 0.0	0.00 $\pm$ 0.0	0.00 $\pm$ 0.0

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(continued)

Time after surgery	Vehicle	Control (RN624)	REGN268
Day 1	-72.4 ± 4.4	-62.5 ± 10.6	-59.9 ± 8.9
Day 2	-72.7 ± 3.5	-55.2 ± 9.4	-34.4 ± 21.3
Day 3	-63.8 ± 7.4	-5.3 ± 12.1	-19.8 ± 18.8
Day 4	-52.1 ± 7.8	-6.4 ± 8.7	6.9 ± 4.4
Day 5	-32.7 ± 10.0	-5.3 ± 5.6	6.8 ± 7.8

Table 15

Time after surgery	Vehicle	Control (RN624)	REGN268
Day 0	49.7 ± 0.9	49.0 ± 0.5	50.3 ± 0.7
Day 1	35.3 ± 1.5	44.8 ± 1.9	39.5 ± 3.4
Day 2	34.3 ± 1.9	42.7 ± 1.8	40.7 ± 2.0
Day 3	34.1 ± 2.5	48.7 ± 1.9	42.0 ± 3.3
Day 4	42.2 ± 0.8	47.2 ± 1.2	44.8 ± 1.0
Day 5	48.6 ± 1.3	49.7 ± 0.7	48.8 ± 0.8

[0083] To study whether anti-NGF antibodies could relieve established pain in the post-operative incision pain model, REGN475 (25 mg/kg, n=7), RN624 (25 mg/kg, n=7), and IgG1 control antibody (25 mg/kg, n=7) were intraperitoneally (i.p.) injected on day 1 post-surgery after performing the behavioral work. Thermal hyperalgesia was studied in the Hargreaves' test and mechanical allodynia was tested in the von Frey test. In this latter test, mice were tested after being acclimated for 2-3 hours for 4 days in an apparatus with a wire mesh floor. The test was performed by applying, in ascending order, a series of von Frey hairs through the wire mesh onto the plantar surface of the hind paw with the incision. A response was considered positive if the paw was raised from the platform in response to application of the filament. Starting from the thinnest hair, each von Frey filament was applied up to five times until a response was observed. The result from the Hargreaves' test (Table 16) showed that the REGN475 antibody treatment led to a significant reversal of the thermal hyperalgesia by 72 hours post-surgery ($p < 0.001-0.01$). This return to baseline was not observed in the RN624 treated cohort of mice, which behaved similarly to the IgG control treated group. In the von Frey test (Paw Withdrawal Threshold) (g) (Table 17), both anti-NGF antibodies caused similar relief of mechanical allodynia ($p < 0.001-0.05$) (IgG1 control = AVASTIN®, 25 mg/kg, n=7; RN624, 25 mg/kg, n=7; REGN475, 25 mg/kg, n=7).

Table 16

Time after anti-NGF treatment	IgG1 Control	RN624	REGN475
Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Day 1	-66.5 ± 9.0	-74.7 ± 4.3	-72.6 ± 5.4
6 hr	-79.8 ± 3.8	-68.1 ± 5.2	-59.3 ± 9.6
23 hr	-77.6 ± 3.6	-40.5 ± 8.9	-37.0 ± 15.0
47 hr	-61.2 ± 6.6	-37.6 ± 7.2	-30.5 ± 10.8
72 hr	-57.0 ± 7.9	-47.2 ± 8.0	2.1 ± 17.3

Table 17

Time after anti-NGF Treatment	IgG1 Control	RN624	REGN475
Baseline	1.314 ± 0.137	1.314 ± 0.137	1.286 ± 0.074
Day 1	0.011 ± 0.002	0.010 ± 0.002	0.010 ± 0.002

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(continued)

Time after anti-NGF Treatment	IgG1 Control	RN624	REGN475
5 hr	0.011 $\pm$ 0.002	0.083 $\pm$ 0.053	0.034 $\pm$ 0.009
22 hr	0.029 $\pm$ 0.004	0.610 $\pm$ 0.123	0.714 $\pm$ 0.074
45 hr	0.190 $\pm$ 0.135	0.909 $\pm$ 0.216	1.086 $\pm$ 0.184
70 hr	0.194 $\pm$ 0.034	1.143 $\pm$ 0.189	1.571 $\pm$ 0.437

[0084] On day 4, after the behavioral tests from post incision pain model was completed, the mice's sera were collected and analyzed for circulating levels of neurotrophin-3 (NT-3) using a sandwich ELISA. The limit of detection (~40 pg/ml) was defined as two standard deviations (2σ) above background with a minimum of five NT-3 standards to define the response to concentration curve. NT-3 levels from mice treated with RN624 (mean $\pm$ std dev pg/ml, Table 18) showed a significant increase (172 ± 114 pg/ml, $n=7$) from those treated with either REGN475 (not detected =ND, $n=7$) or IgG control (AVASTIN®; ND, $n=7$).

Table 18

Group	Serum NT-3
RN624	172 ± 114
REGN475	ND
IgG1 control	ND

[0085] For comparison, naïve C57BL/6 mice under isoflurane were given one s.c. injection (50 mg/kg) of REGN475, RN624 or IgG1 control mAb (AVASTIN®) and their sera were analyzed at 1, 7 and 14 days post treatment for NT-3 levels using a sandwich ELISA. The limit of detection (~40 pg/ml) was defined as two standard deviations (2σ) above background with a minimum of five NT-3 standards to define the response to concentration curve. NT-3 levels (Table 19) in RN624 treated mice (131-199 pg/ml, $n=6$) were elevated compared to REGN475 (ND, $n=6$) or IgG control (ND, $n=6$), as observed with the post-operative incision pain model described above.

Table 19

Group	Serum NT-3
Day 1	
RN624	131 ± 41
REGN475	ND
IgG1 Control	ND
Day 7	
RN624	199 ± 15
REGN475	ND
IgG1 Control	ND
Day 14	
RN624	196 ± 35
REGN475	ND
IgG1 Control	ND

[0086] Acute gout joint pain model. A mouse model of joint pain caused by injection of monosodium urate (MSU) crystals into the ankle was used to study the efficacy of the antibodies of the invention to treat gout arthritic joint pain. Endotoxin-free MSU crystals (0.5 mg/20 μ l) were injected intra-articularly into the ankle of C57BL/6 mice and the mice were then tested for heel thermal pain in the Hargreaves' test for up to 3 days post-MSU crystals injection. The acclimation

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parameters and apparatus setting for the Hargreaves' test is as described above. Test mAb 7E05-F6 (REGN268; n=7), 6E07-D10 (REGN263; n=7), or control humanized mAb (RN624; n=7), or vehicle (n=7) was s.c. injected at 10 mg/kg 1 hr prior to the MSU crystals ankle injection. As shown in Tables 20 and 21, the test antibodies significantly reduced the joint pain, compared to the control mice that received vehicle only ($p<0.001-0.05$).

Table 20

Time after MSU crystals ankle injection	Vehicle	Control (RN624)	REGN268	REGN263
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Day 1	-62.4 $\pm$ 3.1	-33.3 $\pm$ 5.2	-28.1 $\pm$ 7.8	-36.3 $\pm$ 3.8
Day 2	-44.2 $\pm$ 3.5	-4.5 $\pm$ 11.2	29 $\pm$ 19.3	16.8 $\pm$ 22.3
Day 3	-24.9 $\pm$ 7.9	-3.2 $\pm$ 12.0	12.1 $\pm$ 15.5	4.5 $\pm$ 15.5
Day 4	-11.6 $\pm$ 10.5	28.3 $\pm$ 18.7	19.9 $\pm$ 16.5	-9.0 $\pm$ 5.5

Table 21

Time after MSU crystals ankle injection	Vehicle	Control (RN624)	REGN268	REGN263
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Day 1	-62.6 $\pm$ 2.7	-36.0 $\pm$ 6.8	-46.7 $\pm$ 4.2	-53.9 $\pm$ 4.0
Day 2	-54.8 $\pm$ 2.7	-11.8 $\pm$ 9.8	-28.5 $\pm$ 8.4	-35.3 $\pm$ 8.5
Day 3	-31.8 $\pm$ 3.4	-5.3 $\pm$ 8.2	-12.6 $\pm$ 9.0	-28.5 $\pm$ 8.6

[0087] The ability of an anti-NGF antibody to relieve established pain in the acute gout model was further studied in mice injected with an IL-1 antagonist (IL-1 trap (rinolacept), Economides et al. (2003) Nature 9:47-52) or colchicine. A day after injecting the MSU crystals into the ankles, mice were injected with mL-1 trap (35 mg/kg; n=7), colchicine (1 mg/kg; n=7), control mAb RN624 (10 mg/kg; n=7), or vehicle (n=7), and tested for thermal hyperalgesia as described above. Additionally, another cohort of mice (n=3) received co-treatment with both mL-1 trap and the control RN624. Combination therapy of anti-NGF antibody and IL-1 antagonist significantly relieved the established thermal hyperalgesia compared to treatment with vehicle only ($p<0.001-0.05$), or either anti-NGF antibody alone ($p<0.001$) or IL-1 antagonist alone ($p<0.001$) at Day 2 post-treatment (Table 22).

Table 22

Time	Vehicle	mIL-1 Trap	Colchicine	Control (RN624)	mIL-1Trap + RN624
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.1
Day 1 post MSU injection	-51.9 $\pm$ 3.0	-52.9 $\pm$ 2.6	-52.8 $\pm$ 2.1	-51.9 $\pm$ 2.4	-46.6 $\pm$ 4.3
7 hr post treatment	-54.8 $\pm$ 2.0	-50.6 $\pm$ 1.8	-33.1 $\pm$ 4.9	-53.2 $\pm$ 3.0	-43.3 $\pm$ 4.4
Day 1 post treatment	-46.8 $\pm$ 2.1	-31.9 $\pm$ 6.2	-23.1 $\pm$ 7.1	-32.0 $\pm$ 10.6	-3.7 $\pm$ 11.0
Day 2 post treatment	-37.3 $\pm$ 3.6	-9.1 $\pm$ 9.4	-23.0 $\pm$ 7.6	-27.6 $\pm$ 8.3	40.0 $\pm$ 29.1
Day 3 post treatment	-26.9 $\pm$ 4.4	-12.4 $\pm$ 10.4	-14.3 $\pm$ 9.8	-9.1 $\pm$ 10.9	21.9 $\pm$ 19.9

[0088] Neuropathic pain. The mouse Seltzer model of neuropathic pain (Malmberg et al. (1998) Pain 76:215-222) was used with C57BL/6 male mice, in which a partial nerve injury was produced by tying a tight ligature with a 7-0 silk suture around approximately 1/3 to 1/2 the diameter of the sciatic nerve of one single thigh per mouse. Post-surgery, the mice were allowed to recover for at least two days and then they were studied for several weeks post-surgery for thermal hyperalgesia in the Hargreaves' test. Controls were sham-operated mice in which the sciatic nerve was exposed and elevated but not tied. Following surgery, the mice were tested at day 4 and at day 7 post-surgery to confirm that the thermal hyperalgesia had developed. At day 7 post-surgery, the mice were injected s.c. with mAb REGN268 (100 mg/kg), IgG1 control (AVASTIN® 100 mg/kg), and with vehicle. REGN268 significantly relieved established thermal hyperalgesia in this nerve injury model (Table 23; $p<0.05$). This pain relief was not observed in the sham-operated mice. Results

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expressed as mean percent change from Hargreaves baseline $\pm$ SEM (sham-vehicle, n=3; sham-100 mg/kg IgG1 control (AVASTIN®), n=4; sham-100 mg/kg REGN268, n=5; Seltzer-vehicle, n=5; Seltzer-100 mg/kg IgG1 control (AVASTIN®), n=5; Seltzer- 100 mg/kg REGN268, n=8).

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Table 23

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Days after Surgery	Sham-Vehicle	Sham- IgG1 control	Sham-REGN268	Seltzer-Vehicle	Seltzer-IgG1 control	Seltzer-REGN268
0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
4	8.5 $\pm$ 3.9	-7.2 $\pm$ 3.7	12.0 $\pm$ 4.0	-42.5 $\pm$ 3.0	-46.9 $\pm$ 6.5	-46.4 $\pm$ 3.7
7	4.5 $\pm$ 1.3	8.7 $\pm$ 13.2	8.7 $\pm$ 7.7	-45.7 $\pm$ 1.5	-55.3 $\pm$ 6.4	-46.5 $\pm$ 2.7
8	10.3 $\pm$ 1.7	-9.4 $\pm$ 4.1	3.0 $\pm$ 5.1	-53.2 $\pm$ 3.2	-55.6 $\pm$ 4.3	-2.4 $\pm$ 6.8
11	5.0 $\pm$ 2.3	14.7 $\pm$ 11.4	1.5 $\pm$ 5.7	-61.5 $\pm$ 4.2	-57.3 $\pm$ 5.1	4.2 $\pm$ 11.2
13	15.4 $\pm$ 2.6	-6.9 $\pm$ 3.3	28.7 $\pm$ 13.8	-61.4 $\pm$ 3.8	-59.7 $\pm$ 6.5	1.2 $\pm$ 5.7
16	4.2 $\pm$ 4.0	2.3 $\pm$ 3.0	9.0 $\pm$ 1.4	-52.2 $\pm$ 5.3	-51.2 $\pm$ 4.0	2.1 $\pm$ 12.1
18	10.2 $\pm$ 7.8	0.2 $\pm$ 2.8	6.3 $\pm$ 4.8	-54.9 $\pm$ 4.4	-57.7 $\pm$ 4.6	2.2 $\pm$ 100
20	7.8 $\pm$ 6.0	3.6 $\pm$ 2.4	5.0 $\pm$ 4.5	-53.8 $\pm$ 4.5	-53.2 $\pm$ 4.9	-20.8 $\pm$ 8.1
24	7.6 $\pm$ 5.6	1.5 $\pm$ 2.9	11.1 $\pm$ 3.2	-56.4 $\pm$ 3.0	-54.9 $\pm$ 4.1	-26.4 $\pm$ 6.8
28	11.1 $\pm$ 6.0	0.7 $\pm$ 2.5	10.9 $\pm$ 5.0	-53.9 $\pm$ 2.1	-51.81 $\pm$ 4.1	-5.4 $\pm$ 15.0
31	11.7 $\pm$ 6.6	1.1 $\pm$ 2.3	5.1 $\pm$ 1.8	-49.6 $\pm$ 4.1	-49.7 $\pm$ 2.5	-23.3 $\pm$ 11.7

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[0089] In the second experiment, in order to see whether anti-NGF treatment could relieve thermal hyperalgesia past day 7 post-surgery, anti-NGF REGN268 (100 mg/kg) was injected s.c. at days 7, 14, or 21 post-surgery. Significant pain relief was obtained at all 3 time points compared to IgG1 control (AVASTIN® 100 mg/kg; p<0.05) (Table 24, mean percent change from Hargreaves baseline $\pm$ SEM; 100 mg/kg IgG1 control, n=6; 100 mg/kg REGN268, n=7).

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Table 24

Days After Surgery	Day 7		Day 14		Day 21	
	IgG1 control	REGN268	IgG1 control	REGN268	IgG1 control	REGN268
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Day 5	-53.5 $\pm$ 5.9	-51.4 $\pm$ 5.6	-60.0 $\pm$ 4.8	-54.2 $\pm$ 5.2	-55.5 $\pm$ 5.0	-55.5 $\pm$ 6.0
Day 7	-55.4 $\pm$ 4.4	-50.0 $\pm$ 6.6	-54.4 $\pm$ 6.4	-47.9 $\pm$ 3.6	-47.2 $\pm$ 4.8	-40.7 $\pm$ 8.5
Day 8	-56.7 $\pm$ 3.8	17.3 $\pm$ 13.5	-55.3 $\pm$ 6.1	-47.2 $\pm$ 3.2	-47.9 $\pm$ 4.7	-41.2 $\pm$ 7.3
Day 10	-64.3 $\pm$ 2.6	-6.4 $\pm$ 7.7	-52.8 $\pm$ 7.2	-62.9 $\pm$ 5.2	-55.0 $\pm$ 6.7	-45.9 $\pm$ 6.9
Day 14	-66.9 $\pm$ 5.1	-4.9 $\pm$ 3.4	-62.1 $\pm$ 5.7	-59.7 $\pm$ 2.1	-63.8 $\pm$ 4.6	-61.2 $\pm$ 3.4
Day 15	-60.6 $\pm$ 4.0	-1.7 $\pm$ 10.5	-63.0 $\pm$ 5.8	-38.5 $\pm$ 7.3	-54.5 $\pm$ 5.0	-47.1 $\pm$ 4.4
Day 17	-58.9 $\pm$ 3.5	-0.8 $\pm$ 10.5	-58.6 $\pm$ 5.7	25.2 $\pm$ 17.0	-52.4 $\pm$ 5.3	-48.4 $\pm$ 4.5
Day 21	-54.1 $\pm$ 9.6	0.9 $\pm$ 9.9	-57.1 $\pm$ 4.4	2.1 $\pm$ 14.8	-55.8 $\pm$ 3.6	-48.1 $\pm$ 5.0
Day 22	-56.3 $\pm$ 4.9	-1.0 $\pm$ 10.0	-55.4 $\pm$ 5.1	-6.4 $\pm$ 7.1	-50.6 $\pm$ 5.3	-34.0 $\pm$ 6.4
Day 24	-55.6 $\pm$ 5.1	-1.0 $\pm$ 10.3	-49.5 $\pm$ 6.6	-2.1 $\pm$ 11.4	-44.7 $\pm$ 5.7	-3.2 $\pm$ 10.8
Day 28	-54.1 $\pm$ 3.5	-9.0 $\pm$ 9.6	-53.6 $\pm$ 5.4	-1.8 $\pm$ 8.5	-46.0 $\pm$ 7.6	13.9 $\pm$ 12.0
Day 32	-41.9 $\pm$ 8.3	-29.1 $\pm$ 7.1	-40.9 $\pm$ 13.1	-10.2 $\pm$ 8.7	-32.8 $\pm$ 4.8	8.0 $\pm$ 12.9
Day 35	-43.9 $\pm$ 6.8	-32.6 $\pm$ 7.4	-42.9 $\pm$ 10.3	-11.8 $\pm$ 7.9	-39.8 $\pm$ 4.5	12.2 $\pm$ 12.4
Day 39	-42.5 $\pm$ 6.9	-29.0 $\pm$ 7.9	-39.0 $\pm$ 11.4	-11.7 $\pm$ 6.7	-34.6 $\pm$ 10.0	12.3 $\pm$ 10.8

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(continued)

Days After Surgery	Day 7		Day 14		Day 21	
	IgG1 control	REGN268	IgG1 control	REGN268	IgG1 control	REGN268
Day 42	-35.0 ± 6.6	-26.1 ± 7.6	-38.1 ± 12.5	-8.9 ± 8.6	-33.9 ± 9.9	13.5 ± 11.5

[0090] In the third experiment, the ability of another anti-NGF antibody REGN475 was tested in the Seltzer model. Following the Seltzer surgery, mice were tested at days 5 and 7 post-surgery to confirm that the thermal hyperalgesia had developed. Then, at day 7 post-surgery the mice were injected by s.c. or i.p. routes with REGN475 (50 mg/kg), control mAb RN624 (50 mg/kg) or IgG1 control (AVASTIN®) (50 mg/kg). Significant pain relief was observed with both anti-NGF antibodies in both cohorts of mice, either injected s.c. (Table 25) or i.p. (Table 26), while control IgG1 showed no effect ($p < 0.001-0.05$) (Mean percent change from Hargreaves baseline ± SEM; 50 mg/kg IgG1 control, n=7; 50 mg/kg RN624, n=7; 50 mg/kg REGN475, n=7).

Table 25

Days after Surgery	IgG1 control	RN624	REGN475
Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
5	-51.2 ± 5.2	-53.5 ± 6.3	-55.2 ± 3.5
7	-47.6 ± 3.9	-48.4 ± 6.2	-50.9 ± 4.3
8	-31.1 ± 11.9	4.5 ± 9.0	10.3 ± 14.1
9	-36.7 ± 14.6	-15.2 ± 8.5	8.2 ± 7.2
12	-47.2 ± 5.5	-4.2 ± 12.0	-20.1 ± 4.3
15	-46.7 ± 8.5	2.1 ± 10.9	-14.1 ± 6.1
19	-28.6 ± 7.5	-11.5 ± 12.1	3.0 ± 10.9
22	-34.9 ± 7.9	-5.7 ± 9.5	-13.7 ± 13.4

Table 26

Days after Surgery	IgG1 control	RN624	REGN475
Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
5	-55.5 ± 3.8	-56.6 ± 2.3	-58.7 ± 2.3
7	-61.6 ± 1.8	-62.3 ± 3.4	-61.7 ± 2.7
8	-59.3 ± 4.0	-3.3 ± 16.0	-8.2 ± 16.1
9	-51.0 ± 4.2	-18.4 ± 12.9	-7.9 ± 9.6
12	-46.5 ± 6.3	-7.0 ± 11.8	-0.1 ± 22.8
15	-43.3 ± 6.6	-16.2 ± 14.8	-10.8 ± 18.0

[0091] To determine the ability of antibodies to neutralize human NGF activities *in vivo*, transgenic mice were made of which the endogenous mouse NGF locus was replaced with the human NGF gene. These mice were used in a Seltzer neuropathic pain model to test REGN268 and control mAbs. Following the Seltzer surgery, these mice were tested at day 4 and at day 8 post-surgery to confirm that the thermal hyperalgesia had developed. Then, at day 8 post-surgery the mice were injected s.c. with 50 mg/kg mAb REGN268 (n=7), 50 mg/kg control RN624 (n=8), or 50 mg/kg IgG1 control (AVASTIN®) (n=6). The results (Table 27) showed that REGN268 was as efficacious as a humanized anti-NGF antibody (RN624) in relieving the neuropathic pain in the humanized NGF mice, whereas IgG1 control had no effect ($p < 0.05$).

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Table 27

Days after Surgery	IgG1 Control	RN624	REGN268
Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
8	-55.4 ± 5.7	-38.1 ± 6.4	-40.8 ± 6.9
10	-54.3 ± 8.0	-23.0 ± 7.7	-16.8 ± 5.4
12	-44.8 ± 7.9	-18.4 ± 8.4	-15.1 ± 10.1
14	-41.3 ± 7.0	5.0 ± 23.6	-6.7 ± 12.9
16	-42.5 ± 8.8	-12.7 ± 9.5	5.2 ± 16.3
20	-44.2 ± 8.9	-15.7 ± 13.0	-8.0 ± 13.7

Example 11. Effect of Anti-NGF on Animal Motor Function

[0092] In order to study whether anti-NGF treatment could alter motor function, motor coordination in the rotarod test in naive C57BL/6 male mice was assessed. Animals were first trained to stay on a rotarod (Columbus Instruments, 3.5 cm diameter, 9 cm wide) rotating at progressively higher speeds (maximum speed 10 rpm). Mice remained at 10 rpm in training until they could walk for 60 sec consecutively, or until they had spent a total of 2 min walking on the rotarod at 10 rpm each day for three consecutive days. After training, each mouse was placed on the rotarod at 10 rpm three times consecutively (with a brief break between trials), and the latency to fall off was recorded. Animals were removed after 1 min, and assigned a score of 60 sec if they did not fall off. The median score of 3 trials for each mouse was used in analysis. After obtaining a baseline reading in the rotarod, mAbs REGN475, RN624, or IgG negative control was injected s.c. at 50 mg/kg or 100 mg/kg. The mice were then tested for up to 20 days post-antibody injection. Results (Table 28, expressed as latency to fall in sec) (mean ± sem) showed that the mice treated with RN624, but not REGN475, had significantly impaired motor coordination ($p < 0.001$ -0.05). Interestingly, it has been reported that NT-3 and TrkC knock-out mice displayed abnormal movements and postures and lost proprioception (Ernfors et al. (1994) Cell 77:503-512; and Klein et al. (1994) Nature 368:249-251). Besides the rotarod, Hargreaves' and von Frey tests on naive mice injected with anti-NGF antibodies were also conducted. No statistically significant differences were observed for any group of mice in the Hargreaves' and von Frey tests during the 20 days post-antibody administration (n=6 for each group).

Table 28

Time after anti-NGF treatment	100mg/kg IgG1 control	50mg/kg RN624	100mg/kg RN624	50mg/kg REGN475	100mg/kg REGN475
Baseline	57.7 ± 1.6	54.2 ± 4.6	60.0 ± 0.0	55.0	60.0 ± 0.0
Day 1	59.2 ± 0.7	43.2 ± 3.7	32.8 ± 2.2	58.0 ± 1.3	58.4 ± 1.5
Day 4	52.8 ± 4.8	36.3 ± 4.3	32.5 ± 3.2	52.5 ± 4.3	53.2 ± 3.3
Day 7	57.7 ± 1.8	47.2 ± 3.7	37.5 ± 5.2	58.0 ± 1.3	60.0 ± 0.0
Day 11	58.7 ± 1.0	50.0 ± 4.7	44.7 ± 6.2	55.2 ± 2.1	60.0 ± 0.0
Day 15	57.8 ± 1.6	56.7 ± 2.6	36.0 ± 1.7	55.2 ± 2.2	57.7 ± 1.6
Day 20	57.8 ± 1.8	57.8 ± 1.3	45.7 ± 5.0	51.8 ± 3.3	53.7 ± 3.1

Example 12. Treatment of Patient Suffering from Post-Herpetic Neuralgia

[0093] A patient who has developed chronic pain at the site of a shingles rash is diagnosed with post-herpetic neuralgia. The patient is treated by administration of therapeutically-effective amount of a pharmaceutically acceptable composition comprising an anti-NGF mAb of the invention. Administration may be by subcutaneous or intravenous injection, at the anti-NGF antibody concentrations of, preferably, between 0.1 to 10 mg/kg body weight. Frequency of treatment may be every 1-12 weeks, or as needed. Within several days after administration of the anti-NGF antibody composition, the patient's pain is substantially alleviated. Repeated administration of the anti-NGF mAb composition maintains this pain relief.

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Example 13. Treatment of Patient Suffering from Osteoarthritis Pain

[0094] A patient suffering from moderate to severe pain caused by osteoarthritis in any joint is treated by administering the therapeutically-effective amount of a pharmaceutically acceptable composition comprising an anti-NGF mAb of the invention. The composition can be administered intravenously at the concentrations of the anti-NGF antibody between 10 µg/kg body weight to 10 mg/kg body weight. Frequency of treatment may be every 1-12 weeks, or as needed. Within several days of the administration of the anti-NGF antibody composition, the patient's pain is substantially alleviated and regain mobility of the affected joint. The treatment can be repeated as long as necessary.

SEQUENCE LISTING

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

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<400> 30

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Gln Ser Val Ser Arg His
1 5

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15 <210> 32
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<400> 32
Ser Ala Ser

25 1

<210> 33
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30 <212> DNA
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35 <400> 33
cagcagtata gtagctcacc gatcacc 27

<210> 34
40 <211> 9
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45 <223> Synthetic

<400> 34

50 Gln Gln Tyr Ser Ser Ser Pro Ile Thr
1 5

<210> 35
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<223> Synthetic

<400> 35

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5      gaggtgcagc  tgggtggagtc  tggggggaggc  ttggtacagc  ctgggggggtc  cctgagactc  60
      tcctgtgcag  cctcgggatt  caccttcaga  gcctacgaca  tgcactgggt  ccgccaaaca  120
      gcaggaaaag  gtctggagtg  ggtctcagct  attggttctg  ctgggtgacac  atactattca  180
      ggctccgtga  agggccgatt  caccatctcc  agagaaaatg  ccaagaagtc  cttgtatctt  240
      caaatgaata  gcctgagagc  cgggggacacg  gctgtgtatt  tttgtgcaag  agaggcaact  300
10     ggaactacga  actactacta  cggtatggac  gtctggggcc  aagggaccac  ggtcaccgtc  360
      tcctccg                                     367

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<210> 36

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<212> PRT

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<220>

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20

<400> 36

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

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40

<210> 37

<211> 24

<212> DNA

<213> Artificial Sequence

45

<220>

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<400> 37

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50

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<211> 8

<212> PRT

<213> Artificial Sequence

55

<220>

<223> Synthetic

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<400> 38

5 Gly Phe Thr Phe Arg Ala Tyr Asp
1 5

<210> 39
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10 <213> Artificial Sequence

<220>
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15 <400> 39
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<210> 40
<211> 7
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25 <400> 40

30 Ile Gly Ser Ala Gly Asp Thr
1 5

<210> 41
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35 <213> Artificial Sequence

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40 <400> 41
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<210> 42
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50 <400> 42

Ala Arg Glu Ala Thr Gly Thr Thr Asn Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

55 <210> 43
<211> 325
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<213> Artificial Sequence

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<400> 43

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cctggccaga ctcccaaaact cctcatcttt ggtgcgtcca ggagggccac tggcatccca 180
gacaggttca gtggcagcgg gtctggaaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtg ttactgtcag caatatggta gctcaccgat caccttcggc 300
caagggacac gactggagat taaac                                     325

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15

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<220>

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cagaatatta gcggcaggtc c 21

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EP 2 187 964 B1

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 1 5
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 15 ggtgcgtcc 9

 <210> 48
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 25 <400> 48

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 30
 <210> 49
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 <400> 49
 40 cagcaatatg glagctcacc gatcacc 27

 <210> 50
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 1 5
 55
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EP 2 187 964 B1

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<400> 51

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tcctgtgcag cctctggatt caccttcagt aacttcgaca tgcactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtgcagct attggttctg ctggtgacac atactatccg 180
gactccgtga gggggccgatt caccatctcc agagaaaatg ccaagaactc cttgtttctt 240
caaatgaaca gcctacgaga cggggacacg gctgtgtatt attgtgcaag agaggggaact 300
ggaactacga actattacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcgtcag                                     367

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15

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<400> 52

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

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

          115          120

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45

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<211> 24

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<210> 54

<211> 8

<212> PRT

<213> Artificial Sequence

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 Gly Phe Thr Phe Ser Asn Phe Asp
 1 5

 10 <210> 55
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 15 <220>
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 <400> 55
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 20
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 25
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 <400> 56
 30
 Ile Gly Ser Ala Gly Asp Thr
 1 5

 35 <210> 57
 <211> 48
 <212> DNA
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 40 <220>
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 <400> 57
 gcaagagagg gaactggaac tacgaactat tactacggtg tggacgctc 48
 45
 <210> 58
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 50 <220>
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 <400> 58

 55 Ala Arg Glu Gly Thr Gly Thr Thr Asn Tyr Tyr Tyr Gly Met Asp Val
 1 5 10 15

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<210> 59
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 <212> DNA
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<220>
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 ggccaggtc ccaggctcct catctatggt gttccagca ggaccactgg catcccagac 180
 aggttcagtg gcagtggtc tgggacagac ttactctca ccatcagtag actggagcct 240
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 gggacacgac tggagattaa tc 322

<210> 60
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 <212> PRT
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<220>
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25

<400> 60

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

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<400> 61
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55

<210> 62
 <211> 6
 <212> PRT
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5 <400> 62
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 1 5

10 <210> 63
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30 <400> 64
 Gly Ala Ser
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35 <210> 65
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40 <220>
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<400> 65
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45 <210> 66
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<400> 66

55 Gln His Tyr Ser Lys Ser Pro Ile Thr
 1 5

<210> 67
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<212> DNA

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5 <223> Synthetic

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      acaggaaaag  gtctggagtg  ggtctcagct  attggtgctg  ctgggtgacac  atactattca  180
      ggctccgtga  agggccgatt  caccatcgcc  agagaaaatg  gcaagaactc  cctgtatctt  240
      caaatgaatg  gcctgagagc  cggggacacg  gctgtgtatt  actgtgcaag  agagggaact  300
      ggaactacga  actactacta  cggtatggac  gtctggggcc  aagggaccac  ggtcaccgtc  360
15      tcctctg                                     367

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<210> 68

<211> 122

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 68

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

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<210> 69

45 <211> 24

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<213> Artificial Sequence

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50 <223> Synthetic

<400> 69

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55 <210> 70

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<212> PRT

<213> Artificial Sequence

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 10 <210> 71
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 15 <220>
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 <400> 72
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 Ile Gly Ala Ala Gly Asp Thr
 1 5

 35 <210> 73
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 40 <220>
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 <400> 73
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 <211> 16
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 <400> 74
 55

 Ala Arg Glu Gly Thr Gly Thr Thr Asn Tyr Tyr Tyr Gly Met Asp Val
 1 5 10 15

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<210> 75
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 <212> DNA
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<220>
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 ctctcctgca gggccagtca gagtgttagc agctacttag cctgggtacca gcagacctct 120
 ggccaggctc ccaggctcct catcttttgt gcgtccagca gggccactgg catcccagac 180
 aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcaacag actggaacct 240
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 gggacacgac tggatattaa tc 322

20

<210> 76
 <211> 107
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 <213> Artificial Sequence

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<220>
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30

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

45

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<400> 77
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<210> 78
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 1 5

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 <400> 79
 ggtgcgtcc 9
 20
 <210> 80
 <211> 3
 <212> PRT
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 25
 <220>
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 <400> 80
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 Gly Ala Ser
 1

 35 <210> 81
 <211> 27
 <212> DNA
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 40 <220>
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 <400> 81
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 45
 <210> 82
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 50
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 <223> Synthetic

 <400> 82
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 Gln Gln Tyr Ala Ser Ser Pro Ile Thr
 1 5

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<210> 83
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
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<400> 83

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 cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatgggtg aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga ccagcctgag atcggaagac acggccgtgt attactgttc aacgattttt 300
 ggagtggtta ccaactttga caactggggc caggaacccc tggtcaccgt ctccctca 357

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<210> 84
 <211> 119
 <212> PRT
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<220>
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25

<400> 84

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

45

<210> 85
 <211> 24
 <212> DNA
 <213> Artificial Sequence

50

<220>
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<400> 85

55

ggattcacc tcactgaatt atcc 24

<210> 86
 <211> 8

EP 2 187 964 B1

<212> PRT
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<220>
<223> Synthetic

<400> 86

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Gly Phe Thr Leu Thr Glu Leu Ser
1 5

15

<210> 87
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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<400> 87
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25

<210> 88
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 88

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Phe Asp Pro Glu Asp Gly Glu Thr
1 5

40

<210> 89
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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<400> 89
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<210> 90
<211> 12
<212> PRT
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<220>
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55

<400> 90

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Ser Thr Ile Phe Gly Val Val Thr Asn Phe Asp Asn
1 5 10

5 <210> 91
<211> 324
<212> DNA
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10 <220>
<223> Synthetic

<400> 91

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atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcattcaatt tgcaaagtgg ggtcccatca 180
agattcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
20 gaagatcttg caagttatta ctgtcaacag tataatagat acccgtggac gttcggccaa 300
gggaccaagc tggagatcaa acga 324

<210> 92
<211> 107
25 <212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

30 <400> 92

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

<210> 93
<211> 18
50 <212> DNA
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<220>
<223> Synthetic

55 <400> 93
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<210> 94
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 <220>
 <223> Synthetic
 <400> 94
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 Gln Ala Ile Arg Asn Asp
 1 5
 <210> 95
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 <211> 9
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 <210> 96
 <211> 3
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 Ala Ala Phe
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 <210> 97
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 <400> 97
 caacagtata atagataccc gtggacg 27
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 <211> 9
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Gln Gln Tyr Asn Arg Tyr Pro Trp Thr
 1 5

<210> 99
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 <212> DNA
 <213> Artificial Sequence

<220>
 10 <223> Synthetic
 <400> 99

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 cccggcaagg gcctggagtg gatgggcggc ttcgaccccg aggacggcga gaccatctac 180
 gcccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgctc caccatcttc 300
 20 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357

<210> 100
 <211> 119
 <212> PRT
 25 <213> Artificial Sequence

<220>
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 30 <400> 100

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

<210> 101
 50 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 55 <223> Synthetic
 <400> 101

EP 2 187 964 B1

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 ggcaaggccc ccaagcggct gatctacgcc gccttcaacc tgcagtccgg cgtgccctcc 180
 cggttctccg gctccggctc cggaaccgag ttacacctga ccatctcttc cctgcagccc 240
 gaggacttcg ccacctacta ctgccagcag tacaaccggg acccctggac cttcggccag 300
 ggcaccaagg tggagatcaa gcgg 324

<210> 102

10 <211> 108

<212> PRT

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 102

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

35 <210> 103

<211> 357

<212> DNA

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 103

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 tcctgcaagg tgtccggctt caccctgacc gagctgtcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg gatggggcggc ttcgaccccg aggacggcga gaccatctac 180
 50 gccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgtc caccatcttc 300
 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357

55 <210> 104

<211> 119

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 104

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

<210> 105

<211> 324

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 105

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 ggcaaggccc ccaagcggct gatctacgcc gccttctccc tgcagtcagg cgtgccctcc 180
 cggttctccg gctccggctc cggcaccgag ttcaccctga ccctctctc cctgcagccc 240

 gaggacttcg ccacctacta ctgccagcag tacaaccggt acccctggac cttcggccag 300
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<210> 106

<211> 108

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<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 106

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EP 2 187 964 B1

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

<210> 107

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 107

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 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga ccagcctgag atcggaagac acggccgtgt attactgttc aacgattttt 300
 ggagtggtta ccaactttga caactggggc cagggaaacc tggtcaccgt ctctctca 357

<210> 108

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 108

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

EP 2 187 964 B1

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

10 <210> 109
 <211> 324
 <212> DNA
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 109

20 gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgcaggaga cagagtcacc 60
 atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagcgcct gatctatgct gcattcaatt tgcaaagtgg ggtcccatca 180
 agattcagcg gcagtggatc tgggacagaa ttcaactctca caatcagtag cctgcagcct 240
 25 gaagatcttg caagttatta ctgtcaacag tataatagat acccgtggac gttcggccaa 300
 gggaccaagg tggaaatcaa acga 324

<210> 110
 <211> 108
 30 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

35 <400> 110

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

<210> 111
 <211> 357
 55 <212> DNA
 <213> Artificial Sequence

<220>

EP 2 187 964 B1

<223> Synthetic

<400> 111

5 cagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

10 tcctgcaagg tttccggatt caccctcact gaattatcca ttactgggt ggcacaggct 120
 cctggaaaag ggcttgagtg gatgggaggt ttgatcctg aagatgggtg aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga ccagcctgag atcggaagac acggccgtgt attactgttc aacgattttt 300
 ggagtggtta ccaactttga caactggggc cagggaaccc tggtcaccgt ctctca 357

15 <210> 112

<211> 119

<212> PRT

<213> Artificial Sequence

20 <220>

<223> Synthetic

<400> 112

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

<210> 113

<211> 324

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 113

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 atcaattgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagcgctt gatctatgct gcattctcct tgcaaagtgg ggtcccatca 180
 agattcagcg gcagtggatc tgggacagaa ttactctca caatcagtag cctgcagcct 240
 gaagatcttg caagttatta ctgtcaacag tataatagat acccgtggac gttcggccaa 300
 gggaccaagg tggaaatcaa acga 324

EP 2 187 964 B1

<210> 114
 <211> 108
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 114

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ala Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Arg Asn Asp

15

20 25 30
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45
 Tyr Ala Ala Phe Ser 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 Leu Ala Ser Tyr Tyr Cys Gln Gln Tyr Asn Arg Tyr Pro Trp
 85 90 95
 25 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 115
 <211> 357
 <212> DNA
 <213> Artificial Sequence

30

<220>
 <223> Synthetic

35

<400> 115

40

gaagtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggct 60
 tcctgcaagg ttcccgata caccctcact gaattatcca tacactgggt gcgacaggct 120
 cctggaaaag ggcttgaatg gatgggaggt ttgatcctg aacatggtac aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgt aatgattttt 300
 ggcgtggtta ccaattttga caactggggc cagggaacca cggtcaccgt ctctctca 357

45

<210> 116
 <211> 119
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

<400> 116

55

EP 2 187 964 B1

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

<210> 117

<211> 24

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 117

ggatacacc tcactgaatt atcc 24

<210> 118

30 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 118

40 Gly Tyr Thr Leu Thr Glu Leu Ser
 1 5

<210> 119

<211> 24

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 119

tttgatcctg aacatggtac aaca 24

<210> 120

55 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

EP 2 187 964 B1

<223> Synthetic

<400> 120

5 Phe Asp Pro Glu His Gly Thr Thr
1 5

<210> 121
<211> 36
10 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

15 <400> 121
gtaatgattt ttggcgtggt taccaatttt gacaac 36

<210> 122
20 <211> 12
<212> PRT
<213> Artificial Sequence

<220>
25 <223> Synthetic

<400> 122

30 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn
1 5 10

<210> 123
<211> 321
35 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

40 <400> 123

45 gacatcgtga tgacccagtc tccatcctcc ctgtctgcat ccgtgagaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca cactcagcag cctgcagcct 240
gaagattttg caacttatta ttgttcacag tataataatt acccgtggac gttcggccaa 300
gggaccaagg tggagatcaa a 321

50 <210> 124
<211> 107
<212> PRT
<213> Artificial Sequence

55 <220>
<223> Synthetic

EP 2 187 964 B1

<400> 124

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

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<210> 125

<211> 18

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 125

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<210> 126

30 <211> 6

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 126

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      Gln Gly Ile Arg Asn Asp
      1           5
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<210> 127

<211> 9

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 127

gctgcatcc 9

<210> 128

55 <211> 3

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

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 <210> 129
 10 <211> 27
 <212> DNA
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 <220>
 15 <223> Synthetic

 <400> 129
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 20 <210> 130
 <211> 9
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 25 <220>
 <223> Synthetic

 <400> 130

 30 Ser Gln Tyr Asn Asn Tyr Pro Trp Thr
 1 5

 <210> 131
 35 <211> 357
 <212> DNA
 <213> Artificial Sequence

 <220>
 40 <223> Synthetic

 <400> 131

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 tcctgcaagg tgtccggcta caccctgacc gagctgtcca tgcactgggt gcggcaggcc 120
 ccggcaagg gcctggagt gatgggcggc ttcgaccccg agcacggcac caccatctac 180
 gccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgt gatgatcttc 300
 50 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357

 <210> 132
 <211> 119
 <212> PRT
 55 <213> Artificial Sequence

 <220>
 <223> Synthetic

EP 2 187 964 B1

<400> 132

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

20 <210> 133
 <211> 321
 <212> DNA
 <213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 133

30 gacatccaga tgacccagtc cccctcctcc ctgtccgcct ccgtgggcga ccgggtgacc 60
 atcacctgcc gggcctccca gggcatccgg aacgacctgg gctggtacca gcagaagccc 120
 ggcaaggccc ccaagcggct gatctacgcc gcctcctccc tgcagtcagg cgtgccctcc 180
 cggttctccg gctccggctc cggaaccgag ttcaccctga ccatctctc cctgcagccc 240
 35 gaggacttcg ccacctacta ctgctcccag tacaacaact acccctggac cttcggccag 300
 ggcaccaagg tggagatcaa g 321

40 <210> 134
 <211> 107
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Synthetic

<400> 134

50

55

EP 2 187 964 B1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30
 5 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 10 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 Ser Gln Tyr Asn Asn Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 15 <210> 135
 <211> 357
 <212> DNA
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 20 <220>
 <223> Synthetic
 25 <400> 135
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 tcctgcaagg ttcccgata caccctcact gaattatcca tacactgggt gcgacaggct 120
 cctggaaaag ggcttgaatg gatgggaggt ttgatcctg aacatggtac aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgt aatgattttt 300
 ggcgtgggta ccaattttga caactggggc caggggtaccc tggtcaccgt ctccctca 357
 35 <210> 136
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 40 <220>
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 45 <400> 136
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 55

EP 2 187 964 B1

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<210>	137
<211>	321
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25 $\langle 220 \rangle$
 $\langle 223 \rangle$ Synthetic

<400> 137

30	gacatccaga	tgaccagtc	tccatcctcc	ctgtctgcat	ccgtgagaga	cagagtcacc	60
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	gggaaagccc	ctaagcgcc	gatctatgct	gcattccagtt	tgcaaatgg	ggtcccatca	180
	aggttcagcg	gcagtggatc	tgggacagaa	ttcactctca	cactcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ttgttcacag	tataataatt	acccgtggac	gttcggccaa	300
35	gggaccaagg	tggagatcaa	a				321

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<210>	138
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<212>	PRT
<213>	Artificial Sequence

<220>
<223> Synthetic

45 <400> 138

50

55

EP 2 187 964 B1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Arg
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg 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 Glu Phe Thr Leu Thr Leu Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Tyr Asn Asn Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 139
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 <212> DNA
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 <223> Synthetic
 <400> 139
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 tcctgcaagg ttcccgatt caccctcact gaattatcca ttcactgggt gcgacaggct 120
 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctgc 240
 atggaactga gcagtctgag atctgaagac acggccgtgt attactgttc aacgattttt 300
 ggagtggtta ccaactttga caactggggc cagggaaacc tggtcaccgt ctccctca 357
 <210> 140
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 <223> Synthetic
 <400> 140

EP 2 187 964 B1

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

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20 <212> DNA

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<220>

<223> Synthetic

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<400> 141

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<211> 8

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<400> 142

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<400> 143

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<211> 8

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EP 2 187 964 B1

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<210> 145

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<223> Synthetic

<400> 145

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<211> 12

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<220>

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<400> 146

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Ser	Thr	Ile	Phe	Gly	Val	Val	Thr	Asn	Phe	Asp	Asn
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<211> 321

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gggaaagccc	ctaaacgcct	gatctatgct	gcattcaatt	tgcaaagtgg	gggtcccatca	180
agattcagcg	gcagtggatc	tgggacagaa	ttcactctca	caatcagtag	cctgcagcct	240
gaagatcttg	caagttatta	ctgtcaacag	tataatagat	acccgtggac	gttcggccaa	300
gggaccaagc	tggagatcaa	a				321

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<210> 148

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

EP 2 187 964 B1

<400> 148

	Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Ala	Gly
	1				5					10					15	
5	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ala	Ile	Arg	Asn	Asp
				20					25					30		
	Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
			35					40					45			
	Tyr	Ala	Ala	Phe	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
10		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	Leu	Ala	Ser	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Arg	Tyr	Pro	Trp
				85						90					95	
15	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
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20 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

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<400> 149

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<210> 150

30 <211> 6

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35 <223> Synthetic

<400> 150

40 Gln Ala Ile Arg Asn Asp
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<210> 151

<211> 9

45 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

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<400> 151

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<210> 152

55 $\langle 211 \rangle$ 3

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 15 <213> Artificial Sequence

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 20 <400> 153
 caacagtata atagataccc gtggacg 27

 <210> 154
 <211> 9
 25 <212> PRT
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 30
 <400> 154

 Gln Gln Tyr Asn Arg Tyr Pro Trp Thr
 35 1 5

 <210> 155
 <211> 357
 <212> DNA
 40 <213> Artificial Sequence

 <220>
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 45 <400> 155

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 tcctgcaagg ttcccgatt caccctcact gaattatcca ttactgggt gcgacaggct 120
 50 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatgggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctgc 240
 atggaactga gcagtctgag atctgaagac acggccgtgt attactgttc aacgattttt 300
 ggagtgggta ccaactttga caactggggc cagggaaccc tggtcaccgt ctccctca 357

 55 <210> 156
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EP 2 187 964 B1

<220>

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      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 Val Ser Gly Phe Thr Leu Thr Glu Leu
      20
10    Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
      35           40           45
      Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe
      50           55           60
      Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Cys
15
      65           70           75           80
      Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85           90           95
20    Ser Thr Ile Phe Gly Val Val Thr Asn Phe Asp Asn Trp Gly Gln Gly
      100           105           110
      Thr Leu Val Thr Val Ser Ser
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<210> 157

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<211> 321

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<223> Synthetic

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      atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
      gggaaagccc ctaaagcct gatctatgct gcattcaatt tgcaaagtgg ggtcccatca 180
      agattcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
      gaagatcttg caagttatta ctgtcaacag tataatagat acccgtggac gttcggccaa 300
40    gggaccaagg tggagatcaa a                                     321

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<210> 158

<211> 107

<212> PRT

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<213> Artificial Sequence

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<223> Synthetic

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<400> 158

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EP 2 187 964 B1

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

<210> 159
 <211> 357
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<220>
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<400> 159

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cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatggtga agtaatttat 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggaactga ggagcctgag atctgaggac acggccgtgt tttatttgtt aatgattttt 300
 ggagtgggta ccaactttga caattggggc cagggaacca cggtcaccgt ctccctca 357

<210> 160
 <211> 119
 <212> PRT
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<400> 160

EP 2 187 964 B1

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 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Val Ser Gly Phe Thr Leu Asn Glu Leu
 20 25 30
 10 Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu Asp Gly Glu Val Ile Tyr Ala Gln Lys Phe
 50 55 60
 15 Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Arg Ser Leu Arg Ser Glu Asp Thr Ala Val Phe Tyr Cys
 85 90 95
 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn Trp Gly Gln Gly
 100 105 110
 20 Thr Thr Val Thr Val Ser Ser
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<210> 161

<211> 24

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 161

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<210> 162

30 <211> 8

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35 <223> Synthetic

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40 Gly Phe Thr Leu Asn Glu Leu Ser
 1 5

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<223> Synthetic

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<400> 163

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EP 2 187 964 B1

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 Gly Phe Asp Pro Glu Asp Gly Glu Val
 1 5

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 20 <210> 166
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 25 <220>
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 <400> 166

 30 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn
 1 5 10

 <210> 167
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 35 <212> DNA
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 atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagcgcct gatctatggg gcattcagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
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 <210> 168
 <211> 107
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EP 2 187 964 B1

<400> 168

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

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<210> 169

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20 <212> DNA

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<400> 169

cagggcatta gaaatgat 18

<210> 170

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<213> Artificial Sequence

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35 <223> Synthetic

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      Gln Gly Ile Arg Asn Asp
      1           5

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<210> 171

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<400> 171

ggtgcattc 9

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EP 2 187 964 B1

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 Gly Ala Phe
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 Leu Gln Tyr Asn Thr Tyr Pro Trp Thr
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 <210> 175
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 tcctgcaagg tgtccggctt caccctgaac gagctgtcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg gatgggaggc ttcgaccccg aggacggcga ggtgatctac 180
 gcccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
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 50 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357

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EP 2 187 964 B1

<400> 176

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<210> 177

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	atcacctgcc	gggcctccca	gggcatacgg	aacgacctgg	gctggtacca	gcagaagccc	120
35	ggcaaggccc	ccaagcggt	gatctacggc	gccttctccc	tgcagtccgg	cgtgccctcc	180
	cggttctccg	gctccggctc	cggcacccag	ttcacccctga	ccatctcctc	cctgcagccc	240
	gaggacttcg	ccacctacta	ctgcctgcag	tacaacacct	acccttggac	cttcggccag	300
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40 <210> 178

<211> 107

<212> PRT

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45 <220>

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<400> 178

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55

EP 2 187 964 B1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30
 5 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45
 Tyr Gly Ala Phe Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 10 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 Leu Gln Tyr Asn Thr Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 15
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 cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatggtga agtaatttat 180
 30 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggaactga ggagcctgag atctgaggac acggccgtgt tttatttgtt aatgattttt 300
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EP 2 187 964 B1

[illegible]

<210> 181

 $\langle 211 \rangle$ 321

20 <212> DNA

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<223> Synthetic

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<400> 181

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	atcacttgcc	gggcaagtca	gggcattaga	aatgatttag	gctgggtatca	gcagaaacca	120
	gggaaagccc	ctaagcgcc	gatctatggt	gcattcagtt	tgcaaagtgg	ggtcccatca	180
	aggttcagcg	cgagtggatc	tgggacagaa	ttcactctca	caatcagcag	cctgcagcct	240
	gaagattttg	caactttatta	ctgtctacag	tataatactt	atccgtggac	gttcggccaa	300
	gggaccaagq	tggaaatcaa	a				321

35

<210> 182

<211> 107

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<400> 182

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50

55

EP 2 187 964 B1

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 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30
 5 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45
 Tyr Gly Ala Phe Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 10 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 Leu Gln Tyr Asn Thr Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 15 <210> 183
 <211> 357
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 25 <400> 183
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 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aacatggtga aacaatctac 180
 30 gcacagaagt tccagggcag agtcaccatg accgaggact catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aatgattttt 300
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 45 <400> 184
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EP 2 187 964 B1

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 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu Leu
 20 25 30
 Ser Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu His Gly Glu Thr Ile Tyr Ala Gln Lys Phe
 50 55 60
 10 Gln Gly Arg Val Thr Met Thr Glu Asp Ser Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Met Ile Phe Gly Val Val Thr Asn Phe Asp Ser Trp Gly Leu Gly
 100 105 110
 15 Thr Leu Val Thr Val Ser Ser
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30 <210> 186
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35 <220>
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40 Gly Tyr Thr Leu Thr Glu Leu Ser
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EP 2 187 964 B1

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 Phe Asp Pro Glu His Gly Glu Thr
 1 5

 <210> 189
 10 <211> 36
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 20 <210> 190
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 Ala Met Ile Phe Gly Val Val Thr Asn Phe Asp Ser
 1 5 10

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 gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtctacag tataatagtt acccgtggac gttcggccaa 300
 50 gggaccaagc tggagatcaa a 321

 <210> 192
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 55 <213> Artificial Sequence

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EP 2 187 964 B1

<400> 192

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

<210> 193

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20 <212> DNA

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<400> 193

cagggcatta gaaatgat 18

<210> 194

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40 Gln Gly Ile Arg Asn Asp
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<210> 195

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<213> Artificial Sequence

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50 <400> 195

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EP 2 187 964 B1

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<400> 197

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25 <223> Synthetic

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30 Leu Gln Tyr Asn Ser Tyr Pro Trp Thr

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35 <210> 199

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40 <220>

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	ccgggcaagg	gcctggagtg	gatggcgccg	ttcgaccccg	agcaccgcga	gaccatctac	180
	gccagaagt	tccagggccg	ggtgacctg	accgaggaca	ctctcaccga	caccgcctac	240
50	atggagctgt	cctccctgcg	gtccgaggac	accgcgctgt	actactgcgc	catgatcttc	300
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<210> 200

<211> 119

55 <212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

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<223> Synthetic

<400> 200

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

<210> 201

<211> 321

<212> DNA

25 <213> Artificial Sequence

<220>

<223> Synthetic

30 <400> 201

35 gacatccaga tgacccagtc cccctcctcc ctgtccgcct ccgtgggcga ccgggtgacc 60
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 ggcaaggccc ccaagcggtc gatctacgcc gcctcctccc tgcagtcagg cgtgccctcc 180
 cggttctccg gctccggctc cggcaccgag ttcaccctga ccctctctc cctgcagccc 240
 gaggacttcg ccacctacta ctgcctgcag tacaactcct acccctggac cttcggccag 300
 ggcaccaagg tggagatcaa g 321

40 <210> 202

<211> 107

<212> PRT

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 202

50

55

EP 2 187 964 B1

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

15

<210> 203

<211> 357

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 203

25

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 tcttgcaagg tttccggata caccctcact gaattatcca tgtactgggt gcgacaggct 120
 cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aacatggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggact catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aatgattttt 300
 ggagtgggta ccaactttga ctctctggggc ctgggaaccc tggtcactgt ctctctca 357

30

<210> 204

35

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

40

<223> Synthetic

<400> 204

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

55

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

<210> 205
<211> 321
10 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic
15 <400> 205

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20 atcacttgcc gggcaagtca gggcattaga aatgatttag gctgggatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcattccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag tataatagtt acccgtggac gttcggccaa 300
gggaccaagg tggagatcaa a 321

25 <210> 206
<211> 107
<212> PRT
<213> Artificial Sequence

30 <220>
<223> Synthetic

35 <400> 206

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

50 <210> 207
<211> 375
<212> DNA
<213> Artificial Sequence

55 <220>
<223> Synthetic

EP 2 187 964 B1

<400> 207

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 tcctgtgcag cccctggatt caactttgat gattatgcc a tgcactgggt ccggcaaact 120
 ccaggaagg gcctggagtg ggtctcaggt attagttaga atagtggtag tataggctat 180

10 gcggactctg tgaagggccg atttaccatc tccagagaca acgccaagaa ctccctgtat 240
 cttcaaatga acagtctgag acctgaggac acggccttgt attactgtgc aaaagaagg 300
 gtatggttcg gaaaattgtt ctcatcctac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

<210> 208

15 <211> 125

<212> PRT

<213> Artificial Sequence

<220>

20 <223> Synthetic

<400> 208

25 Glu 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 Pro Gly Phe Asn 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
 30 Ser Gly Ile Ser Trp Asn Ser Gly Thr 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 Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 35 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

40

<210> 209

<211> 24

<212> DNA

<213> Artificial Sequence

45

<220>

<223> Synthetic

<400> 209

50 ggattcaact ttgatgatta tgcc 24

<210> 210

<211> 8

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 187 964 B1

<400> 210

5 Gly Phe Asn Phe Asp Asp Tyr Ala
1 5

<210> 211
<211> 24
<212> DNA
10 <213> Artificial Sequence

<220>
<223> Synthetic

15 <400> 211
attagttgga atagtggtac tata 24

<210> 212
<211> 8
20 <212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

25 <400> 212

30 Ile Ser Trp Asn Ser Gly Thr Ile
1 5

<210> 213
<211> 54
<212> DNA
35 <213> Artificial Sequence

<220>
<223> Synthetic

40 <400> 213
gcaaaagaag gggatgggt cggaaaattg ttctcatcct acggtatgga cgtc 54

<210> 214
<211> 18
45 <212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

50 <400> 214

55 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
1 5 10 15
Asp Val

<210> 215

EP 2 187 964 B1

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

5 <220>
 <223> Synthetic

<400> 215

10 gacatccgga tgacccagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtggtact tacaacttag actggtacca gcagaaacct 120
 ggccaggctc ccaggctcct catctttggt gcaccacca gggccactgg tatccagacc 180
 aggttcagtg gcagtgggtc tgggacagag ttcaactcct ccatcaccag cctgcagtct 240
 15 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 gggaccaagg tggaaatcaa a 321

<210> 216
 <211> 107
 20 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 216

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

<210> 217
 <211> 18
 45 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

50 <400> 217
 cagagtgtta cttacaac 18

<210> 218
 55 <211> 6
 <212> PRT
 <213> Artificial Sequence

EP 2 187 964 B1

<220>
 <223> Synthetic

 <400> 218
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 Gln Ser Val Thr Tyr Asn
 1 5

 <210> 219
 10 <211> 9
 <212> DNA
 <213> Artificial Sequence

 <220>
 15 <223> Synthetic

 <400> 219
 ggtgcatcc 9

 20 <210> 220
 <211> 3
 <212> PRT
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 220

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 Gly Ala Ser
 1

 <210> 221
 <211> 27
 35 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic
 40
 <400> 221
 cagcagtata ataactggcc gtacact 27

 <210> 222
 45 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>
 50 <223> Synthetic

 <400> 222

 55 Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
 1 5

 <210> 223
 <211> 375

EP 2 187 964 B1

<212> DNA

<213> Artificial Sequence

<220>

5 <223> Synthetic

<400> 223

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10   gaggtgcagc tgggtggagtc cggcggcggc ctggtgcagc cgggccggtc cctgcccgtg 60
      tcctgcgccg cccccggctt caacttcgac gactacgcca tgcactgggt gcggcaggcc 120
      cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggcac catcggctac 180
      gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
      ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
      gtgtggttcg gcaagctgtt ctccctctac ggcattggac tgtggggcca gggcaccacc 360
15   gtgaccgtgt cctcc                                     375

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<210> 224

<211> 125

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 224

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

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<210> 225

45 <211> 324

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Synthetic

<400> 225

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EP 2 187 964 B1

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 ctgtcctgcc gggcctccca gtccgtgacc tacaacctgg actggtacca gcagaagccc 120
 gggcaggccc cccggctgct gatctacggc gcctccaccc gggccaccgg catccccgcc 180
 5 cggttctccg gctccggctc cggcaccgag ttcaacctga ccatctcttc cctgcagtcc 240
 gaggacttcg ccgtgtacta ctgccagcag tacaacaact ggccctacac cttcggccag 300
 ggcaccaagc tggagatcaa gcgg 324

<210> 226

10 <211> 108

<212> PRT

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 226

20 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 Val Thr Tyr Asn
 20 25 30
 Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 25 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 Asn Asn Trp Pro Tyr
 30 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> 227

35 <211> 375

<212> DNA

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 227

45 gaggtgcagc tgggtggagtc cggcggcggc ctggtgcagc ccggccggtc cctgcggctg 60
 tcctgcgccg cctccggctt caacttcgac gactacgcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggcac catcggctac 180
 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
 ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
 gtgtggttcg gcaagctgtt ctccctctac ggcattggacg tgtggggcca gggcaccacc 360
 50 gtgaccgtgt cctcc 375

<210> 228

<211> 125

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 187 964 B1

<400> 228

5 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 Asn 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
 10 Ser Gly Ile Ser Trp Asn Ser Gly Thr 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
 15 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

20 <210> 229
 <211> 324
 <212> DNA
 <213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 229

30 gagatcgtga tgacccagtc ccccgccacc ctgtccgtgt ccccgggcga gcggggccacc 60
 ctgtcctgcc gggcctccca gtccgtgacc tacaacctgg cctgggtacca gcagaagccc 120
 ggccaggccc cccggctgct gatctacggc gcctccaccc gggccaccgg catccccgcc 180
 cggttctccg gctccggctc cggcaccgag ttcaccctga ccattctctc cctgcagtcc 240
 35 gaggacttcg ccgtgtacta ctgccagcag tacaacaact ggccctacac cttcgggccag 300
 ggcaccaagc tggagatcaa gcggg 324

40 <210> 230
 <211> 108
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Synthetic

<400> 230

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55

EP 2 187 964 B1

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 Val Thr Tyr Asn
 20 25 30
 5 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
 10 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

15

<210> 231

<211> 375

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 231

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 ccagggaagg gcctggagtg ggtctcaggt attagtgg a atagtgtac tataggctat 180
 gcggactctg tgaagggccg atttaccatc tccagagaca acgccaagaa ctccctgtat 240
 30 cttcaaatga acagtctgag acctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gaaaattgtt ctcatcctac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

35

<210> 232

<211> 125

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 232

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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 Pro Gly Phe Asn 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
 50 Ser Gly Ile Ser Trp Asn Ser Gly Thr 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 Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95

55

EP 2 187 964 B1

Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

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<210> 233
<211> 324
<212> DNA
<213> Artificial Sequence

10
<220>
<223> Synthetic

15
<400> 233

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ctctcctgca gggccagtca gagtgttact tacaacttag actggtacca gcagaaacct 120
ggccaggctc ccaggctcct catcttttgt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcaccag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
gggaccaagc tggagatcaa acga 324

25
<210> 234
<211> 108
<212> PRT
<213> Artificial Sequence

30
<220>
<223> Synthetic

35
<400> 234

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

50
<210> 235
<211> 375
<212> DNA
<213> Artificial Sequence

55
<220>
<223> Synthetic

<400> 235

EP 2 187 964 B1

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 ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
 5 gcggaactctg tgaagggccg atttaaccatc tccagagaca acgccaagaa ctccctgtat 240
 cttcaaataga acagtctgag acctgaggac acggccttgt attactgtgc aaaagaaggg 300

gtatggttcg gaaaattggt ctcatactac ggtatggacg tctggggcca agggaccacg 360
 10 gtcaccgtct cctca 375

<210> 236

<211> 125

<212> PRT

15 <213> Artificial Sequence

<220>

<223> Synthetic

20 <400> 236

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

<210> 237

40 <211> 324

<212> DNA

<213> Artificial Sequence

<220>

45 <223> Synthetic

<400> 237

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 ctctcctgca gggccagtc gagtggtact tacaacttag cctggtacca gcagaaacct 120
 ggccaggctc ccaggctcct catcttttgt gcatccacca gggccactgg tateccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcaactctca ccatcaccag cctgcagctc 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 55 gggaccaagc tggagatcaa acga 324

<210> 238

<211> 108

EP 2 187 964 B1

<212> PRT

<213> Artificial Sequence

<220>

5 <223> Synthetic

<400> 238

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

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25 <210> 239

<211> 357

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30 <220>

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<400> 239

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      tcctgcaagg ttcccgata caccctcact gaattatcca tacactgggt gcgacaggct 120
      cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatggtga aacaatctac 180
      gcacagaagt tccagggcag agtcatcatg accgaggaca catctacaga cacagcctat 240
40      atggagctga gcagcctgag atctgaggac acggccgtgt attattgtgt aatgattttt 300
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EP 2 187 964 B1

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

<400> 241

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<210> 242

30 <211> 8

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<213> Artificial Sequence

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35 <223> Synthetic

<400> 242

40 Gly Tyr Thr Leu Thr Glu Leu Ser
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<210> 243

<211> 24

45 <212> DNA

<213> Artificial Sequence

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50 <400> 243

tttgatcctg aagatggtga aaca 24

<210> 244

55 <211> 8

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EP 2 187 964 B1

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Phe	Asp	Pro	Glu	Asp	Gly	Glu	Thr
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<211> 36

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15

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<211> 12

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 246

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Val	Met	Ile	Phe	Gly	Val	Val	Thr	Asn	Phe	Asp	Asn
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<212> DNA

<213> Artificial Sequence

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<400> 247

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gggaaagccc	ctaagcgcct	gatctatgct	gcattccagtt	tgcaaagtgg	ggtcccatca	180
aggttcagcg	gcagtggatc	tgggacagaa	tccactctca	caatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ttgttcacag	tataatagtt	accctgggac	gttcggccaa	300
gggaccaagg	tggagatcaa	a				321

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<210> 248

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<211> 107

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 248

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

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<210> 249

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<220>

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<400> 249

30 cagggcatta gaaatgat 18

<210> 250

<211> 6

<212> PRT

35 <213> Artificial Sequence

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<400> 250

Gln Gly Ile Arg Asn Asp
 1 5

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<211> 9

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<213> Artificial Sequence

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<400> 251

55 gctgcatcc 9

<210> 252

<211> 3

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EP 2 187 964 B1

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 20 tcacagtata atagttaccc gtggacg 27
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 30 <400> 254
 Ser Gln Tyr Asn Ser Tyr Pro Trp Thr
 1 5
 35 <210> 255
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 <212> DNA
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 40 <220>
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 tcctgcaagg tgtccggcta caccctgacc gagctgtcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg gatggggcggc ttcgaccccg aggacggcga gaccatctac 180
 50 gccagaaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgt gatgatcttc 300
 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357
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EP 2 187 964 B1

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<400> 256

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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 Val Ser Gly Tyr Thr Leu Thr Glu Leu
 20 25 30
 Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
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<210> 257

<211> 321

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<212> DNA

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<220>

<223> Synthetic

30

<400> 257

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 ggcaaggccc ccaagcggt gatctacgcc gcctcctccc tgcagtcagg cgtgccctcc 180
 cggttctccg gctccggctc cggcaccgag ttcaccctga ccctctctc cctgcagccc 240
 gaggacttcg ccacctacta ctgctcccag tacaactcct acccctggac ctccggccag 300
 ggcaccaagg tggagatcaa g 321

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<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 258

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EP 2 187 964 B1

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

<210> 259

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 259

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 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatggtga aacaatctac 180
 gcacagaagt tccagggcag agtcatcatg accgaggaca catctacaga cacagcctat 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attattgtgt aatgattttt 300
 ggcggtgtta ccaactttga caactggggc cagggaaccc tggtcaccgt ctccctca 357

<210> 260

<211> 119

<212> PRT

<213> Artificial Sequence

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EP 2 187 964 B1

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<210> 261

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20 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

25

<400> 261

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gggaaagccc	ctaagcgct	gatctatgct	gcattccagtt	tgcaaagtg	ggtcccatca	180
aggttcagcg	gcagtggtac	tgggacagaa	tccactctca	caatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ttgttcacag	tataatagtt	accctgggac	gttcggccaa	300
gggaccaag	tggaaatcaa	a				321

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<210> 262

<211> 107

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<213> Artificial Sequence

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 $\langle 220 \rangle$

<223> Synthetic

<400> 262

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EP 2 187 964 B1

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

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 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatgggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaagac acggccgtgt attactgttc aacgattttt 300
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<211> 119

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<223> Synthetic

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50

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EP 2 187 964 B1

Glu 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 Val Ser Gly Phe Thr Leu Thr Glu Leu
 20 25 30
 Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
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 100 105 110
 Thr Leu Val Thr Val Ser Ser
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<400> 265
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<210> 266
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<220>
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<400> 266

Gly Phe Thr Leu Thr Glu Leu Ser
 1 5

<210> 267
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<220>
 <223> Synthetic

<400> 267
 ttgtacctg aagatggtga aaca 24

<210> 268
 <211> 8
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EP 2 187 964 B1

<220>
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 <400> 268
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 Phe Asp Pro Glu Asp Gly Glu Thr
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 <210> 269
 10 <211> 36
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 <400> 269
 tcaacgattt ttggagtggg taccaacttt gacaac 36

 20 <210> 270
 <211> 12
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 25 <220>
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 <400> 270

 30
 Ser Thr Ile Phe Gly Val Val Thr Asn Phe Asp Asn
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 <210> 271
 35 <211> 321
 <212> DNA
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 40 <223> Synthetic

 <400> 271

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 atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagcgctt ggtctatgct gcattcaatt tgcaaagtgg ggtcccatca 180
 agattcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
 gaagatcttg caacttatta ctgtctacag tataaatagtt acccgtggac gttcggccaa 300
 50 gggaccaaag tggatatcaa a 321

 <210> 272
 <211> 107
 <212> PRT
 55 <213> Artificial Sequence

 <220>
 <223> Synthetic

EP 2 187 964 B1

<400> 272

5 Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ala Gly
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 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Arg Asn Asp

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

20 <210> 273
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 <212> DNA
 <213> Artificial Sequence

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 <223> Synthetic

 <400> 273
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30 <210> 274
 <211> 6
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 <213> Artificial Sequence

35 <220>
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40 <400> 274

 Gln Ala Ile Arg Asn Asp
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45 <210> 275
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 <212> DNA
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50 <220>
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 <400> 275
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55 <210> 276
 <211> 3
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EP 2 187 964 B1

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 <400> 276
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 Ala Ala Phe
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 <210> 277
 10 <211> 27
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 <400> 277
 ctacagtata atagttaccc gtggacg 27

 <210> 278
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 <400> 278

 30 Leu Gln Tyr Asn Ser Tyr Pro Trp Thr
 1 5

 <210> 279
 35 <211> 357
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 40 <223> Synthetic

 <400> 279

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 tcctgcaagg tgtccggctt caccctgacc gagctgtcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg gatgggcggc ttcgaccccg aggacggcga gaccatctac 180
 gcccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgtc caccatcttc 300
 50 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtccctcc 357

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EP 2 187 964 B1

<400> 280

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<210> 281
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atcacctgcc	gggcctccca	ggccatccgg	aacgacctgg	gctggtacca	gcagaagccc	120
ggcaaggccc	ccaagcggt	gatctacgcc	gccttctccc	tgcagtcgg	cgtgccctcc	180
cggttctccg	gctccggctc	cggcacccgag	ttcacccctga	ccatctcctc	cctgcagccc	240
gaggacttcg	ccacctacta	ctgcctgcag	tacaactcct	accocctggac	cttcggccag	300
ggcaccaagc	tggagatcaa	g				321

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

<220>
<223> Synthetic

<400> 282

EP 2 187 964 B1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Arg Asn Asp
 20 25 30
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45
 Tyr Ala Ala Phe Ser 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 Leu Gln Tyr Asn Ser Tyr Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 283
 <211> 357
 <212> DNA
 <213> Artificial Sequence
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 <223> Synthetic
 <400> 283
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 tcctgcaagg ttcccgatt caccctcact gaattatcca ttactgggt gcgacaggct 120
 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatggtga aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaagac acggccgtgt attactgttc aacgattttt 300
 ggagtgggta ccaactttga caactggggc cagggaaacc tggtcaccgt ctctc 357
 <210> 284
 <211> 119
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 <213> Artificial Sequence
 <220>
 <223> Synthetic
 <400> 284

EP 2 187 964 B1

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

<210> 285

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 285

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 gggaaagccc ctaagcgcct ggtctatgct gcattcaatt tgcaaagtgg ggtcccatca 180
 agattcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
 gaagatcttg caacttatta ctgtctacag tataaatagtt acccgtggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> 286

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 286

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

EP 2 187 964 B1

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

<210> 287
 10 <211> 375
 <212> DNA
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<220>
 15 <223> Synthetic

<400> 287

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 ccaggaagg gcctggaatg ggtctcaggt attagttgga atagtggaac tatagtctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgtcaagaa caccctgtat 240
 ctgcaaatga aaagtctgag agatgaggac acggccgtat attactgtgc aaaagaaggg 300
 gtatggttcg ggagattatt ttcatacctac ggtatggacg tctggggcca agggaccctg 360
 25 gtcaccgtct cctca 375

<210> 288
 <211> 125
 <212> PRT
 30 <213> Artificial Sequence

<220>
 <223> Synthetic

35 <400> 288

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

<210> 289
 55 <211> 24
 <212> DNA
 <213> Artificial Sequence

EP 2 187 964 B1

<220>
 <223> Synthetic

5 <400> 289
 ggattcactt ttgatgatta ttcc 24

10 <210> 290
 <211> 8
 <212> PRT
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15 <220>
 <223> Synthetic

20 <400> 290
 Gly Phe Thr Phe Asp Asp Tyr Ser
 1 5

25 <210> 291
 <211> 24
 <212> DNA
 <213> Artificial Sequence

30 <220>
 <223> Synthetic

35 <400> 291
 attagttgga atagtggaac tata 24

40 <210> 292
 <211> 8
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Synthetic

50 <400> 292

55 Ile Ser Trp Asn Ser Gly Thr Ile
 1 5

55 <210> 293
 <211> 54
 <212> DNA
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55 <220>
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55 <400> 293
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<210> 294
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EP 2 187 964 B1

<212> PRT

<213> Artificial Sequence

<220>

5 <223> Synthetic

<400> 294

10 Ala Lys Glu Gly Val Trp Phe Gly Arg Leu Phe Ser Ser Tyr Gly Met

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20 <220>

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<400> 295

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 ctctcctgca gggccagtc gagtgtagc agcaacttag cctggtacca gcagagacct 120
 ggcagcctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
 30 gaagattttg cagtttatta ctgtcaacag tatagtaact ggccgtacac ttttggccag 300
 gggaccaagg tggagatcaa a 321

<210> 296

<211> 107

35 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 296

45 Asp Ile Arg 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 Pro Ser Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Pro 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 Asn Trp Pro Tyr
 85 90 95
 55 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 297

EP 2 187 964 B1

<211> 18
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5 <220>
 <223> Synthetic

<400> 297
 ccgagtgta gcagcaac 18

10 <210> 298
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15 <220>
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<400> 298

20 Pro Ser Val Ser Ser Asn
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<210> 299
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25 <220>
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 ggtgcatcc 9

30 <210> 300
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35 <220>
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<400> 300

40 Gly Ala Ser
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<210> 301
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45 <220>
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<400> 301
 caacagtata gtaactggcc gtacact 27

EP 2 187 964 B1

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

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Gln Gln Tyr Ser Asn Trp Pro Tyr Thr
 1 5

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<400> 303

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 tctctgcgcc cctccggctt caccttcgac gactactcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggcac catcggctac 180
 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
 ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
 gtgtgtgttcg gccggctgtt ctccctoctac ggcatggacg tgtggggcca gggcaccacc 360
 gtgaccgtgt cctcc 375

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<210> 304
 <211> 125
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 304

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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
 Ser 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 Thr 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 Glu Gly Val Trp Phe Gly Arg Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

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EP 2 187 964 B1

<210> 305
 <211> 321
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 305

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 ctgtcctgcc gggcctcccc ctccgtgtcc tccaacctgg cctggtacca gcagaagccc 120
 ggccaggccc cccggtctgt gatctacggc gcctccacccc ggccacacgg catccccgcc 180
 cggttctccg gctccggctc cggcaaccgag ttaccacctga ccatctcttc cctgcagtc 240
 gaggacttcg ccgtgtacta ctgccagcag tactccaact ggccctacac cttcggccag 300
 ggcaccaagc tggagatcaa g 321

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<210> 306
 <211> 107
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

25

<400> 306

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 Pro Ser Val 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 Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

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35

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<210> 307
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 <212> DNA
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<220>
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<400> 307

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EP 2 187 964 B1

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 tcctgtgcag cctctggatt cacttttgat gattattcca tgcactgggt ccggcaaggt 120
 ccagggaagg gcctggaatg ggtctcaggt attagttaga atagtggaac tatagtctat 180
 5 gcggaactctg tgaagggccg attcaccatc tccagagaca acgtcaagaa caccctgtat 240
 ctgcaaatga aaagtctgag agatgaggac acggccgtat attactgtgc aaaagaaggg 300
 gtatgggttcg ggagattatt ttcacacctac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

<210> 308

10 <211> 125

<212> PRT

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 308

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

35

<210> 309

<211> 321

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 309

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 ctctcctgca gggccagtcg gagtggttagc agcaacttag cctggtacca gcagagacct 120
 ggccagcctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
 50 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtc 240
 gaagattttg cagtttatta ctgtcaacag tatagtaact ggccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

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<210> 310

<211> 107

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 310

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

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20

<210> 311

<211> 375

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

<400> 311

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      tcctgtgcag cctctagatt cacctttgaa gattatgccca tgcactgggt ccggcaagct 120
      ccagggaagg gcctggaatg ggtctcaggg attagtggga atagtggtag tatagggttat 180
35    gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
      ctgcgaatga acagtctgag agctgatgac acggccttgt attatttgtt aaaagaaggg 300
      gtatggttcg ggaagttatt ctcatectac ggtctggacg tctggggcca agggaccacg 360
      gtcaccgtct cctca
      375

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<210> 312

<211> 125

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 312

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55

EP 2 187 964 B1

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

<210> 313

<211> 24

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 313

agattcacct ttgaagatta tgcc 24

<210> 314

30 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 314

40 Arg Phe Thr Phe Glu Asp Tyr Ala
 1 5

<210> 315

<211> 24

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 315

attagttgga atagtggttag tata 24

<210> 316

55 <211> 8

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

<220>
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 <400> 316
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 Ile Ser Trp Asn Ser Gly Ser Ile
 1 5

 <210> 317
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 <400> 317
 gtaaagaag gggatgggt cggaagta ttctatcct acggtctgga cgtc 54

 20 <210> 318
 <211> 16
 <212> PRT
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 318

 30 Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Leu Asp Val
 1 5 10 15

 <210> 319
 <211> 321
 35 <212> DNA
 <213> Artificial Sequence

 <220>
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 <400> 319

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 45 ctctcttgca gggccagtc gagtgtagc agcaacttag cctggtacca gcagaaacct 120
 gaccaggctc ccaggctcct catctatggt tcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 gggaccaagg tggagatcaa a 321

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 <212> PRT
 <213> Artificial Sequence
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 <220>
 <223> Synthetic

EP 2 187 964 B1

<400> 320

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

<210> 321

<211> 18

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 321

cagagtgtta gcgcaac 18

<210> 322

30 <211> 6

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 322

40 Gln Ser Val Ser Ser Asn
 1 5

<210> 323

<211> 9

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 323

ggttcattcc 9

<210> 324

55 <211> 3

<212> PRT

<213> Artificial Sequence

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<220>
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<400> 324

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Gly Ser Ser

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<210> 325
<211> 27
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<220>
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<400> 325
cagcagtata alaactggcc gtacact 27

<210> 326
<211> 9
<212> PRT
<213> Artificial Sequence

25

<220>
<223> Synthetic

30

<400> 326

Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
1 5

35

<210> 327
<211> 375
<212> DNA
<213> Artificial Sequence

40

<220>
<223> Synthetic

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<400> 327

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tcctgcgccg cctcccgggt cacccttcgag gactacgcc a tgcactgggt gcggcaggcc 120
cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggctc catcggctac 180
gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgt gaaggagggc 300
gtgtggttcg gcaagctgtt ctctctctac ggctggacg tgtggggcca gggcaccacc 360
gtgaccgtgt cctcc 375

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<210> 328
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EP 2 187 964 B1

<220>

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<400> 328

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      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 Glu Asp Tyr
      20          25          30
10    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

15    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
20    Val Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Leu
      100          105          110
      Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

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<210> 329

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<211> 321

<212> DNA

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<223> Synthetic

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      ctgtcctgcc gggcctccca gtccgtgtcc tccaacctgg cctggtacca gcagaagccc 120
      ggccaggccc cccggctgct gatctacggc tctccacccc gggccaccgg catccccgcc 180
      cggttctccg gctccggctc cggcaccgag ttcaccctga ccatctcctc cctgcagtc 240
      gaggacttcg ccgtgtacta ctgccagcag tacaacaact ggccctacac cttcggccag 300
40    ggacaccaagc tggagatcaa g                                     321

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<210> 330

<211> 107

<212> PRT

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<213> Artificial Sequence

<220>

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<400> 330

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EP 2 187 964 B1

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 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 5 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ser Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 10 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 Asn Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 15
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 <211> 375
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 <213> Artificial Sequence
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 <220>
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 <400> 331
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 30 tctgtgcag cctctagatt cacctttgaa gattatgcc a tgcactgggt ccggcaagct 120
 ccaggaagg gcctggaatg ggtctcaggg attagttgga atagtggtag tataggttat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcgaatga acagtctgag agctgatgac acggccttgt attatttgtt aaaagaaggg 300
 gtatggttcg ggaagttatt ctcatcctac ggtctggacg tctggggcca agggaccacg 360
 35 gtcaccgtct cctca 375
 <210> 332
 <211> 125
 <212> PRT
 40 <213> Artificial Sequence
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 45 <400> 332
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EP 2 187 964 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Glu 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 Arg Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Val Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Leu
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 333

<211> 321

<212> DNA

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<220>

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<400> 333

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 ctctcttgca gggccagtca gagggttagc agcaacttag cctggtacca gcagaaacct 120
 gaccaggctc ccaggctcct catctatggt tcatccacca gggccactgg tatccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

35

<210> 334

<211> 107

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 334

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

50

55

EP 2 187 964 B1

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

15 <210> 335
 <211> 375
 <212> DNA
 <213> Artificial Sequence

20 <220>
 <223> Synthetic
 <400> 335

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 tcctgtgcag cccctggatt caactttgat gattatgcc a tgcactgggt ccggcaagct 120
 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 30 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaagg 300
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 gtcaccgtct cctca 375

35 <210> 336
 <211> 125
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> Synthetic
 <400> 336

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EP 2 187 964 B1

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	1				5				10					15		
	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Pro	Gly	Phe	Asn	Phe	Asp	Asp	Tyr
				20					25					30		
5	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
10	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	Glu	Gly	Val	Trp	Phe	Gly	Lys	Leu	Phe	Ser	Ser	Tyr	Gly	Met
				100				105						110		
15	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
			115					120					125			

<210> 337

<211> 24

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 337

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<210> 338

30 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 338

					Gly	Phe	Asn	Phe	Asp	Asp	Tyr	Ala
					1				5			

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<211> 24

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 339

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<210> 340

55 <211> 8

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<213> Artificial Sequence

<220>

EP 2 187 964 B1

<223> Synthetic

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Ile	Ser	Trp	Asn	Ser	Gly	Ser	Ile
1				5			

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<211> 54

<212> DNA

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 341

gcaaaagaag gggatgggt cggaaaatta ttctatcct acggtatgga cgltc 54

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<210> 342

<211> 18

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 342

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Ala	Lys	Glu	Gly	Val	Trp	Phe	Gly	Lys	Leu	Phe	Ser	Ser	Tyr	Gly	Met
1				5					10					15	
Asp	Val														

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<210> 343

<211> 321

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 343

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ctctcctgca	gggccagtc	gagtgttagc	agcaacttag	actggtacca	gcagaaacct	120
ggccaggctc	ccaggtcct	cactatggt	gcacccacca	gggccactgg	tatcccagcc	180
aggttcagt	gcagtgggtc	tgggacagag	ttcactctca	ccatcagcag	cctgcagtct	240
gaagattttg	cagtttatta	ctgtcagcag	tataataact	ggccgtacac	ttttggccag	300
gggaccaagc	tgagatcaa	a				321

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<210> 344

<211> 107

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<212> PRT

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 344

5	Asp	Val	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	Val	Ser	Ser	Asn
				20					25						30	
10	Leu	Asp	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	
15	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Asn	Trp	Pro	Tyr
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
				100					105							

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<210> 345
<211> 18
<212> DNA
<213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 345
cagagtgtta qcagcaac 18

<210> 346
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 346

Ser Gln Ser Val Ser Ser Asn
1 5

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<210>	347
<211>	9
<212>	DNA
<213>	Artificial Sequence

50 $\langle 220 \rangle$
 $\langle 223 \rangle$ Synthetic

<400> 347
ggtgcatcc 9

55 <210> 348
<211> 3
<212> PRT
<213> Artificial Sequence

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<220>
 <223> Synthetic

 <400> 348
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 Gly Ala Ser
 1

 10 <210> 349
 <211> 27
 <212> DNA
 <213> Artificial Sequence

 15 <220>
 <223> Synthetic

 <400> 349
 cagcagtata ataactggcc gtacact 27
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 <210> 350
 <211> 9
 <212> PRT
 <213> Artificial Sequence
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 <220>
 <223> Synthetic

 <400> 350
 30

 Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
 1 5

 35 <210> 351
 <211> 375
 <212> DNA
 <213> Artificial Sequence

 40 <220>
 <223> Synthetic

 <400> 351

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 tcctgcgcgc cctccggctt caacttcgac gactacgcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggctc catcggctac 180
 gccgactccg tgaaggggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
 50 ctgcagatga actccctgcg ggcogaggac accgccctgt actactgcgc caaggagggc 300
 gtgtggttcg gcaagctgtt ctccctcctac ggcatggacg tgtggggcca gggcaccacc 360
 gtgaccgtgt cctcc 375

 55 <210> 352
 <211> 125
 <212> PRT
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EP 2 187 964 B1

<220>

<223> Synthetic

<400> 352

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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 Asn 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 Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 353

<211> 321

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 353

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 ggccaggccc cccggctgct gatctacggc gcctccaccc gggccaccgg catccccgcc 180
 cggttctccg gctccggctc cggcaccgag ttcaccctga ccattctctc cctgcagtcc 240
 gaggacttcg ccgtgtacta ctgccagcag tacaacaact ggccctacac cttcgggccag 300
 ggcaccaagc tggagatcaa g 321

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<210> 354

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 354

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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 Val Ser Ser Asn
 20 25 30
 5 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
 10 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 15
 <210> 355
 <211> 375
 <212> DNA
 <213> Artificial Sequence
 20
 <220>
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 <400> 355
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 tcctgtgcag cccctggatt caactttgat gattatgcc a tgcactgggt ccggcaagct 120
 ccaggaagg gacctggagt ggtctcaggt attagtgg a atagtggtag tataggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 30 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gaaaattatt ctcatcctac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375
 <210> 356
 35 <211> 125
 <212> PRT
 <213> Artificial Sequence
 <220>
 40 <223> Synthetic
 <400> 356
 45
 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 Pro Gly Phe Asn 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
 50 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
 55

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 5 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

 <210> 357
 <211> 320
 10 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic

 15 <400> 357

 20 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtggttag agcaacttag actggtacca gcagaaacct 120
 ggccaggtc ccaggctcct catctatggt gcattccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccattcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 ggaccaagct ggagatcaaa 320

 25 <210> 358
 <211> 107
 <212> PRT
 <213> Artificial Sequence

 30 <220>
 <223> Synthetic

 <400> 358

 35 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 Val Ser Ser Asn
 20 25 30
 40 Leu Asp 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
 45 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 Asn Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 50 <210> 359
 <211> 375
 <212> DNA
 <213> Artificial Sequence

 55 <220>
 <223> Synthetic

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<400> 359

5 gaggtgcagc tgggtgcagtc tgggggagggc ttggtacagc ctggcaggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttgat gattatgcc a tgcactgggt ccggcaaggt 120
 ccaggaaggg gcctggagtg ggtctcaggt attagttaga atagtggtag tataggctat 180

10 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gggagttatt ttcatactac ggtatggacg tctggggcca agggaccctg 360
 gtcaccgtct cctca 375

<210> 360

15 <211> 125

<212> PRT

<213> Artificial Sequence

<220>

20 <223> Synthetic

<400> 360

25 Glu 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 Gly Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 30 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
 35 Ala Lys Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

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<210> 361

<211> 24

<212> DNA

<213> Artificial Sequence

45

<220>

<223> Synthetic

<400> 361

50 ggattcacct ttgatgatta tgcc 24

<210> 362

<211> 8

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 187 964 B1

<400> 362

5 Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 363
<211> 24
<212> DNA
10 <213> Artificial Sequence

<220>
<223> Synthetic

15 <400> 363
attagtggga atagtggtag tata 24

<210> 364
<211> 8
20 <212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

25 <400> 364

30 Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> 365
<211> 54
<212> DNA
35 <213> Artificial Sequence

<220>
<223> Synthetic

40 <400> 365
gcaaaagaag gggatgggt cggggagtta tttcatcct acggtatgga cgtc 54

<210> 366
<211> 18
<212> PRT
45 <213> Artificial Sequence

<220>
<223> Synthetic

50 <400> 366

55 Ala Lys Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
1 5 10 15
Asp Val

<210> 367
<211> 321

EP 2 187 964 B1

<212> DNA

<213> Artificial Sequence

<220>

5 <223> Synthetic

<400> 367

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10      gaaattgtgc tgactcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
      ctctcctgca gggccagtcc gagtgttagc agcaacttag cctggtacca gcagaaacct 120
      ggccagcctc ccaggctcct catctatggc gcatccacca gggccactgg tatcccagcc 180
      aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagtct 240
      gaagattttg cagtttatta ctgtcagcag tatagtaact ggccgtacac ttttggccag 300
15      gggaccaagc tggagatcaa a                                     321

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<210> 368

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 368

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

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<210> 369

<211> 18

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 369

ccgagtgtta gcagcaac 18

<210> 370

<211> 6

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> Synthetic
 <400> 370
 5 Pro Ser Val Ser Ser Asn
 1 5
 <210> 371
 <211> 9
 10 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 15 <400> 371
 ggtgcatcc 9
 <210> 372
 20 <211> 3
 <212> PRT
 <213> Artificial Sequence
 <220>
 25 <223> Synthetic
 <400> 372
 Gly Ala Ser
 30 1
 <210> 373
 <211> 27
 <212> DNA
 35 <213> Artificial Sequence
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 40 <400> 373
 cagcagtata gtaactggcc gtacact 27
 <210> 374
 <211> 9
 45 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 50 <400> 374
 Gln Gln Tyr Ser Asn Trp Pro Tyr Thr
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 <210> 375
 <211> 375
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EP 2 187 964 B1

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 375

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 tcctgcgccg cctccggctt caccttcgac gactacgcca tgcactgggt gcggcaggcc 120
 10 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggctc catcggctac 180
 gccgactccg tgaaggggccg gttcaccatc tccggggaca acgccaagaa ctccctgtac 240
 ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
 gtgtggttcg gcgagctgtt ctcctcctac ggcatggacg tgtggggcca gggcaccacc 360
 gtgaccgtgt cctcc 375

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<210> 376

<211> 125

<212> PRT

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 376

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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
 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
 35 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 Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 40 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 377

<211> 321

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 377

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 ctgtcctgcc gggcctcccc ctccgtgtcc tccaacctgg cctgggtacca gcagaagccc 120
 ggccaggccc cccggctgct gatctacggc gcctccaccc gggccaccgg catccccgcc 180
 5 cggttctccg gctccggctc cggaaccgag ttaccacctga ccatctcttc cctgcagtc 240
 gaggacttcg ccgtgtacta ctgccagcag tactccaact ggccctacac cttcgggccag 300
 ggaccaagc tggagatcaa g 321

<210> 378

10 <211> 107

<212> PRT

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 378

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 Pro Ser Val 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
 25 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 Asn Trp Pro Tyr
 85 90 95
 30 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 379

35 <211> 375

<212> DNA

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 379

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
 45 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaaggt 120
 ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgc aaaagaagg 300
 gtatggttcg gggagttatt ttcatacctac ggtatggacg tctggggcca agggaccacg 360
 50 gtcaccgtct cctca 375

<210> 380

<211> 125

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 380

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	1				5					10					15	
	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
10				20					25					30		
	Ala	Met	His	Trp	Val	Arg	Gln	Gly	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				
15	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	Glu	Gly	Val	Trp	Phe	Gly	Glu	Leu	Phe	Ser	Ser	Tyr	Gly	Met
				100					105					110		
	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser			
			115					120					125			

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<210> 381
<211> 321
<212> DNA
<213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 381

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		ggccagcctc	ccaggctcct	catctatggt	gcattccacca	gggccactgg	tatcccagcc	180
		aggttcagtg	gcagttgggtc	tgggacagag	ttcactctca	ccatcagcag	cctgcagtc	240
35		gaagattttg	cagttttatta	ctgtcagcag	tatagtaact	ggcgtacac	ttttggccag	300
		gggaccaagc	tggagatcaa	a				321

40 <210> 382
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
<223> Synthetic

<400> 382

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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 Pro Ser Val Ser Ser Asn
 20 25 30
 5 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro 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
 10 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

15

<210> 383

<211> 375

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 383

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 tcctgtgcag cctctggatt cacctttgat gattatgccat tgcactgggt ccggcaaggc 120
 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 30 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gggagttatt ttcatacctac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

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<210> 384

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

40

<223> Synthetic

<400> 384

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 Gly Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 50 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

55

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Ala Lys Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

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<210> 385
<211> 24
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

15
<400> 385
ggattcacct ttgatgattia tgcc 24

20
<210> 386
<211> 8
<212> PRT
<213> Artificial Sequence

25
<220>
<223> Synthetic

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Gly Phe Thr Phe Asp Asp Tyr Ala
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attagttgga atagtggtag tata 24

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Ile Ser Trp Asn Ser Gly Ser Ile
1 5

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<210> 389
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<212> DNA

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<213> Artificial Sequence

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gcaaaagaag gggatgggt cggggagtta tttcatcct acggtatgga cgtc 54

<210> 390
10 <211> 18
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15 <220>
<223> Synthetic

<400> 390

20 Ala Lys Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
1 5 10 15
Asp Val

<210> 391
25 <211> 321
<212> DNA
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<220>
30 <223> Synthetic

<400> 391

35 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtcg gagtggttagc agcaacttag cctggtacca gcagaaacct 120
ggccagcctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tatagtaact ggccgtacac ttttggccag 300
40 gggaccaagg tggagatcaa a 321

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45 <213> Artificial Sequence

<220>
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50 <400> 392

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	Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Val	Ser	Pro	Gly
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	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Pro	Ser	Val	Ser	Ser	Asn
				20					25						30	
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	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
10	65				70						75				80	
	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Ser	Asn	Trp	Pro	Tyr
				85						90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
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35 <400> 394

Pro Ser Val Ser Ser Asn
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45 <220>
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ggtgcatcc 9

<210> 396
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<220>
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EP 2 187 964 B1

<400> 396

Gly Ala Ser
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<210> 397
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<400> 397

15 cagcagtata gtaactggcc gtacact 27

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<211> 9
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25 <400> 398

Gln Gln Tyr Ser Asn Trp Pro Tyr Thr
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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
45 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaggg 300
gtatggttcg gggagttatt ttcatacctac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

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<210> 400
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<400> 400

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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
 5 Ala Met His Trp Val Arg Gln Gly 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
 10 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 Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 15 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 401

<211> 321

20 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

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<400> 401

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 ggccagcctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tatagtaact ggccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

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<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 402

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EP 2 187 964 B1

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 Pro Ser Val Ser Ser Asn
 20 25 30
 5 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro 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
 10 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

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<210> 403

<211> 357

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

<400> 403

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 tcctgcaagg ttcccgatt cactctcact gaattatcca ttactgggt gcgacaggct 120
 cctggaaaag ggcttgagt gatgggaggt ttgatcctg aagatgggtg aacaatctcc 180
 30 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggaactga gcagcctgag atctgaagac acggccatat attactgttc aacgattttt 300
 ggagtgggta ccaactttga caactggggc cagggaacca cggtcaccgt ctccctca 357

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<220>

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

50

55

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Ser Val Lys Val Ser Cys Lys Val Ser Gly Phe Thr Leu Thr Glu Leu
 20 25 30
 Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Ile Ser Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ser Thr Ile Phe Gly Val Val Thr Asn Phe Asp Asn Trp Gly Gln Gly
 100 105 110
 Thr Thr Val Thr Val Ser Ser
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<400> 405

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<223> Synthetic

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Gly Phe Thr Leu Thr Glu Leu Ser

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1 5

<210> 407

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<223> Synthetic

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<400> 407

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<212> PRT

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EP 2 187 964 B1

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<400> 408

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5

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<212> DNA

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tcaacgattt ttggagtggg taccaacttt gacaac 36

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<211> 12

<212> PRT

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<213> Artificial Sequence

<220>

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<400> 410

Ser	Thr	Ile	Phe	Gly	Val	Val	Thr	Asn	Phe	Asp	Asn
1				5					10		

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<223> Synthetic

<400> 411

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gggaaagccc	ctaagcgcct	gatctatgct	gcattcaatt	tgcaaagtgg	ggtcccatca	180
agattcagcg	gcagtggatc	tgggacagaa	ttcactctca	caatcagtag	cctgcagcct	240
gaagatcttg	caagttatta	ctgtcaacag	tataatagat	acccgtggac	gttcggccaa	300
gggaccaagc	tgagatcaa	a				321

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<210> 412

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<212> PRT

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EP 2 187 964 B1

<223> Synthetic

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

<210> 413

<211> 18

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

<400> 413

30 caggccatta gaaatgat 18

<210> 414

<211> 6

<212> PRT

35 <213> Artificial Sequence

<220>

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40 <400> 414

Gln Ala Ile Arg Asn Asp
1 5

45 <210> 415

<211> 9

<212> DNA

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50 <220>

<223> Synthetic

<400> 415

gctgcattc 9

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<210> 416

 $\langle 211 \rangle$ 3

<212> PRT

EP 2 187 964 B1

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5 <400> 416

Ala Ala Phe
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10 <210> 417
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15 <220>
<223> Synthetic

<400> 417

20 caacagtata atagataccc gtggacg 27

<210> 418
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<212> PRT
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25 <220>
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30 <400> 418

Gln Gln Tyr Asn Arg Tyr Pro Trp Thr
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35 <210> 419
<211> 357
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40 <220>
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<400> 419

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tcctgcaagg ttcccgatt cactctcact gaattatcca ttactgggt gcgacaggct 120
cctggaaaag ggcttgagt gatgggaggt tttgatcctg aagatgggtga aacaatctcc 180
gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
atggaactga gcagcctgag atctgaagac acggccatat attactgttc aacgattttt 300
50 ggagtgggta ccaactttga caactggggc caggggaaccc tggtcaccgt ctccctca 357

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<223> Synthetic

<400> 420

[illegible]

<210> 421

$\langle 211 \rangle$ 321

<212> DNA

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 $\langle 220 \rangle$

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	atcacttgcc	gggcaagtca	ggccattaga	aatgatttag	gctgggtatca	gcagaaacca	120
35	gggaaagccc	ctaagcgcc	gatctatgct	gcattcaatt	tgcaaagtgg	ggtcccatca	180
	agattcagcg	gcagtgga	tgggacagaa	ttcactctca	caatcagtag	cctgcagcct	240
	gaagattctt	caagttatta	ctgtcaacag	tataatagat	acccggtggac	gttcggccaa	300
	gggaccaagg	tggaaatcaa	a				321

40 <210> 422

<211> 107

<212> PRT

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 422

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55

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

15

<210> 423

<211> 375

<212> DNA

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<220>

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<400> 423

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 tcctgtgcag cccctggatt caactttgat gattatgccca tgcactgggt ccggcaaact 120
 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tataggctat 180
 gcggactctg tgaagggccg atttaccatc tccagagaca acgccaagaa ctccctgtat 240
 cttcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gaaaattgtt ctcacccctac ggtatggacg tctggggcca agggaccacg 360
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<210> 424

<211> 125

<212> PRT

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<220>

<223> Synthetic

<400> 424

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EP 2 187 964 B1

5 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 Pro Gly Phe Asn Phe Asp Asp Tyr
 20 25 30
 10 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 Thr Ile Gly Tyr Ala Asp Ser Val
 50 55 60
 15 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 Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 20 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 425

<211> 24

20 <212> DNA

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<400> 425

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<210> 426

30 <211> 8

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35 <223> Synthetic

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40 Gly Phe Asn Phe Asp Asp Tyr Ala
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<211> 24

45 <212> DNA

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50 <400> 427

attagttgga atagtggtac tata 24

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EP 2 187 964 B1

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<210> 429

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<220>

<223> Synthetic

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<400> 429

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<210> 430

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 $\langle 220 \rangle$

25

<223> Synthetic

<400> 430

30 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
1 5 10 15
Asp Val

<210> 431

35

<211> 321

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 $\langle 220 \rangle$

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<223> Synthetic

<400> 431

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	ctctcctgca	gggccagtcg	gactgttact	tacaacttag	actggtacca	gcagaagcct	120
	ggccaggctc	ccaggctcct	catctttggt	gcatccacca	gggccactgg	tatcccagcc	180
	aggttcagtg	gcagtgggtc	tgggacagag	ttcactctca	ccatcaccag	cctgcagctc	240
	gaagattttg	cagttttatta	ctgtcaacag	tataataact	ggcgtacac	ttttggccag	300
50	gggaccaagc	tggagatcaa	a				321

<210> 432

<211> 107

<212> PRT

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<213> Artificial Sequence

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<223> Synthetic

EP 2 187 964 B1

<400> 432

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

<210> 433

<211> 18

20 <212> DNA

<213> Artificial Sequence

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<400> 433

cggactgtta cttacaac 18

<210> 434

30 <211> 6

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<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 434

40 Arg Thr Val Thr Tyr Asn
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<210> 435

<211> 9

45 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

50 <400> 435

ggtgcatcc 9

<210> 436

55 <211> 3

<212> PRT

<213> Artificial Sequence

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EP 2 187 964 B1

<223> Synthetic

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5 Gly Ala Ser
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15 <400> 437
caacagtata ataactggcc gtacact 27

<210> 438
20 <211> 9
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30 Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
1 5

<210> 439
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35 <212> DNA
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<220>
<223> Synthetic

40 <400> 439

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tcctgtgcag cccctggatt caactttgat gattatgcc a tgcactgggt ccggcaagct 120
ccaggaagg gcctggagtg ggtctcaggt attagtgg a atagtggtag tattggctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac tcggccttgt atttctgtgc aaaagaagg 300
gtatgggttcg gaaaattatt ttcatacctac ggtatggacg tctggggcca agggaccacg 360
gtcaccgtct cctca 375

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55 <220>
<223> Synthetic

EP 2 187 964 B1

<400> 440

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 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Pro Gly Phe Asn 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
 10
 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 Ser Ala Leu Tyr Phe Cys
 15 85 90 95
 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

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<210> 441

<211> 24

<212> DNA

<213> Artificial Sequence

25

<220>

<223> Synthetic

<400> 441

30 ggattcaact ttgatgatta tgcc 24

<210> 442

<211> 8

<212> PRT

35 <213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 442

 Gly Phe Asn Phe Asp Asp Tyr Ala
 1 5

45

<210> 443

<211> 24

<212> DNA

<213> Artificial Sequence

50

<220>

<223> Synthetic

<400> 443

55 attagttgga atagtggtag tatt 24

<210> 444

<211> 8

EP 2 187 964 B1

<212> PRT
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<220>
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<400> 444

10 Ile Ser Trp Asn Ser Gly Ser Ile
 1 5

<210> 445
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 <213> Artificial Sequence

<220>
 <223> Synthetic

20 <400> 445
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<210> 446
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<220>
 <223> Synthetic

30 <400> 446

35 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 1 5 10 15
 Asp Val

<210> 447
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 447

50 gaaatagtgt tgacgcagtc tccagccacc ctgtctgcgt ctccagggga cagagcctcc 60
 ctctcctgca gggccagtca gagtgttacc ttcaacttag actggtacca gcagaaacct 120
 ggccagcctc ccaggtcct catctatggt gcatccacca gggcctctgg tatccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcaactctca ccatcagcgg cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 55 gggaccaaag tggatatcaa a 321

<210> 448
 <211> 107

EP 2 187 964 B1

<212> PRT

<213> Artificial Sequence

<220>

5 <223> Synthetic

<400> 448

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

 Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
 100 105

25

<210> 449

<211> 18

<212> DNA

<213> Artificial Sequence

30

<220>

<223> Synthetic

<400> 449

35 cagagtgtta ccttcaac 18

<210> 450

<211> 6

<212> PRT

40

<213> Artificial Sequence

<220>

<223> Synthetic

45

<400> 450

 Gln Ser Val Thr Phe Asn
 1 5

50

<210> 451

<211> 9

<212> DNA

<213> Artificial Sequence

55

<220>

<223> Synthetic

<400> 451

EP 2 187 964 B1

5 ggtgcatcc 9
 <210> 452
 <211> 3
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 10 <400> 452
 Gly Ala Ser
 15 1
 <210> 453
 <211> 27
 <212> DNA
 <213> Artificial Sequence
 20 <220>
 <223> Synthetic
 <400> 453
 25 cagcagtata ataactggcc gtacact 27
 <210> 454
 <211> 9
 <212> PRT
 30 <213> Artificial Sequence
 <220>
 <223> Synthetic
 35 <400> 454
 Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
 40 1 5
 <210> 455
 <211> 375
 <212> DNA
 <213> Artificial Sequence
 45 <220>
 <223> Synthetic
 <400> 455
 50 gaggtgcagc tgggtggagtc cggcgggcggc ctggtgcagc ccggccgggtc cctgcgggctg 60
 tcctgcgccg cctccggctt caacttcgac gactacgcc a tgcaactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggctc catcggtac 180
 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
 55 ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
 gtgtgggtcg gcaagctgtt ctctctctac ggcattggacg tgtggggcca gggcaccacc 360
 gtgaccgtgt cctcc 375

EP 2 187 964 B1

<210> 456
 <211> 125
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Synthetic

<400> 456

10

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      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 Asn Phe Asp Asp Tyr
      20      25      30
15      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
20      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 Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
      100      105      110
25      Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120      125

```

<210> 457
 <211> 321
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

35

<400> 457

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      gagatcgtga tgacccagtc ccccgccacc ctgtccgtgt ccccggcga gcgggccacc 60
40      ctgtcctgcc gggcctccca gtcogtgacc ttcaacctgg cctggtacca gcagaagccc 120
      ggccagcccg cccggctgct gatctacggc gcctccaccc gggccaccgg catccccgcc 180
      cggttctccg gctccggctc cggcaccgag ttcaccctga ccattctctc cctgcagtcc 240
      gaggacttcg ccgtgtacta ctgccagcag tacaacaact ggccctacac cttcggccag 300
      ggcaccaagc tggagatcaa g                                     321

```

45

<210> 458
 <211> 107
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

<400> 458

55

EP 2 187 964 B1

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 Val Thr Phe Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Ala 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 Asn Asn Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

15

<210> 459

<211> 375

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 459

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gaggtgcagc tgggtggagtc tggggggcggc ttggttcagc ctggcggggtc cctgagactc 60
 tcctgtgcag cccctggatt caactttgat gattatgcc a tgcactgggt ccggcaagct 120
 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag tattggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaatga acagtctgag agctgaggac tcggccttgt atttctgtgc aaaagaagg 300
 gtatggttcg gaaaattatt ttcatactac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

35

<210> 460

<211> 125

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 460

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50

55

EP 2 187 964 B1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Pro Gly Phe Asn Phe Asp Asp Tyr
 20 25 30
 5 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
 10 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 Ser Ala Leu Tyr Phe Cys
 85 90 95
 Ala Lys Glu Gly Val Trp Phe Gly Lys Leu Phe Ser Ser Tyr Gly Met
 100 105 110
 15 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 461

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 461

30 gaaatagtga tgacgcagtc tccagccacc ctgtctgcgt ctccagggga cagagcctcc 60
 ctctcctgca gggccagtca gagtgttacc ttcaacttag actggtacca gcagaaacct 120
 ggccagcctc ccaggctcct catctatggg gcacccacca gggcctctgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcgg cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

35

<210> 462

<211> 107

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 462

45

50

55

EP 2 187 964 B1

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

15

<210> 463

<211> 375

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 463

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 tcctgtgcag cctctggatt cacctttgat gattatgcc a tgcactgggt ccggcaaggt 120
 ccagggaagg gcctagagtg ggtctcaggt attagtggga atagtgggta taaagactat 180
 30 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtccctgtat 240
 ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgc aaaagaaggg 300
 gtatggttcg gagaattatt ttcatactac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

35

<210> 464

<211> 125

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 464

45

50

55

EP 2 187 964 B1

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

<210> 465

<211> 24

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 465

ggattcacct ttgatgattg tgcc 24

<210> 466

30 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 466

40 Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

<210> 467

<211> 24

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 467

attagttgga atagtggta taaa 24

<210> 468

55 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

EP 2 187 964 B1

<223> Synthetic

<400> 468

5 Ile Ser Trp Asn Ser Gly Tyr Lys
1 5

<210> 469

<211> 54

10 <212> DNA

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

15

<400> 469

gcaaaagaag gggtatggt cggagaatta ttctatcct acggtatgga cgtc 54

<210> 470

20 <211> 18

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

25 <223> Synthetic

<400> 470

30 Ala Lys Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
1 5 10 15
Asp Val

<210> 471

35 <211> 321

<212> DNA

<213> Artificial Sequence

 $\langle 220 \rangle$

40 <223> Synthetic

<400> 471

45	gaaattgtga	tgaagcagtc	tccagccacc	ctgtctgtgt	ctccagggga	aagagccacc	60
	ctctcctgca	gggccagtc	gagtgtagc	agcaacttag	cctggtacca	gcagaaacct	120
	ggccagcctc	ccaggctcct	catctatggt	acatccacca	gggccactgg	tatcccagcc	180
	aggttcagt	gcagtggtc	tgggacagag	ttcactctca	ccatcagaag	cctgcagctc	240
	gaagatttg	cagttttatta	ctgtcagcag	tatagtaact	ggccatacac	ttttggccag	300
50	gggaccaaag	tggatatcaa	a				321

<210> 472

<211> 107

<212> PRT

55 <213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

EP 2 187 964 B1

<400> 472

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

<210> 473

<211> 18

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 473

ccgagtggtta gcagcaac 18

<210> 474

30 <211> 6

<212> PRT

<213> Artificial Sequence

<220>

35 <223> Synthetic

<400> 474

40 Pro Ser Val Ser Ser Asn
 1 5

<210> 475

<211> 9

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 475

ggtacatcc 9

<210> 476

<211> 3

55 <212> PRT

<213> Artificial Sequence

<220>

EP 2 187 964 B1

<223> Synthetic

<400> 476

5 Gly Thr Ser
1

<210> 477
<211> 27
10 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

15 <400> 477
cagcagtata gtaactggcc atacact 27

<210> 478
20 <211> 9
<212> PRT
<213> Artificial Sequence

<220>
25 <223> Synthetic

<400> 478

30 Gln Gln Tyr Ser Asn Trp Pro Tyr Thr
1 5

<210> 479
<211> 375
35 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

40 <400> 479

45 gaggtgcagc tgggtggagtc cggcgggcggc ctggtgcagc cgggccggtc cctgcccgtg 60
tcttgcgccg cctccggctt caccttcgac gactacgcca tgcactgggt gcggcaggcc 120

50 cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggcta caagggctac 180
gccgactccg tgaagggccg gtccaccatc tcccgggaca acgccaagaa ctccctgtac 240
ctgcagatga actccctgcg ggccgaggac accgccctgt actactgcgc caaggagggc 300
gtgtggttcg gcgagctgtt ctccctcctac ggcatggacg tgtggggcca gggcaccacc 360
gtgaccgtgt cctcc 375

55 <210> 480
<211> 125
<212> PRT
<213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 480

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      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
10    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 Tyr Lys 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
15    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 Glu Gly Val Trp Phe Gly Glu Leu Phe Ser Ser Tyr Gly Met
      100          105          110
20    Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

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<210> 481

<211> 321

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 481

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      gagatcgtga tgacccagtc ccccgccacc ctgtccgtgt ccccgggcga gcggggccacc 60
35    ctgtcctgcc gggcctcccc ctccgtgtcc tccaacctgg cctggtacca gcagaagccc 120
      ggccaggccc cccggctgct gatctacggc acctccaccc gggccaccgg catccccgcc 180
      cgttctccg gctccggctc cggcaccgag ttcaccctga ccctctctc cctgcagtcc 240
      gaggacttcg ccgtgtacta ctgccagcag tactccaact ggccctacac cttcgggccag 300
      ggcaccaagc tggagatcaa g                                     321

```

40

<210> 482

<211> 107

<212> PRT

<213> Artificial Sequence

45

<220>

<223> Synthetic

<400> 482

50

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      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 Pro Ser Val Ser Ser Asn

```

55

EP 2 187 964 B1

```

                20                25                30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
                35                40                45
5  Tyr Gly Thr 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 Asn Trp Pro Tyr
                85                90                95
10  Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                100                105

```

<210> 483

<211> 375

15 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

20

<400> 483

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gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctggcaggtc cctgagactc 60
25  tcctgtgcag cctctggatt cacctttgat gattatgcc a tgcactgggt ccggcaaggt 120
    ccaggaagg gcctagagtg ggtctcaggt attagtgg a atagtggta taaagactat 180
    gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtccctgtat 240
    ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgc aaaagaaggg 300
    gtatggttcg gagaattatt ttcatactac ggtatggacg tctggggcca agggaccacg 360
30  gtcaccgtct cctca                                     375

```

<210> 484

<211> 125

<212> PRT

35 <213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 484

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

```

EP 2 187 964 B1

<210> 485
 <211> 321
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Synthetic

<400> 485

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gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtgtagc agcaacttag cctggtacca gcagaaacct 120
 ggccagcctc ccaggctcct catctatggc acatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagaag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tatagtaact ggccatacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

15

<210> 486
 <211> 107
 <212> PRT
 <213> Artificial Sequence

20

<220>
 <223> Synthetic

25

<400> 486

30

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

40

<210> 487
 <211> 375
 <212> DNA
 <213> Artificial Sequence

45

<220>
 <223> Synthetic

50

<400> 487

55

EP 2 187 964 B1

gaggtgcagc tgggtgcagtc tgggggagggc ttggtacagc ccggtaggtc cctgagactc 60
 tcctgtacag cctctaaatt cacccttgaa gattatgcca tgcactgggt ccggcaagtt 120
 ccagggaagg gcctggaatg ggtctcaggg attagtggga atagtggtaa cataggctat 180
 5 gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcgaatga atagtctgag agctgatgac acggccttgt attactgtgt gaaggaaggg 300
 gtatggttcg ggaagtcatt ttcatactac ggtttggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

10 <210> 488
 <211> 125
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 488

20 Glu 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 Thr Ala Ser Lys Phe Thr Phe Glu Asp Tyr
 20 25 30
 25 Ala Met His Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Ser Trp Asn Ser Gly Asn 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
 30 Leu Arg Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Val Lys Glu Gly Val Trp Phe Gly Lys Ser Phe Ser Ser Tyr Gly Leu
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 35 115 120 125

<210> 489
 <211> 24
 <212> DNA
 40 <213> Artificial Sequence

<220>
 <223> Synthetic

45 <400> 489
 aaattcacct tgaagatta tgcc 24

<210> 490
 <211> 8
 50 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

55 <400> 490

EP 2 187 964 B1

Lys Phe Thr Phe Glu Asp Tyr Ala
 1 5

5 <210> 491
 <211> 24
 <212> DNA
 <213> Artificial Sequence

10 <220>
 <223> Synthetic

<400> 491
 attagtggga atagtggtaa cata 24

15 <210> 492
 <211> 8
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> Synthetic

<400> 492

25 Ile Ser Trp Asn Ser Gly Asn Ile
 1 5

30 <210> 493
 <211> 54
 <212> DNA
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

<400> 493
 gtgaaggaag gggtatgggt cggaagtca ttatcatcct acggttgga cgtc 54

40 <210> 494
 <211> 18
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Synthetic

<400> 494

50 Val Lys Glu Gly Val Trp Phe Gly Lys Ser Phe Ser Ser Tyr Gly Leu
 1 5 10 15
 Asp Val

55 <210> 495
 <211> 321
 <212> DNA
 <213> Artificial Sequence

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<220>

<223> Synthetic

<400> 495

5

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gaaatagtga tgacacagtc tccagccacc ctgtctgtgt ctccggggga aagagccacc 60
ctctcttgca gggccagtca gagggttagc agcaacttag cctggtatca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tgtcccagcc 180
10 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcaacat tataattact ggccgtacac ttttggccag 300
gggaccaaaag tggatatcaa a 321

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<210> 496

15

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

20

<223> Synthetic

<400> 496

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25      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 Val Ser Ser Asn

                20                25                30
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 Val 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
35      65         70         75         80
      Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Trp Pro Tyr
        85         90         95
      Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
        100        105

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40

<210> 497

<211> 18

<212> DNA

<213> Artificial Sequence

45

<220>

<223> Synthetic

<400> 497

50

cagagtgtta gcagcaac 18

<210> 498

<211> 6

<212> PRT

55

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 498

 Gln Ser Val Ser Ser Asn
 1 5
 5
 <210> 499
 <211> 9
 <212> DNA
 <213> Artificial Sequence
 10
 <220>
 <223> Synthetic

 <400> 499
 15 ggtgcatcc 9

 <210> 500
 <211> 3
 <212> PRT
 20 <213> Artificial Sequence

 <220>
 <223> Synthetic

 25 <400>

 Gly Ala Ser
 1
 30
 <210> 501
 <211> 27
 <212> DNA
 <213> Artificial Sequence
 35
 <220>
 <223> Synthetic

 <400> 501
 40 caacattata attactggcc gtacact 27

 <210> 502
 <211> 9
 <212> PRT
 45 <213> Artificial Sequence

 <220>
 <223> Synthetic

 50 <400> 502

 Gln His Tyr Asn Tyr Trp Pro Tyr Thr
 1 5
 55
 <210> 503
 <211> 375
 <212> DNA
 <213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 503

5

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gaggtgcagc tgggtggagtc cggcgggcggc ctggtgcagc ccggccggtc cctgcggtctg 60
tcctgcgcgc cctccaagtt caccttcgag gactacgcca tgcactgggt gcggcaggcc 120
cccggcaagg gcctggagtg ggtgtccggc atctcctgga actccggcaa catcgggtac 180
gccgactccg tgaaggggcg gttcaccatc tcccgggaca acgccaagaa ctccctgtac 240
10 ctgcagatga actccctgcg ggccgaggac accgccctgt actactgctg gaaggagggc 300
gtgtggttcg gcaagtcctt ctctctctac ggccctggacg tgtggggcca gggcaccacc 360
gtgaccgtgt cctcc 375

```

<210> 504

15

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

20

<223> Synthetic

<400> 504

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25      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 Lys Phe Thr Phe Glu Asp Tyr
        20             25             30
      Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35             40             45
30      Ser Gly Ile Ser Trp Asn Ser Gly Asn 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
35
        85             90             95
      Val Lys Glu Gly Val Trp Phe Gly Lys Ser Phe Ser Ser Tyr Gly Leu
        100            105            110
40      Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115            120            125

```

<210> 505

<211> 321

<212> DNA

45

<213> Artificial Sequence

<220>

<223> Synthetic

50

<400> 505

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ctgtcctgcc gggcctccca gtccgtgtcc tccaacctgg cctggtacca gcagaagccc 120
55 gggcaggccc cccggtctgt gatctacggc gcctccaccc gggccaccgg catccccgcc 180
cggttctccg gctccggctc cggcaccgag ttcaccctga ccatctctc cctgcagtcc 240
gaggacttcg ccgtgtacta ctgccagcac tacaactact ggccctacac cttcgggccag 300
ggaccaagc tggagatcaa g 321

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<210> 506
 <211> 107
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Synthetic

<400> 506

10

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      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 Val Ser Ser Asn
      20      25      30
15    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
20    65      70      75      80
      Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Trp Pro Tyr
      85      90      95
      Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100     105

```

25

<210> 507
 <211> 375
 <212> DNA
 <213> Artificial Sequence

30

<220>
 <223> Synthetic

<400> 507

35

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      gaggtgcagc tgggtggagtc tgggggagggc ttggtacagc ccggtaggtc cctgagactc 60
      tctgtacag cctctaaatt cacctttgaa gattatgcc a tgcactgggt ccggcaagtt 120
      ccagggaagg gcctggaatg ggtctcaggg attagtggga atagtggtaa cataggctat 180
40    gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

      ctgcgaatga atagtctgag agctgatgac acggccttgt attactgtgt gaaggaaggg 300
      gtatggttcg ggaagtcatt ttcatactac ggtttggacg tctggggcca agggaccacg 360
45    gtcaccgtct cctca                                     375

```

45

<210> 508
 <211> 125
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

<400> 508

55

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

<210> 509

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 509

30 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccggggga aagagccacc 60
 ctctcttgca gggccagtca gagggttagc agcaacttag cctgggtatca gcagaaacct 120
 ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tgtcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcaacat tataattact ggccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

35

<210> 510

<211> 107

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 510

45

50 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 Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

55

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35 40 45
 Tyr Gly Ala Ser Thr Arg Ala Thr Gly Val 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
 5 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Trp Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 10
 <210> 511
 <211> 357
 <212> DNA
 <213> Artificial Sequence
 15
 <220>
 <223> Synthetic
 20
 <400> 511
 25
 gaagtgcagc tgggtgcagtc tggggctgat gtgaagaagc ctgggggcctc agtgaaggctc 60
 tcctgcaagg tttccggata caccctcact gaattatcca tacactgggt gcgacaggct 120
 cctggaaaag ggcttgaatg gatgggaggt ttgatcctg aacatgggtac aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgt aatgattttt 300
 ggcgtgggta ccaattttga caactggggc caggaacca cggtcaccgt ctctctca 357
 30
 <210> 512
 <211> 119
 <212> PRT
 <213> Artificial Sequence
 35
 <220>
 <223> Synthetic
 40
 <400> 512
 45
 Glu Val Gln Leu Val Gln Ser Gly Ala Asp Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu Leu
 20 25 30
 Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Phe Asp Pro Glu His Gly Thr Thr Ile Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn Trp Gly Gln Gly
 100 105 110
 Thr Thr Val Thr Val Ser Ser
 115
 55
 <210> 513
 <211> 24
 <212> DNA

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<213> Artificial Sequence
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 <223> Synthetic
 5
 <400> 513
 ggatacacc tcactgaatt atcc 24
 <210> 514
 10 <211> 8
 <212> PRT
 <213> Artificial Sequence
 <220>
 15 <223> Synthetic
 <400> 514
 20 Gly Tyr Thr Leu Thr Glu Leu Ser
 1 5
 <210> 515
 <211> 24
 <212> DNA
 25 <213> Artificial Sequence
 <220>
 <223> Synthetic
 30 <400> 515
 ttgatcctg aacatggtac aaca 24
 <210> 516
 <211> 8
 35 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 40 <400> 516
 45 Phe Asp Pro Glu His Gly Thr Thr
 1 5
 <210> 517
 <211> 36
 <212> DNA
 <213> Artificial Sequence
 50 <220>
 <223> Synthetic
 <400> 517
 55 gtaatgatt ttggcgtggt taccaatttt gacaac 36
 <210> 518
 <211> 12

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<212> PRT
 <213> Artificial Sequence

<220>
 5 <223> Synthetic

<400> 518

10 Val Met Ile Phe Gly Val Val Thr Asn Phe Asp Asn
 1 5 10

<210> 519
 <211> 321
 15 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

20 <400> 519

25 gacattgtga tgacccagtc tccatcctcc ctgtctgcat ccgtgagaga cagagtcacc 60
 atcacttgcc gggcaagtca gggcattaga aatgagttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttcactctca cattcagcag cctgcagcct 240
 gaagattttg caacttacta ttgttcacag gataacaatt tcccgtggac gtttggccaa 300
 gggaccaagg tggaaatcaa a 321

30 <210> 520
 <211> 107
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

40 <400> 520

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

55 <210> 521
 <211> 18
 <212> DNA

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<213> Artificial Sequence
 <220>
 <223> Synthetic
 5
 <400> 521
 cagggcatta gaaatgag 18
 <210> 522
 10 <211> 6
 <212> PRT
 <213> Artificial Sequence
 <220>
 15 <223> Synthetic
 <400> 522
 20 Gln Gly Ile Arg Asn Glu
 1 5
 <210> 523
 <211> 9
 25 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 30
 <400> 523
 gctgcatcc 9
 <210> 524
 35 <211> 3
 <212> PRT
 <213> Artificial Sequence
 <220>
 40 <223> Synthetic
 <400> 524
 Ala Ala Ser
 45 1
 <210> 525
 <211> 27
 <212> DNA
 50 <213> Artificial Sequence
 <220>
 <223> Synthetic
 55 <400> 525
 tcacaggata acaatttccc gtggacg 27
 <210> 526

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

5

<220>
 <223> Synthetic

<400> 526

10

Ser Gln Asp Asn Asn Phe Pro Trp Thr
 1 5

<210> 527
 <211> 357
 <212> DNA
 <213> Artificial Sequence

15

<220>
 <223> Synthetic

20

<400> 527

25

caggtgcagc tgggtgcagtc cggcgccgag gtgaagaagc ccggcgccctc cgtgaagggtg 60
 tcctgcaagg tgtccggcta caccctgacc gagctgtcca tgcactgggt gcggcaggcc 120
 cccggcaagg gcctggagtg gatgggcccgt ttcgaccccg agcacggcac caccatctac 180
 gccagaagt tccagggccg ggtgaccatg accgaggaca cctccaccga caccgcctac 240
 atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgt gatgatcttc 300
 ggcgtggtga ccaacttcga caactggggc cagggcaccc tggtgaccgt gtcctcc 357

30

<210> 528
 <211> 119
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Synthetic

<400> 528

40

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

55

<210> 529

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

5 <220>
 <223> Synthetic

<400> 529

10 gacatccaga tgacccagtc cccctcctcc ctgtccgcct ccgtgggcca ccgggtgacc 60
 atcacctgcc gggcctccca gggcatccgg aacgagctgg gctggtacca gcagaagccc 120
 ggcaaggccc ccaagcggct gatctacgcc gcctcctccc tgcagtcagg cgtgccctcc 180
 cggttctccg gctccggctc cggcaaccgag ttcaccctga ccctctcttc cctgcagccc 240
 15 gaggacttcg ccacctacta ctgctcccag gacaacaact tcccctggac cttcggccag 300
 ggcaccaagg tggagatcaa g 321

<210> 530
 <211> 107
 20 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 530

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

<210> 531
 <211> 357
 45 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

50 <400> 531

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5 caggtgcagc tgggtgcagtc tggggctgat gtgaagaagc ctggggcctc agtgaaggct 60
 tcctgcaagg ttcccgata caccctcact gaattatcca tacactgggt gcgacaggct 120
 cctggaaaag ggcttgaatg gatgggaggt tttgatcctg aacatgggtac aacaatctac 180
 gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgt aatgattttt 300
 ggcgtggtta ccaattttga caactggggc cagggaaccc tggtcaccgt ctctctca 357

<210> 532

10 <211> 119

<212> PRT

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 532

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

35

<210> 533

<211> 321

<212> DNA

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 533

45

50 gacatccaga tgacccagtc tccatcctcc ctgtctgcat ccgtgagaga cagagtcacc 60
 atcacttgcc gggcaagtca gggcattaga aatgagttag gctggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttcactctca cattcagcag cctgcagcct 240
 gaagattttg caacttacta ttgttcacag gataacaatt tcccgtggac gtttggccaa 300
 gggaccaagg tggaaatcaa a 321

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<210> 534

<211> 107

<212> PRT

<213> Artificial Sequence

EP 2 187 964 B1

<220>

<223> Synthetic

<400> 534

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

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20

<210> 535

<211> 8

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<220>

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<221> VARIANT

<222> (1) ... (8)

<223> Xaa = Any Amino Acid

<400> 535

35

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      Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      1           5

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40

<210> 536

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

45

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(8)

50

<223> Xaa = Any Amino Acid

<400> 536

55

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      Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      1           5

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<210> 537

<211> 18

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<212> PRT
 <213> Artificial Sequence

5 <220>
 <223> Synthetic

10 <220>
 <221> VARIANT
 <222> (1)...(18)
 <223> Xaa = Any AMino Acid

<400> 537

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

<210> 538
 <211> 6
 20 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <220>
 <221> VARIANT
 <222> (1) ... (6)
 <223> Xaa = Any Amino Acid

30 <400> 538

35				Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				1				5	

<210> 539
 <211> 3
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> Synthetic

45 <220>
 <221> VARIANT
 <222> (1)...(3)
 <223> Xaa = Any Amino Acid

50 <400> 539
 Xaa Xaa Xaa

1

55 <210> 540
 <211> 9
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Synthetic

<220>

5 <221> VARIANT

<222> (1) ... (9)

<223> Xaa = Any Amino Acid

<400> 540

10

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 541

15 <211> 330

<212> PRT

<213> Artificial Sequence

<220>

20 <223> Synthetic

<400> 541

25 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
30 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
35 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
40 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
45 165 170 175
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu

50

55

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180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 5 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
 10 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
 15 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

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25 <220>
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30 <400> 542

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
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 Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 5 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
 10 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
 15 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
 20 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
 25 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
 30 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
 35 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
 40 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
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<210> 543

45 <211> 327

<212> PRT

<213> Artificial Sequence

<220>

50 <223> Synthetic

<400> 543

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	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
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	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
				20						25					30	
5	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
10	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	
15	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
20	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		
25	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
30	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
35			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
40																
	305					310					315				320	
	Leu	Ser	Leu	Ser	Leu	Gly	Lys									
					325											
45																
50																
55																

Patentkrav

5 **1.** Humant antistof, eller et antigenbindende fragment af et antistof, der specifikt binder human nervevækstfaktor (human nerve growth factor (NGF)) med en K_D på 1 pM eller mindre, målt ved overfladeplasmonresonans, hvor antistoffet eller antistoffragmentet omfatter

10 (a) en komplementaritetsbestemmende region 3 for den tunge kæde (HCDR3) og en CDR3 for den lette kæde (LCDR3), hvor HCDR3 og LCDR3 omfatter de i henholdsvis SEQ ID NO:90 og 98 anførte aminosyresekvenser, og

 (b) en HCDR1, HCDR2, LCDR1 og LCDR2, hvor HCDR1 er SEQ ID NO:86, HCDR2 er SEQ ID NO:88, LCDR1 er SEQ ID NO:94 og LCDR2 er SEQ ID NO:96.

15

2. Humant antistof, eller et antigenbindende fragment, ifølge krav 1, der specifikt binder human NGF med en K_D på 0,5 pM eller mindre.

20 **3.** Humant antistof, eller et antigenbindende fragment, ifølge krav 1 eller 2, hvor nævnte antistof, eller et antigenbindende fragment deraf, omfatter en variabel region for den tunge kæde (HCVR) og en variabel region for den lette kæde (LCVR), hvor HCVR og LCVR omfatter de i henholdsvis SEQ ID NO:108 og 110 anførte aminosyresekvenser.

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4. Humant antistof, eller et antigenbindende fragment, ifølge krav 1, 2 eller 3, der binder human NGF med en K_D , der er cirka 2-fold til cirka 10-fold højere, end den K_D , hvormed antistoffet eller fragmentet binder rotte- og mus-NGF.

30

5. Nukleinsyremolekyle, der koder det humane antistof, eller det antigenbindende fragment, ifølge et hvilket som helst af kravene 1 til 4.

5 **6.** Ekspressionsvektor, der omfatter nukleinsyremolekylet ifølge krav 5.

10 **7.** Fremgangsmåde til fremstilling af et anti-humant NGF-antistof, eller et antigenbindende fragment af et antistof, der omfatter de trin at indføre ekspressions-vektoren ifølge krav 6 i en isoleret værtscelle, at dyrke cellen under betingelser, der tillader fremstilling af antistoffet eller antistoffragmentet, og at udvinde det således fremstillede antistof eller antistoffragment, hvor det foretrækkes, at værtscellen er en *E. coli*-celle, en CHO-celle eller en COS-celle.

15 **8.** Farmaceutisk sammensætning, der omfatter et antistof, eller et antigenbindende fragment af et antistof, ifølge et hvilket som helst af kravene 1 til 4 og en farmaceutisk acceptabel bærer.

20 **9.** Farmaceutisk sammensætning ifølge krav 8, der yderligere omfatter et yderligere terapeutisk middel, der vælges blandt en interleukin-1(IL-1)-inhibitor, et antiepileptisk lægemiddel, en cytokin-antagonist og et neurotrophin.

25 **10.** Antistof, eller et antigenbindende fragment af et antistof, ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i en fremgangsmåde til at svække eller inhibere en NGF-medieret sygdom eller tilstand hos et menneske valgt blandt inflammatorisk smerte, postoperativ incisions-smerte, neuropatisk smerte, fraktur-smerte, gigtled-smerter, post-herpetisk neuralgi, smerte, der
30 hidrører fra forbrændinger, cancer-smerter, smerte fra osteoarthritis, eller smerte fra rheumatoid arthritis, ischias, smerter associeret med seglcellekriser,

eller post-herpetisk neuralgi.

5 **11.** Anvendelse af et antistof, eller et antigenbindende fragment af et antistof, ifølge et hvilket som helst af kravene 1 til 4 i fremstillingen af et medikament til anvendelse i en fremgangsmåde til at svække eller inhibere en NGF-medieret sygdom eller tilstand hos et menneske valgt blandt inflammatorisk smerte, postoperativ incisions-smerte, neuropatisk smerte, fraktur-smerte, gigtled-smerter, post-herpetisk neuralgi, smerte, der hidrører fra forbrændinger, cancer-
10 smerter, smerte fra osteoarthritis eller smerte fra rheumatoid arthritis, ischias, smerter associeret med seglcellekriser, eller post-herpetisk neuralgi.

15 **12.** Antistof, eller et antigenbindende fragment, ifølge et hvilket som helst af kravene 1 til 4 til anvendelse ifølge krav 10, hvor den nævnte fremgangsmåde omfatter at administrere et første og et andet terapeutisk middel til et menneske, der har behov for dette, hvor det første terapeutiske middel er det nævnte antistof, eller det antigenbindende fragment, og hvor det foretrækkes, at
20 det andet terapeutiske middel er en interleukin-1(IL-1)-inhibitor, et antiepileptisk legemiddel, en cytokin-antagonist, eller et neurotrophin.

25 **13.** Anvendelse ifølge krav 11 af det nævnte antistof, eller det antigenbindende fragment, ifølge et hvilket som helst af kravene 1 til 4, hvor den nævnte fremgangsmåde omfatter at administrere et første og et andet terapeutisk middel til en menneskelig patient, der har behov for dette, hvor det første terapeutiske middel er det nævnte antistof, eller det antigenbindende fragment, og hvor det foretrækkes, at det andet terapeutiske middel er en interleukin-
30 (IL-1)-inhibitor, et antiepileptisk legemiddel, en cytokin-antagonist, eller et neurotrophin.

14. Antistof eller antigenbindende fragment ifølge et hvilket som helst af kravene 1 til 4 til anvendelse ifølge krav 10 eller 12, hvor den NGF-medierede tilstand eller sygdom inhiberes uden signifikant forringelse af motorisk koordination.

5

15. Anvendelse ifølge krav 11 eller 13 af nævnte antistof eller antigenbindende fragment ifølge et hvilket som helst af kravene 1 til 4, hvor den NGF-medierede tilstand eller sygdom inhiberes uden signifikant forringelse af motorisk koordination.

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