ANTI-EGFR ANTIBODIES AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to antibodies, and antigen-binding fragments thereof, which are specific for human EGFR, and methods of use thereof.

BACKGROUND

[0002] Epidermal growth factor receptor (EGFR, also known as HER1 or ErbB1) is a member of the ErbB/HER family of type 1 receptor tyrosine kinases (RTKs). Other members of this family include ErbB2 (HER2 or Neu), ErbB3 (HER3) and ErbB4 (HER4). Known ligands for EGFR include epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α). Ligand binding to EGFR induces tyrosine phosphorylation and receptor dimerization with other ErbB family members.

[0003] RTKs such as EGFR function to allow cells to respond to diverse external stimuli. However, aberrant activation and/or overexpression of EGFR is associated with the development and progression of several human cancers. Accordingly, EGFR is a target for anti-cancer therapies. Approved drugs targeting EGFR include small molecule inhibitors such as gefitinib (Iressa®) and erlotinib (Tarceva®), and anti-EGFR antibodies such as cetuximab (Erbitux®) and panitumumab (Vectibix®). Anti-EGFR antibodies are mentioned in, *e.g.*, US 4,943,533, US 5,844,093, US 7,060,808, US 7,247,301, US 7,595,378, US 7,723,484, and US 7,939,072. Nonetheless, there is a need in the art for novel EGFR antagonists, such as anti-EGFR antibodies, for the treatment of cancer and other related disorders.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides antibodies that bind human EGFR. The antibodies of the invention are useful, *inter alia*, for inhibiting EGFR-mediated signaling and for treating diseases and disorders caused by or related to EGFR activity and/or signaling. The antibodies of the invention are also useful for inducing cell death in cells that express high levels of EGFR on their surfaces.

[0005] The antibodies of the invention 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 affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

[0006] The present invention provides antibodies, or antigen-binding fragments thereof comprising a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, and 370, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0007] The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, and 378, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0008] The present invention also provides an antibody or antigen-binding fragment thereof comprising a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, and 370/378.

[0009] The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, and 376, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, and 384, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0010] In certain embodiments, the antibody or antigen-binding portion of an antibody comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NO: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304, 312/320, 328/336, 344/352, 360/368, and 376/384.

[0011] The present invention also provides an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, and 372, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, and 374, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, and 380, or a substantially similar sequence thereof having at least

90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, and 382, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0012] Certain non-limiting, exemplary antibodies and antigen-binding fragments of the invention comprise HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, having the amino acid sequences selected from the group consisting of: SEQ ID NOs: 4-6-8-12-14-16 (*e.g.* H1M085N); 20-22-24-28-30-32 (*e.g.* H1M086N); 36-38-40-44-46-48 (*e.g.* H1M089N); 52-54-56-60-62-64 (*e.g.* H1M102N); 68-70-72-76-78-80 (*e.g.* H1M103N); 84-86-88-92-94-96 (*e.g.* H1M116N); 100-102-104-108-110-112 (*e.g.* H1H134P); 116-118-120-124-126-128 (*e.g.* H1H136P); 132-134-136-140-142-144 (*e.g.* H1H141P); 148-150-152-156-158-160 (*e.g.*, H1H142P); 164-166-168-172-174-176 (*e.g.* H1H143P); 180-182-184-188-190-192 (*e.g.*, H1H144P); 196-198-200-204-206-208 (*e.g.* H1H145P); 212-214-216-220-222-224 (*e.g.* H1H147P); 228-230-232-236-238-240 (*e.g.* H1H151P); 244-246-248-252-254-256 (*e.g.* H1H153P); 260-262-264-268-270-272 (*e.g.* H1H155P); 276-278-280-284-286-288 (*e.g.* H1H157P); 292-294-296-300-302-304 (*e.g.* H1H158P); 308-310-312-316-318-320 (*e.g.* H1H159P); 324-326-328-332-334-336 (*e.g.* H1H161P); 340-342-344-348-350-352 (*e.g.* H1H163P); 356-358-360-364-366-368 (*e.g.* H1H169P); and 372-374-376-380-382-384 (*e.g.* H1H171P).

[0013] In a related embodiment, the invention includes an antibody or antigen-binding fragment of an antibody which specifically binds EGFR, wherein the antibody or fragment comprises the heavy and light chain CDR domains contained within heavy and light chain variable region (HCVR/LCVR) sequences selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, and 370/378. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0014] In another aspect, the invention provides nucleic acid molecules encoding anti-EGFR

antibodies or antigen-binding 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 host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0015] In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, and 369, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0016] The present invention also provides an antibody or fragment thereof comprising a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, and 377, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0017] The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 199, 215, 231, 247, 263, 279, 295, 311, 327, 343, 359, and 375, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, 351, 367, and 383, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0018] The present invention also provides an antibody or fragment thereof which further comprises a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339, 355, and 371, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, 341, 357, and 373, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, and 379, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237,

253, 269, 285, 301, 317, 333, 349, 365, and 381, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0019] According to certain embodiments, the antibody or fragment thereof comprises the heavy and light chain CDR sequences encoded by the nucleic acid sequences of SEQ ID NOs: 1 and 9 (*e.g.* H1M085N), 17 and 25 (*e.g.* H1M086N), 33 and 41 (*e.g.* H1M089N), 49 and 57 (*e.g.* H1M102N), 65 and 73 (*e.g.* H1M103N), 81 and 89 (*e.g.* H1M116N), 97 and 105 (*e.g.* H1H134P), 113 and 121 (*e.g.* H1H136P), 129 and 137 (*e.g.* H1H141P), 145 and 153 (*e.g.* H1H142P), 161 and 169 (*e.g.* H1H143P), 177 and 185 (*e.g.* H1H144P), 193 and 201 (*e.g.* H1H145P), 209 and 217 (*e.g.* H1H147P), 225 and 233 (*e.g.* H1H151P), 241 and 249 (*e.g.* H1H153P), 257 and 265 (*e.g.* H1H155P), 273 and 281 (*e.g.* H1H157P), 289 and 297 (*e.g.* H1H158P), 305 and 313 (*e.g.* H1H159P), 321 and 329 (*e.g.* H1H161P), 337 and 345 (*e.g.* H1H163P), 353 and 361 (*e.g.* H1H169P), or 369 and 377 (*e.g.* H1H171P).

[0020] The present invention includes anti-EGFR 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).

[0021] In another aspect, the invention provides a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds EGFR and a pharmaceutically acceptable carrier. In a related aspect, the invention features a composition which is a combination of an anti-EGFR antibody and a second therapeutic agent. In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-EGFR antibody. Exemplary agents that may be advantageously combined with an anti-EGFR antibody include, without limitation, other agents that inhibit EGFR activity (including other antibodies or antigen-binding fragments thereof, peptide inhibitors, small molecule antagonists, etc) and/or agents which do not directly bind EGFR but nonetheless interfere with, block or attenuate EGFR-mediated signaling.

[0022] In yet another aspect, the invention provides methods for inhibiting EGFR activity using an anti-EGFR antibody or antigen-binding portion of an antibody of the invention, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the invention. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of EGFR activity. The anti-EGFR antibodies or antibody fragments of the invention may function to block the interaction between EGFR and an EGFR binding partner (*e.g.*, epidermal growth factor [EGF], transforming growth factor-alpha [TGF-α], etc.), or otherwise inhibit the signaling activity of EGFR.

[0023] The present invention also includes the use of an anti-EGFR antibody or antigen binding portion of an antibody of the invention in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by EGFR activity in a patient.

[0024] Other embodiments will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0025] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0026] 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. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0027] 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

[0028] The expressions "EGFR" and "EGFR fragment," as used herein refer to the human EGFR protein or fragment unless specified as being from a non-human species (*e.g.*, "mouse EGFR," "mouse EGFR fragment," "monkey EGFR," "monkey EGFR fragment," etc.). The extracellular domain of human EGFR has the amino acid sequence shown in, *e.g.*, amino acids 25 to 645 of SEQ ID NO:385.

[0029] As used herein, "an antibody that binds EGFR" or an "anti-EGFR antibody" includes antibodies, and antigen-binding fragments thereof, that bind a soluble fragment of an EGFR protein (*e.g.*, a portion of the extracellular domain of EGFR) and/or cell surface-expressed EGFR. The expression "cell surface-expressed EGFR" means an EGFR protein or portion thereof that is/are expressed on the surface of a cell *in vitro* or *in vivo*, such that at least a portion of the EGFR protein (*e.g.*, amino acids 25 to 645 of SEQ ID NO:385) is exposed to the extracellular side of the cell membrane and accessible to an antigen-binding portion of an antibody. Soluble EGFR molecules include, *e.g.*, monomeric and dimeric EGFR constructs as described in Example 3 herein (*i.e.*, "EGFR.mmh", SEQ ID NO:386, and "EGFR.mFc", SEQ ID NO:387, respectively), or constructs substantially similar thereto.

[0030] The term "antibody", as used herein, means any antigen-binding molecule or molecular complex comprising at least one complementarity determining region (CDR) that specifically binds to or interacts with a particular antigen (*e.g.*, EGFR). The term "antibody" includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L 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. In different embodiments of the invention, the FRs of the anti-EGFR antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0031] The term "antibody", as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0032] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.),

small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0033] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0034] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0035] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (*e.g.*, bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

[0036] The antibodies of the present invention may function through complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). "Complement-dependent cytotoxicity" (CDC) refers to lysis of antigen-expressing cells by an antibody of the invention in the presence of complement. "Antibody-dependent cell-mediated cytotoxicity" (ADCC) refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (*e.g.*, Natural Killer (NK) cells, neutrophils, and macrophages) recognize

bound antibody on a target cell and thereby lead to lysis of the target cell. CDC and ADCC can be measured using assays that are well known and available in the art. (*See*, *e.g.*, U.S. 5,500,362 and 5,821,337, and Clynes *et al.* (1998) Proc. Natl. Acad. Sci. (USA) *95*:652-656). The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[0037] 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.

[0038] 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 V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0039] Human antibodies 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, C_H2 or C_H3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[0041] An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody" for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0042] A "neutralizing" or "blocking" antibody, as used herein, is intended to refer to an antibody whose binding to EGFR: (i) interferes with the interaction between EGFR or an EGFR fragment and an EGFR ligand (*e.g.*, EGF, TGF-α, etc.), and/or (ii) results in inhibition of at least one biological function of EGFR. The inhibition caused by an EGFR neutralizing or blocking antibody need not be complete so long as it is detectable using an appropriate assay. Exemplary assays for detecting EGFR inhibition are described herein.

[0043] The anti-EGFR antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other

embodiments, only certain residues are mutated back to the original germline sequence, *e.g.*, only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (*i.e.*, a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, *e.g.*, wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0044] The present invention also includes anti-EGFR antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes anti-EGFR antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[0045] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0046] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence

as the polypeptide encoded by the reference nucleic acid molecule.

[0047] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. *See, e.g.*, Pearson (1994) Methods Mol. Biol. 24: 307-331. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-1445. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0048] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. *See, e.g.*, GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) supra). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program

BLAST, especially BLASTP or TBLASTN, using default parameters. *See, e.g.*, Altschul *et al.* (1990) J. Mol. Biol. 215:403-410 and Altschul *et al.* (1997) Nucleic Acids Res. 25:3389-402.

Biological Characteristics of the Antibodies

[0049] The present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that bind monomeric or dimeric EGFR molecules with high affinity. For example, the present invention includes antibodies and antigen-binding fragments of antibodies that bind dimeric EGFR with a K_D of less than about 20 pM as measured by surface plasmon resonance, *e.g.*, using the assay format as defined in Example 3 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind dimeric EGFR with a K_D of less than about 15 pM, less than about 10 pM, less than about 8 pM, less than about 6 pM, less than about 4 pM, less than about 2 pM, or less than about 1 pM, as measured by surface plasmon resonance, *e.g.*, using the assay format as defined in Example 3 herein. The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that bind dimeric EGFR with a t½ of greater than about 200 minutes as measured by surface plasmon resonance, *e.g.*, using the assay format as defined in Example 3 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind dimeric EGFR with a t½ of greater than about 210 minutes, greater than about 220 minutes, greater than about 250 minutes, greater than about 260 minutes, greater than about 280 minutes, greater than about 300 minutes, greater than about 320 minutes, greater than about 340 minutes, greater than about 360 minutes, greater than about 380 minutes, greater than about 400 minutes, greater than about 450 minutes, greater than about 500 minutes, greater than about 550 minutes, greater than about 600 minutes, greater than about 650 minutes, greater than about 800 minutes, greater than about 1000 minutes, or more, as measured by surface plasmon resonance, *e.g.*, using the assay format as defined in Example 3 herein.

[0050] The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of EGFR-expressing tumor cells. For example, the present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of tumor cells that express high levels of EGFR on their surface (*e.g.*, A431 epidermoid carcinoma cells), with an IC_{50} (*i.e.*, the concentration resulting in 50% maximal growth inhibition) of less than about 200 pM. IC_{50} values can be determined using the cell growth inhibition assay exemplified in Example 4 herein, or a substantially similar assay. According to certain embodiments of the present invention the anti-EGFR antibodies or antigen-binding fragments thereof are able to inhibit the growth of A431 cells *in vitro* with an IC_{50} of less than about 180 pM, less than about 160 pM, less than about 140 pM, less than about 120 pM, less than about 100 pM, less than about 80 pM, less than about 60 pM, less than about 40 pM, less than about 20 pM, less than about 10 pM, less than about 5 pM, or less than about 2 pM, as determined using the cell growth inhibition assay exemplified in Example 4 herein, or a

substantially similar assay.

[0051] The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that induce antibody-dependent cell-mediated cytotoxicity (ADCC) of cells that express EGFR. Assays for measuring ADCC are known in the art. An exemplary assay format is illustrated in Example 5 herein, in which anti-EGFR antibodies are added to a cellular mixture of peripheral blood mononuclear cells (PBMCs) and A431 epidermoid carcinoma cells (*i.e.*, cells expressing high levels of EGFR). The extent of cell killing is assessed relative to the maximal cell lysis signal observed under conditions in which untreated cells were lysed by addition of digitonin; the extent of ADCC can thereby be expressed in terms of the percent of maximum cell killing. The present invention includes anti-EGFR antibodies that produce a maximum cell killing percentage of greater than about 25%, when tested in the ADCC assay format of Example 5, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention induce ADCC with a maximum cell killing percentage of about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or more, as measured in the ADCC assay format of Example 5 or a substantially similar assay.

[0052] The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit tumor growth *in vitro* or *in vivo*. In certain circumstances, the antibodies or antigen-binding fragments of the present invention cause tumor regression or shrinkage. The present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of human tumor xenografts in immunocompromised mice. For example, as illustrated in Example 6 herein, the exemplary anti-EGFR antibody H1H141P significantly inhibited the growth of head and neck squamous cell carcinoma cells (*e.g.*, FaDu tumor cells), pancreatic tumor cells (BxPC3), and lung tumor cells (Calu3 and NCI-H358), in mouse xenografts models. The invention includes antibodies and antigen-binding fragments thereof that inhibit tumor cell growth in tumor-bearing mice by greater than about 50% (*e.g.*, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or more) as compared to hFc-control-treated tumor-bearing mice.

[0053] The present invention also includes anti-EGFR antibodies and antigen binding fragments thereof that induce internalization of cell surface expressed EGFR.

Epitope Mapping and Related Technologies

[0054] The present invention includes anti-EGFR antibodies which interact with one or more amino acids found within the extracellular domain of human EGFR (*e.g.*, within extracellular domain I, II, III, and/or IV). The epitope to which the antibodies bind may consist of a single contiguous sequence of 3 or more (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids located within the extracellular domain of EGFR. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences)

located within the extracellular domain of EGFR.

[0055] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, *e.g.*, routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), alanine scanning mutational analysis, peptide blots analysis (Reineke, 2004, Methods Mol Biol 248:443-463), and 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). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. *See, e.g.*, Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem. 73*:256A-265A.

[0056] The present invention further includes anti-EGFR antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (*e.g.* H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, H1M116N, H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, H1H171P etc.). Likewise, the present invention also includes anti-EGFR antibodies that compete for binding to EGFR with any of the specific exemplary antibodies described herein (*e.g.* H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, H1M116N, H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, H1H171P etc.).

[0057] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-EGFR antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-EGFR antibody of the invention, the reference antibody is allowed to bind to an EGFR protein (*e.g.*, a soluble portion of the EGFR extracellular domain or cell surface-expressed EGFR). Next, the ability of a test antibody to bind to the EGFR molecule is assessed. If the test antibody is able to bind to EGFR following saturation binding with the reference anti-EGFR antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-EGFR antibody. On the other hand, if the test antibody is not able to bind to the

EGFR molecule following saturation binding with the reference anti-EGFR antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-EGFR antibody of the invention. Additional routine experimentation (*e.g.*, peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present invention, two antibodies bind to the same (or overlapping) epitope if, *e.g.*, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990:50:1495-1502). Alternatively, two antibodies are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0058] To determine if an antibody competes for binding with a reference anti-EGFR antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to an EGFR protein (*e.g.*, a soluble portion of the EGFR extracellular domain or cell surface-expressed EGFR) under saturating conditions followed by assessment of binding of the test antibody to the EGFR molecule. In a second orientation, the test antibody is allowed to bind to an EGFR molecule under saturating conditions followed by assessment of binding of the reference antibody to the EGFR molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the EGFR molecule, then it is concluded that the test antibody and the reference antibody compete for binding to EGFR. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Human Antibodies

[0059] Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human EGFR.

[0060] Using VELOCIMMUNE™ technology or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to EGFR are initially isolated having a human variable region and a mouse constant region. As in the experimental section 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. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0061] The anti-EGFR antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind human EGFR. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the anti-EGFR antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-EGFR antibody or antibody fragment that is essentially bioequivalent to an anti-EGFR antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

[0062] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0063] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0064] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0065] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0066] Bioequivalence may be demonstrated by in vivo and in vitro methods. Bioequivalence measures include, e.g., (a) an in vivo test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0067] Bioequivalent variants of anti-EGFR antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-EGFR antibody variants comprising amino acid changes which modify the glycosylation characteristics of the antibodies, *e.g.*, mutations which eliminate or remove glycosylation.

Species Selectivity and Species Cross-Reactivity

[0068] According to certain embodiments of the invention, the anti-EGFR antibodies bind to human EGFR but not to EGFR from other species. The present invention also includes anti-EGFR antibodies that bind to human EGFR and to EGFR from one or more non-human species. For example, the anti-EGFR antibodies of the invention may bind to human EGFR and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomologous, marmoset, rhesus or chimpanzee EGFR.

Immunoconjugates

[0069] The invention encompasses anti-EGFR monoclonal antibodies conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxic agents include any agent that is detrimental to cells. Examples of suitable cytotoxic agents and chemotherapeutic agents for forming immunoconjugates are known in the art, (see for example, WO 05/103081).

Multispecific Antibodies

[0070] The antibodies of the present invention may be monospecific, bi-specific, 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; Kufer *et al.*, 2004, Trends Biotechnol. 22:238-244. The anti-EGFR antibodies of the present invention 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 bi-specific or a multispecific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for human EGFR or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety.

[0071] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Formulation and Administration

[0072] The invention provides pharmaceutical compositions comprising the anti-EGFR antibodies or antigen-binding fragments thereof of the present invention. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that 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™, Life Technologies, Carlsbad, CA), 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.

[0073] The dose of antibody administered to a patient may vary depending upon the age and

the size of the patient, target disease, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area. When an antibody of the present invention is used for treating a condition or disease associated with EGFR activity in an adult patient, it may be 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. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering anti-EGFR antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (*e.g.*, Mordenti *et al.*, 1991, *Pharmaceut. Res. 8*:1351).

[0074] 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.

[0075] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0076] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX

75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few.

[0077] 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.), 1974, CRC Pres., Boca Raton, Florida. 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, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0078] 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.

[0079] 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 aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and

in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

[0080] The antibodies of the invention are useful, *inter alia*, for the treatment, prevention and/or amelioration of any disease or disorder associated with or mediated by EGFR expression or activity, or treatable by blocking the interaction between EGFR and an EGFR ligand (*e.g.*, EGF or TGF-α) or otherwise inhibiting EGFR activity and/or signaling, and/or promoting receptor internalization and/or decreasing cell surface receptor number. For example, the antibodies and antigen-binding fragments of the present invention are useful for the treatment of tumors that express high levels of EGFR. The antibodies and antigen-binding fragments of the present invention may be used to treat, *e.g.*, primary and/or metastatic tumors arising in the brain and meninges, oropharynx, lung and bronchial tree, gastrointestinal tract, male and female reproductive tract, muscle, bone, skin and appendages, connective tissue, spleen, immune system, blood forming cells and bone marrow, liver and urinary tract, and special sensory organs such as the eye. In certain embodiments, the antibodies and antigen-binding fragments of the invention are used to treat one or more of the following cancers: renal cell carcinoma, pancreatic carcinoma, breast cancer, head and neck cancer, prostate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer (*e.g.*, EGFR-dependent non-small cell lung cancer), synovial sarcoma, thyroid cancer, or melanoma.

Combination Therapies and Formulations

[0081] The present invention includes therapeutic administration regimens which comprise administering an anti-EGFR antibody of the present invention in combination with at least one additional therapeutically active component. Non-limiting examples of such additional therapeutically active components include other EGFR antagonists (*e.g.*, a second anti-EGFR antibody [*e.g.*, cetuximab or panitumumab] or small molecule inhibitor of EGFR [*e.g.*, gefitinib or erlotinib]), an antagonist of another EGFR family member such as Her2/ErbB2, ErbB3 or ErbB4 (*e.g.*, anti-ErbB2, anti-ErbB3 or anti-ErbB4 antibody or small molecule inhibitor of ErbB2, ErbB3 or ErbB4 activity), an antagonist of EGFRvIII (*e.g.*, an antibody that specifically binds EGFRvIII), a cMET anagonist (*e.g.*, an anti-cMET antibody), an IGF1R antagonist (*e.g.*, an anti-IGF1R antibody), a B-raf inhibitor (*e.g.*, vemurafenib, sorafenib, GDC-0879, PLX-4720), a PDGFR-α inhibitor (*e.g.*, an anti-PDGFR-α antibody), a PDGFR-β inhibitor (*e.g.*, an anti-PDGFR-β antibody), a VEGF antagonist (*e.g.*, a VEGF-Trap, *see*, *e.g.*, US 7,087,411 (also referred to herein as a "VEGF-inhibiting fusion protein"), anti-VEGF antibody (*e.g.*, bevacizumab), a small molecule kinase inhibitor of VEGF receptor (*e.g.*, sunitinib, sorafenib or pazopanib)), a DLL4 antagonist (*e.g.*, an anti-DLL4 antibody disclosed in US 2009/0142354 such as REGN421), an

Ang2 antagonist (*e.g.*, an anti-Ang2 antibody disclosed in US 2011/0027286 such as H1H685P), etc. Other agents that may be beneficially administered in combination with the anti-EGFR antibodies of the invention include cytokine inhibitors, including small-molecule cytokine inhibitors and antibodies that bind to cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-11, IL-12, IL-13, IL-17, IL-18, or to their respective receptors.

[0082] The present invention also includes therapeutic combinations comprising any of the anti-EGFR antibodies mentioned herein and an inhibitor of one or more of VEGF, Ang2, DLL4, ErbB2, ErbB3, ErbB4, EGFRvIII, cMet, IGF1R, B-raf, PDGFR-α, PDGFR-β, or any of the aforementioned cytokines, wherein the inhibitor is an aptamer, an antisense molecule, a ribozyme, an siRNA, a peptibody, a nanobody or an antibody fragment (*e.g.*, Fab fragment; $F(ab')_2$ fragment; Fd fragment; Fv fragment; scFv; dAb fragment; or other engineered molecules, such as diabodies, triabodies, tetrabodies, minibodies and minimal recognition units). The anti-EGFR antibodies of the invention may also be administered and/or co-formulated in combination with antivirals, antibiotics, analgesics, corticosteroids and/or NSAIDs. The anti-EGFR antibodies of the invention may also be administered as part of a treatment regimen that also includes radiation treatment and/or conventional chemotherapy.

[0083] The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an anti-EGFR antibody of the present invention; (for purposes of the present disclosure, such administration regimens are considered the administration of an anti-EGFR antibody "in combination with" an additional therapeutically active component). The present invention includes pharmaceutical compositions in which an anti-EGFR antibody of the present invention is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

[0084] The present invention also includes compositions and methods comprising a combination of a "degrading antibody" and a "ligand-blocking antibody." A "degrading antibody" means an anti-EGFR antibody that causes degradation of EGFR in cells without necessarily blocking ligand-receptor interactions. A non-limiting example of a degrading antibody of the present invention is the antibody designated H1H134P. A "ligand-blocking antibody" means an anti-EGFR antibody that blocks the interaction between EGFR and one or more of its ligands (*e.g.*, EGF or TGF-α). A non-limiting example of a ligand-blocking antibody of the present invention is the antibody designated H1H141P. Another example of a ligand blocking antibody is cetuximab. The present inventors have conceived of combining a degrading antibody and a ligand-blocking antibody in order to synergistically or otherwise improve anti-tumor efficacy. Accordingly, the present invention includes pharmaceutical compositions comprising at least one degrading antibody and at least one ligand-blocking antibody. The present invention also includes therapeutic methods comprising administering to a subject a combination of a degrading antibody and a ligand-blocking antibody (either as separate administrations or as co-formulations).

Diagnostic Uses of the Antibodies

[0085] The anti-EGFR antibodies of the present invention may also be used to detect and/or measure EGFR, or EGFR-expressing cells in a sample, *e.g.*, for diagnostic purposes. For example, an anti-EGFR antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by aberrant expression (*e.g.*, over-expression, under-expression, lack of expression, etc.) of EGFR. Exemplary diagnostic assays for EGFR may comprise, *e.g.*, contacting a sample, obtained from a patient, with an anti-EGFR antibody of the invention, wherein the anti-EGFR antibody is labeled with a detectable label or reporter molecule. Alternatively, an unlabeled anti-EGFR antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, beta-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure EGFR in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0086] Samples that can be used in EGFR diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient which contains detectable quantities of EGFR protein, or fragments thereof, under normal or pathological conditions. Generally, levels of EGFR in a particular sample obtained from a healthy patient (*e.g.*, a patient not afflicted with a disease or condition associated with abnormal EGFR levels or activity) will be measured to initially establish a baseline, or standard, level of EGFR. This baseline level of EGFR can then be compared against the levels of EGFR measured in samples obtained from individuals suspected of having a EGFR related disease or condition.

EXAMPLES

[0087] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to EGFR

[0088] An EGFR-expressing cell line was administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human

Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a EGFR-specific immunoassay. When a desired immune response was achieved splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce EGFR-specific antibodies. Using this technique several anti-EGFR chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, and H1M116N.

[0089] Anti-EGFR antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in US 2007/0280945A1. Using this method, several fully human anti-EGFR antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, and H1H171P.

[0090] Certain biological properties of the exemplary anti-EGFR antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2. Heavy and Light Chain Variable Region Amino Acid Sequences

[0091] Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected anti-EGFR antibodies and their corresponding antibody identifiers.

Table 1

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
085N	2	4	6	8	10	12	14	16
086N	18	20	22	24	26	28	30	32
089N	34	36	38	40	42	44	46	48
102N	50	52	54	56	58	60	62	64
103N	66	68	70	72	74	76	78	80
116N	82	84	86	88	90	92	94	96
134P	98	100	102	104	106	108	110	112
136P	114	116	118	120	122	124	126	128
141P	130	132	134	136	138	140	142	144
142P	146	148	150	152	154	156	158	160
143P	162	164	166	168	170	172	174	176
144P	178	180	182	184	186	188	190	192
145P	194	196	198	200	202	204	206	208
147P	210	212	214	216	218	220	222	224
151P	226	228	230	232	234	236	238	240

153P	242	244	246	248	250	252	254	256
155P	258	260	262	264	266	268	270	272
157P	274	276	278	280	282	284	286	288
158P	290	292	294	296	298	300	302	304
159P	306	308	310	312	314	316	318	320
161P	322	324	326	328	330	332	334	336
163P	338	340	342	344	346	348	350	352
169P	354	356	358	360	362	364	366	368
171P	370	372	374	376	378	380	382	384

[0092] Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (*e.g.* "H1H" or "H1M"), followed by a numerical identifier (*e.g.* "085" or "134" as shown in Table 1), followed by a "P" or "N" suffix. Thus, according to this nomenclature, an antibody may be referred to herein as, *e.g.*, "H1M085N" or "H1H134P", etc. The H1H and H1M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an "H1M" antibody has a mouse IgG1 Fc, whereas an "H1H" antibody has a human IgG1 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M antibody can be converted to an H1H antibody, and *vice versa*, but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Table 1 – will remain the same.

Control Constructs Used in the Following Examples

[0093] Various control constructs (anti-EGFR antibodies) were included in the following experiments for comparative purposes. The control constructs are designated as follows: Control I: a chimeric anti-EGFR antibody with heavy and light chain variable sequences of "mAb 225" as set forth in US 7,060,808; and Control II: a commercially available fully human monoclonal anti-EGFR antibody designated as ABX-EGF, also known as Panitumumab or Vectibix®.

Example 3. Antibody Binding to Human EGFR as Determined by Surface Plasmon Resonance

[0094] Equilibrium dissociation constants (K_D values) for antigen binding to selected purified anti-human EGFR monoclonal antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore T100) assay at 37°C. The Biacore sensor surface was derivatized with monoclonal mouse anti-human Fc antibody (GE Biosciences) to capture anti-EGFR monoclonal antibodies, expressed in the human IgG1 Fc format (antibody prefix H1H). Different concentrations of human monomeric (EGFR.mmh; SEQ ID NO:386) and dimeric (EGFR.mFc; SEQ ID NO:387) proteins were injected over the anti-EGFR monoclonal antibody captured surface at a flow rate of 50 µl/min. Antibody-antigen association was monitored for 4-5 minutes while dissociation of antigen from the captured monoclonal antibody surface was monitored for 10 min. Kinetic association (k_a) and dissociation (k_d) rate constants were

determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0 curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d / k_a; and $t_{1/2}$ (min) = (ln2/(60*k_d). Kinetic binding parameters for different anti-EGFR monoclonal antibodies are shown in Table 2.

Table 2: Binding Characteristics of Anti-EGFR Antibodies to Monomeric and Dimeric EGFR

Antibody	Analyte	ka (Ms^{-1})	kd (s^{-1})	K_D (Molar)	$t_{1/2}$ (min)
H1H0085N	EGFR.mmh	1.19E+05	1.85E-03	1.55E-08	6
	EGFR.mFc	3.36E+05	4.05E-05	1.20E-10	286
H1H086N	EGFR.mmh	5.40E+05	7.08E-04	1.31E-09	16
	EGFR.mFc	1.90E+06	1.13E-05	5.98E-12	1018
H1H089N	EGFR.mmh	3.13E+05	6.83E-03	2.18E-08	2
	EGFR.mFc	1.49E+06	4.49E-05	3.01E-11	257
H1H102N	EGFR.mmh	1.66E+05	9.43E-04	5.67E-09	12
	EGFR.mFc	8.63E+05	5.62E-05	6.51E-11	206
H1H103N	EGFR.mmh	1.00E+05	1.39E-03	1.39E-08	8
	EGFR.mFc	3.83E+05	4.19E-05	1.09E-10	276
H1H116N	EGFR.mmh	5.39E+05	2.84E-03	5.27E-09	4
	EGFR.mFc	1.55E+06	3.16E-05	2.03E-11	366
H1H134P	EGFR.mmh	9.30E+05	7.89E-04	8.48E-10	15
	EGFR.mFc	3.09E+06	2.47E-05	7.99E-12	468
H1H136P	EGFR.mmh	NB	NB	NB	NB
	EGFR.mFc	NB	NB	NB	NB
H1H141P	EGFR.mmh	3.96E+05	4.05E-04	1.02E-09	29
	EGFR.mFc	9.03E+05	7.51E-06	8.31E-12	1539
H1H142P	EGFR.mmh	1.58E+05	6.89E-04	4.35E-09	17
	EGFR.mFc	3.61E+05	1.20E-05	3.32E-11	965
H1H143P	EGFR.mmh	1.27E+05	7.27E-04	5.71E-09	16
	EGFR.mFc	3.81E+05	1.35E-05	3.54E-11	856
H1H144P	EGFR.mmh	1.84E+05	9.67E-04	5.25E-09	12
	EGFR.mFc	8.94E+05	1.94E-05	2.17E-11	596
H1H145P	EGFR.mmh	1.37E+05	1.95E-04	1.43E-09	59
	EGFR.mFc	2.52E+05	5.86E-05	2.32E-10	197
H1H147P	EGFR.mmh	6.54E+04	3.76E-04	5.76E-09	31
	EGFR.mFc	1.90E+05	1.26E-05	6.64E-11	914
H1H151P	EGFR.mmh	1.34E+05	1.13E-03	8.40E-09	10

	EGFR.mFc	1.34E+05	1.13E-03	8.40E-09	10
H1H153P	EGFR.mmh	7.61E+04	2.35E-04	3.09E-09	49
	EGFR.mFc	2.34E+05	8.23E-06	3.51E-11	1403
H1H155P	EGFR.mmh	1.76E+05	1.69E-04	9.62E-10	68
	EGFR.mFc	3.29E+05	1.06E-04	3.21E-10	109
H1H157P	EGFR.mmh	NB	NB	NB	NB
	EGFR.mFc	NB	NB	NB	NB
H1H158P	EGFR.mmh	1.31E+05	7.73E-04	5.90E-09	15
	EGFR.mFc	4.08E+05	9.84E-06	2.41E-11	1174
H1H159P	EGFR.mmh	4.76E+05	3.25E-04	6.82E-10	36
	EGFR.mFc	1.64E+06	5.63E-06	3.44E-12	2051
H1H161P	EGFR.mmh	4.89E+05	3.21E-04	6.55E-10	36
	EGFR.mFc	1.73E+06	2.76E-06	1.59E-12	4187
H1H163P	EGFR.mmh	5.11E+05	4.26E-04	8.34E-10	27
	EGFR.mFc	1.81E+06	2.12E-06	1.17E-12	5447
H1H169P	EGFR.mmh	6.65E+05	8.69E-04	1.31E-09	13
	EGFR.mFc	2.29E+06	1.69E-05	7.36E-12	684
H1H171P	EGFR.mmh	7.94E+04	1.13E-03	1.42E-08	10
	EGFR.mFc	3.39E+05	3.48E-05	1.03E-10	332
Control I	EGFR.mmh	1.58E+06	7.38E-03	4.68E-09	2
	EGFR.mFc	3.55E+06	1.08E-04	3.03E-11	107
Control II	EGFR.mmh	7.12E+05	7.62E-04	1.07E-09	15
	EGFR.mFc	1.38E+06	5.82E-05	4.23E-11	198

[0095] As shown in Table 2, several of the anti-EGFR antibodies of the present invention exhibited superior binding properties as compared to the control antibodies. For example, certain anti-EGFR antibodies of the present invention exhibited K_D values less than 10 pM and t½ values greater than 400 minutes, when tested for binding to dimeric EGFR ("EGFR.mFc") in the surface plasmon resonance assay described above; *e.g.*, H1H086N (5.98 pM / 1018 min), H1H134P (7.99 pM / 468 min), H1H141P (8.31 pM / 1539 min), H1H159P (3.44 pM / 2059 min), H1H161P (1.59 pM / 4187 min), and H1H169P (7.36 pM / 684 min). By contrast, Control I exhibited a K_D of 30.3 pM and a t½ of 107 min, and Control II exhibited a K_D of 42.3 pM and a t½ of 198 min when tested for binding to dimeric EGFR under identical experimental conditions.

Example 4. Inhibition of Cell Growth By Anti-EGFR Antibodies

[0096] Anti-EGFR antibodies were tested for their ability to inhibit the growth of A431 epidermoid carcinoma cells *in vitro*. A431 cells have an amplification of the EGFR gene and exhibit a strong dependence on EGFR signaling for growth. A431 cells were seeded at a

density of $5.0x10^3$ cells per well in 96-well plates and incubated in DMEM medium containing 0.5% BSA and 1% penicillin/streptomycin/glutamine. EGFR-specific mAbs were added to cells in 1:3 serial dilutions starting at 60nM. After 7 days viable cells were quantified by staining with Alamar Blue (Invitrogen) and measuring fluorescence with a Flexstation III spectrophotometer. Absorbance values were plotted using a four-parameter logistic equation over the 12-point dilution series (GraphPad Prism). Results are summarized in Table 3.

Table 3: Relative Inhibition of A431 Cell Proliferation by Anti-EGFR Antibodies

Antibody	IC_{50} of A431 Proliferation (Molar)
H1H0085N	1.645E-09
H1H086N	5.459E-10
H1H089N	2.305E-09
H1H102N	2.883E-10
H1H103N	3.89E-09
H1H116N	2.24E-10
H1H134P	1.844E-09
H1H136P	No Inhibition
H1H141P	1.405E-10
H1H142P	5.474E-10
H1H143P	9.968E-11
H1H144P	1.393E-11
H1H145P	No Inhibition
H1H147P	9.769E-11
H1H151P	2.77E-10
H1H153P	No Inhibition
H1H155P	No Inhibition
H1H157P	No Inhibition
H1H158P	No Inhibition
H1H159P	No Inhibition
H1H161P	No Inhibition
H1H163P	No Inhibition
H1H169P	No Inhibition
H1H171P	No Inhibition
Control I	3.346E-10

[0097] As shown in Table 3, the tested antibodies exhibited a broad range of IC_{50} values with some antibodies possessing little to no blocking activity while others displayed IC_{50} values lower than the reference Control I antibody. For example, anti-EGFR antibodies H1H141P, H1H143P,

H1H144P and H1H147P all exhibited IC_{50} values less than 200 pM, whereas, the Control I antibody exhibited an IC_{50} value of greater than 334 pM.

Example 5. Induction of ADCC on A431 Cells By Anti-EGFR Antibodies

[0098] Antibody dependent cell-mediated cytotoxicity (ADCC) is a cellular process which occurs when Fc receptors on natural killer cells are activated to induce the release of cell-lysing enzymes against target cells. The ability of anti-EGFR antibodies to induce ADCC *in vitro* was assessed by using peripheral blood mononuclear cells (PBMC) as effector, or primary "killer" cells, against A431 target cells that endogenously over-express EGFR.

[0099] Briefly, anti-EGFR antibodies over a broad concentration range (40 nM – 0 nM; 1:3 dilutions) were added to a cellular mixture of PBMC and A431 cells (30:1 ratio) in 96-well plates. The plates were incubated for 4 hours at 37°C, 5% CO_2, equilibrated to room temperature for 10 minutes and CytoTox-Glo reagent was added to the wells. Untreated cells in control wells were lysed by addition of digitonin to determine maximal cell lysis signal. The plates were incubated briefly at room temperature and luminescence was measured from each well using a plate reader.

[0100] Cytotoxic response was calculated by subtracting the signal for A431 cells incubated with PBMC without the addition of anti-EGFR antibodies (background) from the signal generated from target cells mixed with PBMC in the presence of anti-EGFR mAbs. The percentage of cytotoxicity was calculated by dividing the cytotoxic response of cells against background by the maximal cytotoxic response obtained from cell lysis via digitonin. Data was analyzed by a four-parameter logistical equation with a sigmoidal dose-response curve (GraphPad Prism). Results are summarized in Table 4. (NA = no activity).

Table 4: ADCC Activity of Selected Anti-EGFR Antibodies

Antibody	EC_{50} (Molar)	Maximum Cell Killing (%)
H1H0085N	3.70E-13	35
H1H086N	2.91E-13	25
H1H089N	5.83E-12	53
H1H102N	4.39E-13	48
H1H103N	7.25E-13	17
H1H116N	2.51E-13	29
H1H134P	4.61E-11	33
H1H136P	1.49E-09	27
H1H141P	2.78E-12	41
H1H142P	1.19E-12	34
H1H143P	NA	13

H1H144P	4.57E-11	43
H1H145P	NA	0
H1H147P	NA	13
H1H151P	5.48E-09	68
H1H153P	2.65E-11	31
H1H155P	1.67E-11	30
H1H157P	2.27E-13	36
H1H158P	2.32E-12	28
H1H159P	2.69E-09	60
H1H161P	9.80E-12	38
H1H163P	2.96E-10	48
H1H169P	4.81E-09	27
H1H171P	8.94E-13	27
Control I	1.86E-12	24

[0101] As shown in Table 4, several anti-EGFR mAbs induced ADCC on A431 cells co-incubated with PBMC effector cells. Additionally, several anti-EGFR mAbs demonstrate a high maximal cell killing percentage comparable to the control antibody (Control I). For example, anti-EGFR antibodies H1H089N, H1H102N, H1H141P, H1H144P, H1H151P, H1H159P and H1H163P each exhibited greater than 40% maximum cell killing in the ADCC assay, whereas the Control I antibody exhibited less than 25% maximum cell killing in this assay.

Example 6. Inhibition of Tumor Growth by An Anti-EGFR Antibody

[0102] The anti-EGFR antibody H1H141P was tested for its ability to inhibit the growth human tumor xenografts in immunocompromised mice. Briefly, 2 x 10^6 FaDu head and neck squamous cell carcinoma cells were implanted subcutaneously into the flank of C.B.-17 SCID mice. After tumors reached an average size of approximately 200 mm^3 mice were randomized into groups for treatment (N=6 mice per group) and injected twice per week subcutaneously with either human Fc control protein (12.5 mg/kg; SEQ ID NO:388) or with H1H141P (10 mg/kg). Mice were treated for 15 days.

[0103] Tumor volumes were measured twice per week throughout the experiment and tumor weights were determined upon excision at the conclusion of the experiment. The average tumor growth (the average change in tumor volume from the start of treatment through the end of the experiment) and the average tumor weights were determined for each group. Results are summarized in Table 5.

Table 5: Inhibition of FaDu Tumor Growth in SCID Mice

Antibody (mg/kg)	Tumor Growth (mm^3) from start of treatment (mean ± SD)	% Decrease in Tumor Growth vs Control	Tumor Weight (g) (mean ± SD)	% Decrease in Tumor Weight vs Control
hFc Control (12.5)	1099 ± 186	-	0.993 ± 0.176	-
H1H141P (10)	55 ± 115	95	0.215 ± 0.120	78

[0104] In a similar experiment, the effect of H1H141P on the growth of BxPC3 pancreatic tumor xenografts was determined, as summarized in Table 6.

Table 6: Inhibition of BxPC3 Tumor Growth in SCID Mice

Antibody (mg/kg)	Tumor Growth (mm^3) from start of treatment (mean ± SD)	% Decrease in Tumor Growth vs Control	Tumor Weight (g) (mean ± SD)	% Decrease in Tumor Weight vs Control
hFc Control (25)	706 ± 277	-	0.926 ± 0.412	-
H1H141P (12.5)	97 ± 59	86	0.275 ± 0.098	70

[0105] In a similar experiment, the effect of H1H141P on the growth of Calu3 lung tumor xenografts was determined, as summarized in Table 7.

Table 7: Inhibition of Calu3 Tumor Growth in SCID Mice

Antibody (mg/kg)	Tumor Growth (mm^3) from start of treatment (mean ± SD)	% Decrease in Tumor Growth vs Control	Tumor Weight (g) (mean ± SD)	% Decrease in Tumor Weight vs Control
hFc Control (25)	656 ± 202	-	0.884 ± 0.275	-
H1H141P (25)	335 ± 58	49	0.582 ± 0.097	34

[0106] In a similar experiment, the effect of H1H141P on the growth of NCI-H358 lung tumor xenografts was determined, as summarized in Table 8.

Table 8: Inhibition of NCI-H358 Tumor Growth in SCID Mice

Antibody (mg/kg)	Tumor Growth (mm^3) from start of treatment (mean ± SD)	% Decrease in Tumor Growth vs Control
hFc Control (25)	329 ± 170	-
H1H141P (12.5)	(-14) ± 47	104

[0107] In a similar experiment, the effect of H1H141P on the growth of A431 epidermoid

carcinoma xenografts was determined, as summarized in Table 9.

Table 9: Inhibition of A431 Tumor Growth in SCID Mice

Antibody (mg/kg)	Tumor Growth (mm^3) from start of treatment (mean ± SD)	% Decrease in Tumor Growth vs Control
hFc Control (25)	134 ± 173	-
H1H141P (12.5)	62 ± 49	95
H1H141P (25)	45 ± 60	97

[0108] Collectively, these findings indicate that H1H141P as a monotherapy can inhibit the growth of multiple human tumor xenografts, representing several different tumor types.

[0109] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. Use of a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof that specifically binds human epidermal growth factor receptor (hEGFR) in the manufacture of a medicament for inhibiting tumor growth in a subject afflicted with a tumor, wherein the antibody or antigen-binding fragment thereof comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:130, and (b) the CDRs of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:138.

2. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair having SEQ ID NOs: 130/138.

3. The use of claim 2, wherein the antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 domains, respectively, having SEQ ID NOs: 132, 134, 136, 140, 142, and 144.

4. The use of claim 1, wherein the tumor is selected from the group consisting of a renal tumor, a pancreatic tumor, a head and neck tumor, a breast tumor, a prostate tumor, a colon tumor, a gastric tumor, an ovarian tumor, a lung tumor, and a skin tumor.

5. The use of claim 1, further comprising a second therapeutic agent.

6. The use of claim 5, wherein the second therapeutic agent is an antibody or antigen-binding fragment thereof that specifically binds HER2, ErbB3, ErbB4, cMet, IGF1R, Ang2, PDGFR-α or PDGFR-β.

7. The use of claim 5, wherein the second therapeutic agent is a VEGF antagonist.

8. The use of claim 7, wherein the VEGF antagonist is a VEGF-Trap.

9. The use of claim 7, wherein the VEGF antagonist is an anti-VEGF antibody.

10. The use of claim 9, wherein the anti-VEGF antibody is bevacizumab.

11. The use of claim 7, wherein the VEGF antagonist is a small molecule kinase inhibitor of VEGF receptor.

12. The use of claim 11, wherein the small molecule kinase inhibitor of VEGF receptor is sunitinib, sorafenib or pazopanib.

13. The use of claim 1, wherein the antibody or antigen-binding fragment thereof is administered as part of a treatment regimen that also includes radiation treatment and/or conventional chemotherapy.

SEQUENCE LISTING

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

<210> 59
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
cagagtgtta gcagcaac   18

<210> 60
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 60
Gln Ser Val Ser Ser Asn
 1   5

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 61
gatgcatcc   9

<210> 62
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62
Asp Ala Ser
 1

<210> 63
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
cagcaatata atacctggtg gacg 24

<210> 64
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64
Gln Gln Tyr Asn Thr Trp Trp Thr
 1   5

<210> 65
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agttacgaca tgcactgggt ccgccaaact 120
acaggaaaag gtctagagtg ggtctcaggt attggtactg ctggagatac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaagatg ccaagaattc cctgtatctt 240
caaatgaata gcctgagagc cggggacacg gctgtatatt actgtgcaag agtgggatat 300
gactggaact tcgtcgcatt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 66
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 66
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Asp Met His Trp Val Arg Gln Thr Thr Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Gly Thr Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
    50   55   60
Gly Arg Phe Thr Ile Ser Arg Glu Asp Ala Lys Asn Ser Leu Tyr Leu
65   70   75   80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95
Arg Val Gly Tyr Asp Trp Asn Phe Val Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 67
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
ggattcacct tcagtagtta cgac   24

<210> 68
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
Gly Phe Thr Phe Ser Ser Tyr Asp
 1   5

<210> 69
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69
attggtactg ctggagatac a   21

<210> 70
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 70
Ile Gly Thr Ala Gly Asp Thr
 1   5

<210> 71
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71
gcaagagtgg gatatgactg gaacttcgtc gcatttgact ac   42

<210> 72
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 72
Ala Arg Val Gly Tyr Asp Trp Asn Phe Val Ala Phe Asp Tyr
 1   5   10

<210> 73
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtcgccacag ctcctgatcc acttggtctc tattcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac acttaaaatc 240
agcagagtgg aggctgagga tgttgggatt tattactgca tgcaagctct tcaaactccg 300
tggacgttcg gccaagggac caaggtggaa atcaaa   336

<210> 74
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1   5   10   15

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


<210> 75
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75
cagagcctcc tgcatagtaa tggatacaac tat                                33

<210> 76
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76
Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
 1               5                  10


<210> 77
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
ttggtctct                                                           9

<210> 78
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
Leu Val Ser
 1
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<210> 79
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
atgcaagctc ttcaaactcc gtggacg 27

<210> 80
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
Met Gln Ala Leu Gln Thr Pro Trp Thr
 1   5

<210> 81
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccgtcagc agtggtgatt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggactggatt gggcacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcactag acacgtctaa gaaccagttc 240
tccctgaagc tgaactctgt gactgccgcg gacacggccg tgtattactg tgcgagaacg 300
gctataactg gaactatgga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 82
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly
            20   25   30
Asp Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Asp
        35   40   45
Trp Ile Gly His Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50   55   60
Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe

```
65                  70                  75                  80
Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95
Cys Ala Arg Thr Ala Ile Thr Gly Thr Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
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<210> 83
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
ggtggctccg tcagcagtgg tgattactac 30

<210> 84
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84

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Gly Gly Ser Val Ser Ser Gly Asp Tyr Tyr
 1               5                  10
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<210> 85
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85
atctattaca gtgggagcac c 21

<210> 86
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 86

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Ile Tyr Tyr Ser Gly Ser Thr
 1               5
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<210> 87
<211> 33
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87
gcgagaacgg ctataactgg aactatggac tac 33

<210> 88
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88
Ala Arg Thr Ala Ile Thr Gly Thr Met Asp Tyr
 1 5 10

<210> 89
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 89
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctgcagggga gagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggttcca gcagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatctacca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca tcatcagcag cctgcagtct 240
gaagattttg cactttatta ctgtcagcag tataatagct ggtggacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 90
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 91
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 91
cagagtgtta gcagcaac 18

<210> 92
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92
Gln Ser Val Ser Ser Asn
1 5

<210> 93
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93
gatgcatct 9

<210> 94
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94
Asp Ala Ser
1

<210> 95
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95
cagcagtata atagctggtg gacg 24

<210> 96
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96
Gln Gln Tyr Asn Ser Trp Trp Thr
 1   5

<210> 97
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 97
gaggtgcagc tggtggagtc tgggggaggc ttggtgcagc ctggcgggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattttgcca ttcactgggt ccggcaaact 120
ccagggaggg gcctggagtg ggtctcaggt cttagttgga atagtgctta catagcctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagga ctccctctat 240
ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgt aaaagataca 300
gacatacacc tttggtttct ctttgacttc tggggccagg gaaccctggt caccgtctcc 360
tca   363

<210> 98
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Phe
            20   25   30
Ala Ile His Trp Val Arg Gln Thr Pro Gly Arg Gly Leu Glu Trp Val
        35   40   45
Ser Gly Leu Ser Trp Asn Ser Ala Tyr Ile Ala Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asp 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
Val Lys Asp Thr Asp Ile His Leu Trp Phe Leu Phe Asp Phe Trp Gly
            100   105   110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 99
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99
ggattcacct ttgatgattt tgcc 24

<210> 100
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100
Gly Phe Thr Phe Asp Asp Phe Ala
 1 5

<210> 101
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 101
cttagttgga atagtgctta cata 24

<210> 102
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 102
Leu Ser Trp Asn Ser Ala Tyr Ile
 1 5

<210> 103
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 103
gtaaaagata cagacataca cctttggttt ctctttgact tc 42

<210> 104
<211> 14
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104
Val Lys Asp Thr Asp Ile His Leu Trp Phe Leu Phe Asp Phe
 1   5   10

<210> 105
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt agttggttgg cctggtatca acagaaacca 120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaagtgg ggtcccatcg 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacaa tataatagtt attcgacgtt cggccaaggg 300
acacgactgg agattaaa   318

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

<220>
<223> Synthetic

<400> 106
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Thr
                85   90   95
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 107
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107

cagagtatta gtagttgg 18

<210> 108
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
Gln Ser Ile Ser Ser Trp
1 5

<210> 109
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
aaggcgtct 9

<210> 110
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110
Lys Ala Ser
1

<210> 111
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 111
caacaatata atagttattc gacg 24

<210> 112
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 112
Gln Gln Tyr Asn Ser Tyr Ser Thr

1 5

<210> 113
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 113
gaggtgcagc tggtggagtc tgggggaggg ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgaca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt atcagtggta gtggagatag cacatactac 180
gcaggctccg tgaagggccg gttcaccatc tccagagaca attccaagaa cactctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gtatgactac 300
agtaactact gggaccacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 114
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Gly Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Tyr Asp Tyr Ser Asn Tyr Trp Asp His Tyr Gly Met Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 115
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 115
ggattcacct ttagcagcta tgac 24

<210> 116
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116
Gly Phe Thr Phe Ser Ser Tyr Asp
 1   5

<210> 117
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117
atcagtggta gtggagatag caca   24

<210> 118
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 118
Ile Ser Gly Ser Gly Asp Ser Thr
 1   5

<210> 119
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119
gcgtatgact acagtaacta ctgggaccac tacggtatgg acgtc   45

<210> 120
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120
Ala Tyr Asp Tyr Ser Asn Tyr Trp Asp His Tyr Gly Met Asp Val
 1   5   10   15

<210> 121

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

<220>
<223> Synthetic

<400> 121
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatactt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 122
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Tyr Ser Arg
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 123
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123
cagagtatta gtagctgg 18

<210> 124
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124

Gln Ser Ile Ser Ser Trp
1 5

<210> 125
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 125
aaggcgtct 9

<210> 126
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126
Lys Ala Ser
1

<210> 127
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127
caacagtata atacttattc tcggacg 27

<210> 128
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128
Gln Gln Tyr Asn Thr Tyr Ser Arg Thr
1 5

<210> 129
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 129
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggaa ctggatccgc 120
cagtacccag ggaagggcct ggagttgatt ggctacatct attacagtgg aatcacctac 180
tacaacccgt ccctcaagag tcgacttacc atttcattag acacgtctaa gaaccagttc 240
tccctgaagc tgagttctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agagtggaac tacgggcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 130
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 130
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20   25   30
Asp Tyr Tyr Trp Asn Trp Ile Arg Gln Tyr Pro Gly Lys Gly Leu Glu
        35   40   45
Leu Ile Gly Tyr Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser
    50   55   60
Leu Lys Ser Arg Leu Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
65   70   75   80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
            100   105   110
Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 131
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131
ggtggctcca tcagcagtgg tgattactac   30

<210> 132
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132
Gly Gly Ser Ile Ser Ser Gly Asp Tyr Tyr
 1   5   10

<210> 133
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133
atctattaca gtggaatcac c 21

<210> 134
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 134
Ile Tyr Tyr Ser Gly Ile Thr
1 5

<210> 135
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 135
gcgagagata gagtggaact acgggctttt gatatc 36

<210> 136
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 136
Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
1 5 10

<210> 137
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 137
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagt aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatcaacgat gcatccaatt tggaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacat tatgatagtc tccctctcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 138
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 138
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 Gln Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Asn Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu
                85   90   95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 139
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139
caggacatta gtaactat 18

<210> 140
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 140
Gln Asp Ile Ser Asn Tyr
 1   5

<210> 141
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 141
gatgcatcc 9

<210> 142
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 142
Asp Ala Ser
1

<210> 143
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143
caacattatg atagtctccc tctcacc 27

<210> 144
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 144
Gln His Tyr Asp Ser Leu Pro Leu Thr
1 5

<210> 145
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 145
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggaa ctggatccgc 120
cagtacccag ggaagggcct ggagttgatt ggctacatct attacagtgg aatcacctac 180
tacaacccgt ccctcaagag tcgacttacc atttcattag acacgtctaa gaaccagttc 240
tccctgaagc tgagttctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300
agagtggaac tacgagcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 146
<211> 120

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20   25   30
Asp Tyr Tyr Trp Asn Trp Ile Arg Gln Tyr Pro Gly Lys Gly Leu Glu
        35   40   45
Leu Ile Gly Tyr Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser
    50   55   60
Leu Lys Ser Arg Leu Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
65   70   75   80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
            100   105   110
Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 147
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147
ggtggctcca tcagcagtgg tgattactac   30

<210> 148
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148
Gly Gly Ser Ile Ser Ser Gly Asp Tyr Tyr
 1   5   10

<210> 149
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149
atctattaca gtggaatcac c   21

<210> 150
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150
Ile Tyr Tyr Ser Gly Ile Thr
 1   5

<210> 151
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151
gcgagagata gagtggaact acgagctttt gatatc   36

<210> 152
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152
Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
 1   5   10

<210> 153
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctataggaga cagaatcacc 60
atctcttgcc aggcgagtca ggacattaac aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctacgat gcatccaatt tggaaacagg gatcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcgg cctgcagcct 240
gaagatattg caacatatta ctgtcaacac tatgatagtc tccctctcac cttcggccaa 300
gggacacgac tggagattaa a   321

<210> 154
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ile Gly
 1   5   10   15
Asp Arg Ile Thr Ile Ser Cys Gln Ala Ser Gln Asp Ile Asn Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Leu Gln Pro
65   70   75   80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu
                85   90   95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 155
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 155
caggacatta acaactat   18

<210> 156
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 156
Gln Asp Ile Asn Asn Tyr
 1   5

<210> 157
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157
gatgcatcc   9

<210> 158
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 158
Asp Ala Ser
 1

<210> 159
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159
caacactatg atagtctccc tctcacc 27

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 160
Gln His Tyr Asp Ser Leu Pro Leu Thr
 1   5

<210> 161
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 161
caggtgcagc tgcaggagtc gggcccagga ctggtgatgc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcaac agtggtgatt actactggaa ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt ggatacatct attacagtga aatcagttat 180
cacaacccgt ccctcaagag tcgagttacc acctcaatag acacgtctac gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tctattactg tgcgagagat 300
agagtggaac tacgagcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 162
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Met Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
            20   25   30

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Asp Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Glu Ile Ser Tyr His Asn Pro Ser
    50                  55                  60
Leu Lys Ser Arg Val Thr Thr Ser Ile Asp Thr Ser Thr Asn Gln Phe
65                  70                  75                  80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95
Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110
Gly Thr Met Val Thr Val Ser Ser
        115                 120
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<210> 163
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163
ggtggctcca tcaacagtgg tgattactac 30

<210> 164
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164
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Gly Gly Ser Ile Asn Ser Gly Asp Tyr Tyr
 1               5                  10
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<210> 165
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165
atctattaca gtgaaatcag t 21

<210> 166
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166
```
Ile Tyr Tyr Ser Glu Ile Ser
 1               5
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<210> 167
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167
gcgagagata gagtggaact acgagctttt gatatc 36

<210> 168
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168
Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
 1   5   10

<210> 169
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacac tatgatagtc tccctctcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 170
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 170
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 Gln Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro

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

<210> 171
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171
caggacatta gcaactat 18

<210> 172
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172
Gln Asp Ile Ser Asn Tyr
1 5

<210> 173
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173
gatgcatcc 9

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174
Asp Ala Ser
1

<210> 175
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175
caacactatg atagtctccc tctcacc 27

<210> 176
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 176
Gln His Tyr Asp Ser Leu Pro Leu Thr
1 5

<210> 177
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 177
caggtgcagc tgcaggagtc gggcccagga ctggtgatgc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcaac agtggtgatt actactggaa ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt ggatacatct attacagtga aatcagttat 180
cacaacccgt ccctcaagag tcgagttacc acctcaatag acacgtctac gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tctattactg tgcgagagat 300
agagtggaac tacgagcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 178
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Met Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
20 25 30
Asp Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Glu Ile Ser Tyr His Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Thr Ser Ile Asp Thr Ser Thr Asn Gln Phe
65 70 75 80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
100 105 110
Gly Thr Met Val Thr Val Ser Ser

115 120

<210> 179
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179
ggtggctcca tcaacagtgg tgattactac 30

<210> 180
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180
Gly Gly Ser Ile Asn Ser Gly Asp Tyr Tyr
1 5 10

<210> 181
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181
atctattaca gtgaaatcag t 21

<210> 182
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182
Ile Tyr Tyr Ser Glu Ile Ser
1 5

<210> 183
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183

gcgagagata gagtggaact acgagctttt gatatc 36

<210> 184
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184
Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
1 5 10

<210> 185
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctacgat gcatccaatt tggagacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacac tatgatagtc tccctctcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 186
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 186
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 Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 187
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
caggacatta gcaactat 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
Gln Asp Ile Ser Asn Tyr
1 5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
gatgcatcc 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
Asp Ala Ser
1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191
caacactatg atagtctccc tctcacc 27

<210> 192
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 192
Gln His Tyr Asp Ser Leu Pro Leu Thr
 1   5

<210> 193
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 193
gaggtgcagc tggtggagtc tgggggaggc gtggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccgtcaagct 120
ccagggaagg gtctggagtg ggtctctctt attagtgggg atggtggtag cacatactat 180
gcagactctg tgaagggccg attcaccatc tccagagaca acagcaaaaa ctccctgtat 240
ctgcaaatga acagtctgag aactgaggac accgccttgt attactgtgc aaaaaattat 300
gatagtagtg gttattacta cccttactac tactactacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca   384

<210> 194
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Leu Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
                85   90   95
Ala Lys Asn Tyr Asp Ser Ser Gly Tyr Tyr Tyr Pro Tyr Tyr Tyr Tyr
            100   105   110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195
ggattcacct ttgatgatta tgcc 24

<210> 196
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196
Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

<210> 197
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197
attagtgggg atggtggtag caca 24

<210> 198
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198
Ile Ser Gly Asp Gly Gly Ser Thr
 1 5

<210> 199
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199
gcaaaaaatt atgatagtag tggttattac tacccttact actactacta cggtatggac 60
gtc 63

<210> 200
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200
Ala Lys Asn Tyr Asp Ser Ser Gly Tyr Tyr Tyr Pro Tyr Tyr Tyr Tyr
 1   5   10   15
Tyr Gly Met Asp Val
            20

<210> 201
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagct tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagtag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a   321

<210> 202
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Arg
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 203
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203
cagagtatta gtagctgg   18

<210> 204

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

<220>
<223> Synthetic

<400> 204
Gln Ser Ile Ser Ser Trp
 1   5

<210> 205
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205
aaggcgtct   9

<210> 206
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206
Lys Ala Ser
 1

<210> 207
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 207
caacagtata atagttattc tcggacg   27

<210> 208
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 208
Gln Gln Tyr Asn Ser Tyr Ser Arg Thr
 1   5

<210> 209
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209
gaggtgcagc tggtggagtc gggcccagga ctggtgcagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcaac agtggtgatt tctactggag ttggatccgc 120
cagcatccag ggaagggcct ggagtggatt ggtcacatat attacagtgg gatcacctac 180
tacagtccgt ccctcaagag tcgacttacc atctcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagttctgt gactgccgcg gacacggccg tgtattactg tgcgagaaag 300
agggtaactg gggaagttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

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

<220>
<223> Synthetic

<400> 210
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
            20   25   30
Asp Phe Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35   40   45
Trp Ile Gly His Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Ser Pro Ser
    50   55   60
Leu Lys Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65   70   75   80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Lys Arg Val Thr Gly Glu Val Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

<220>
<223> Synthetic

<400> 211
ggtggctcca tcaacagtgg tgatttctac 30

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

<220>

<223> Synthetic

<400> 212
Gly Gly Ser Ile Asn Ser Gly Asp Phe Tyr
 1   5   10

<210> 213
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 213
atatattaca gtgggatcac c   21

<210> 214
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214
Ile Tyr Tyr Ser Gly Ile Thr
 1   5

<210> 215
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215
gcgagaaaga gggtaactgg ggaagttgac tac   33

<210> 216
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 216
Ala Arg Lys Arg Val Thr Gly Glu Val Asp Tyr
 1   5   10

<210> 217
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 217
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagaatcacc 60
atcacttgcc aggcgaatca ggacattaac aactatttaa attggtatca gcaaaagcca 120
gggaaagccc ctaagctcct gatctccgat gcatccaatt tggaaacagg ggtcccatca 180
agattcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacag tatgataatc tccctcccac cttcggccaa 300
gggacacgac tggagattaa acga 324

<210> 218
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 218
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Ile Thr Ile Thr Cys Gln Ala Asn Gln Asp Ile Asn Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Ser Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Pro
                85   90   95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
            100   105

<210> 219
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 219
caggacatta acaactat 18

<210> 220
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 220
Gln Asp Ile Asn Asn Tyr
 1   5

<210> 221
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 221
gatgcatcc 9

<210> 222
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 222
Asp Ala Ser
1

<210> 223
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 223
caacagtatg ataatctccc tcccacc 27

<210> 224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 224
Gln Gln Tyr Asp Asn Leu Pro Pro Thr
1 5

<210> 225
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 225
caggtgcagc tgcaggagtc gggcccagga ctggtgaacc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcaat agtggtgatt actactggag ctgggtccgc 120
cagcacccag ggaagggcct ggagtggatt ggatacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atctcagtgg acacgtctaa gaaccagttc 240
tccctgaaac tgagctctgt gactgtcgcg gacacggccg tatattactg tgcgagagtg 300
ggctacagta aagggtactt tgactcctgg ggccagggaa ccctggtcac tgtctcctca 360

<210> 226
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 226
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Asn Pro Ser Gln
 1   5   10   15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
            20   25   30
Asp Tyr Tyr Trp Ser Trp Val Arg Gln His Pro Gly Lys Gly Leu Glu
        35   40   45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50   55   60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65   70   75   80
Ser Leu Lys Leu Ser Ser Val Thr Val Ala Asp Thr Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Val Gly Tyr Ser Lys Gly Tyr Phe Asp Ser Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 227
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 227
ggtggctcca tcaatagtgg tgattactac 30

<210> 228
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 228
Gly Gly Ser Ile Asn Ser Gly Asp Tyr Tyr
 1   5   10

<210> 229
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 229
atctattaca gtgggagcac c 21

<210> 230
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 230
Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> 231
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 231
gcgagagtgg gctacagtaa agggtacttt gactcc 36

<210> 232
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 232
Ala Arg Val Gly Tyr Ser Lys Gly Tyr Phe Asp Ser
1 5 10

<210> 233
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 233
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtga gagtattagt agctggttgg cctggtatca gcagaaacca 120
gggaaagccc ctaaggtcct gatctatgat gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa tacactctca ccatcagcag cctgcagcct 240
gatgactttg caagttatta ctgccaacag tataaaagtt attggacgtt cggccaaggg 300
accaaggtgg aaatcaaa 318

<210> 234
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 234
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
        35   40   45
Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Asp Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Trp Thr
                85   90   95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 235
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 235
gagagtatta gtagctgg   18

<210> 236
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 236
Glu Ser Ile Ser Ser Trp
 1   5

<210> 237
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 237
gatgcgtct   9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238
Asp Ala Ser
 1

<210> 239
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 239
caacagtata aaagttattg gacg 24

<210> 240
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 240
Gln Gln Tyr Lys Ser Tyr Trp Thr
 1   5

<210> 241
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 241
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaagtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt atctatggca tgaactgggt ccgccaggct 120
ccaggcaagg ggctggactg ggtggcagtt atttcagatg atggaagtaa taaagactat 180
gtggactccg tgaggggtcg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag cgctgaagac acggctgtct attactgtgc gaaagatcgt 300
atcactggca ctcattacta cggtttggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 242
<211> 122
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 242
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Lys
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
            20   25   30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
        35   40   45
Ala Val Ile Ser Asp Asp Gly Ser Asn Lys Asp Tyr Val Asp Ser Val
    50   55   60
Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Leu Asp Val Trp
            100   105   110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 243
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 243
ggattcacct tcagtatcta tggc   24

<210> 244
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 244
Gly Phe Thr Phe Ser Ile Tyr Gly
 1   5

<210> 245
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 245
atttcagatg atggaagtaa taaa   24

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

<220>
<223> Synthetic

<400> 246
Ile Ser Asp Asp Gly Ser Asn Lys
 1   5

<210> 247
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 247
gcgaaagatc gtatcactgg cactcattac tacggtttgg acgtc   45

<210> 248
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 248
Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Leu Asp Val
 1   5   10   15

<210> 249
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 249
gacatccaga tgacccagtc tccgtcctca ctgtctgcat ctgtcggaga cagaatcacc 60
atcacttgtc gggcgagtca ggacattgcc aattatttag cctggtttca gcagaaacca 120
ggtaatgccc ctacgtccct gatctatgct gcatccattt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcaccag cctgcagcca 240
gaagattttg caagttatta ctgccaacaa tataatagaa agccgtggac gttcggccga 300
gggaccaagg tggaaatcaa a   321

<210> 250
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 250
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15

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Asp Arg Ile Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asn Tyr
            20                  25                  30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Asn Ala Pro Thr Ser Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Asn Arg Lys Pro Trp
                85                  90                  95
Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 251
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 251
caggacattg ccaattat 18

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 252
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Gln Asp Ile Ala Asn Tyr
 1               5
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<210> 253
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 253
gctgcatcc 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 254
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Ala Ala Ser
 1
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<210> 255
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 255
caacaatata atagaaagcc gtggacg 27

<210> 256
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 256
Gln Gln Tyr Asn Arg Lys Pro Trp Thr
1 5

<210> 257
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 257
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt atctatggca tgcactgggt ccgccaggct 120
ccaggcaagg gactggagtg ggtgacagtt atatcagacg atggaagtaa aaaatactat 180
gtagactccg tgaagggccg attcaccctc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagatcgt 300
ataactggaa ccaactggta cggtatggac gtctggggcc aggggaccac ggtcaccgtc 360
tcctca 366

<210> 258
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 258
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Thr Val Ile Ser Asp Asp Gly Ser Lys Lys Tyr Tyr Val Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Leu Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Arg Ile Thr Gly Thr Asn Trp 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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<210> 259
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 259
ggattcacct tcagtatcta tggc 24

<210> 260
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 260
```
Gly Phe Thr Phe Ser Ile Tyr Gly
 1               5
```

<210> 261
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 261
atatcagacg atggaagtaa aaaa 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 262
```
Ile Ser Asp Asp Gly Ser Lys Lys
 1               5
```

<210> 263
<211> 45

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 263
gcgagagatc gtataactgg aaccaactgg tacggtatgg acgtc 45

<210> 264
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 264
Ala Arg Asp Arg Ile Thr Gly Thr Asn Trp Tyr Gly Met Asp Val
1 5 10 15

<210> 265
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 265
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattagc aattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctttgct gcatccagtt tgcaaagtgg gggcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataatcgtt acccattcac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 266
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

100 105

<210> 267
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 267
caggacatta gcaattat 18

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 268
Gln Asp Ile Ser Asn Tyr
1 5

<210> 269
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 269
gctgcatcc 9

<210> 270
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 270
Ala Ala Ser
1

<210> 271
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 271

caacagtata atcgttaccc attcact 27

<210> 272
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 272
Gln Gln Tyr Asn Arg Tyr Pro Phe Thr
 1   5

<210> 273
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 273
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctcagactc 60
acctgtaaag cctctggatt caccttcagt atctatggca taaactgggt ccgccaggct 120
tcaggcaagg ggctggactg ggtggcagtc atttcagatg atggaagtga taagaagtat 180
gcagattccg tgaagggccg attcaccatc tcccgagaca attccaaaaa cacggtttat 240
ctggaaatga gcagactgag aagtgaggac acggctgttt atttctgtgc gaaagaccgg 300
tttactggaa accactatta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 274
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 274
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Thr Cys Lys Ala Ser Gly Phe Thr Phe Ser Ile Tyr
            20   25   30
Gly Ile Asn Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Asp Trp Val
        35   40   45
Ala Val Ile Ser Asp Asp Gly Ser Asp Lys Lys Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65   70   75   80
Leu Glu Met Ser Arg Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85   90   95
Ala Lys Asp Arg Phe Thr Gly Asn His Tyr Tyr Gly Met Asp Val Trp
            100   105   110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 275

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

<220>
<223> Synthetic

<400> 275
ggattcacct tcagtatcta tggc 24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 276
Gly Phe Thr Phe Ser Ile Tyr Gly
1 5

<210> 277
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 277
atttcagatg atggaagtga taag 24

<210> 278
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 278
Ile Ser Asp Asp Gly Ser Asp Lys
1 5

<210> 279
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 279
gcgaaagacc ggtttactgg aaaccactat tacggtatgg acgtc 45

<210> 280
<211> 15

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 280
Ala Lys Asp Arg Phe Thr Gly Asn His Tyr Tyr Gly Met Asp Val
 1   5   10   15

<210> 281
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 281
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcagt 60
atcacttgtc gggcgagtca ggacattagc gattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccattt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg ctctttatta ctgtcatcag tataatcgtt tcccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa a   321

<210> 282
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 282
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asp Tyr
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35   40   45
Tyr Ala Ala Ser Ile Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Leu Tyr Tyr Cys His Gln Tyr Asn Arg Phe Pro Trp
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 283
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 283
caggacatta gcgattat 18

<210> 284
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 284
Gln Asp Ile Ser Asp Tyr
1 5

<210> 285
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 285
gctgcatcc 9

<210> 286
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 286
Ala Ala Ser
1

<210> 287
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 287
catcagtata atcgtttccc gtggacg 27

<210> 288
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 288

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His Gln Tyr Asn Arg Phe Pro Trp Thr
 1               5
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<210> 289
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 289
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggggtc cctgagactc 60
tcgtgtgcag cctctggatt cacgttcagt atctatggca tacactgggt ccgccaggct 120
ccaggcaagg gactggagtg ggtggcagtc atatctgatg atggaagtaa taaaaagtat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctatat tttactgtgc gaaagatcgg 300
ataactggaa cccactacta cggaatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 290
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 290
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
            20                  25                  30
Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Ser Asp Asp Gly Ser Asn Lys Lys Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Phe Tyr Cys
                85                  90                  95
Ala Lys Asp Arg Ile Thr Gly Thr His 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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<210> 291
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 291
ggattcacgt tcagtatcta tggc 24

<210> 292

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

<220>
<223> Synthetic

<400> 292
Gly Phe Thr Phe Ser Ile Tyr Gly
 1   5

<210> 293
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 293
atatctgatg atggaagtaa taaa   24

<210> 294
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 294
Ile Ser Asp Asp Gly Ser Asn Lys
 1   5

<210> 295
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 295
gcgaaagatc ggataactgg aacccactac tacggaatgg acgtc   45

<210> 296
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 296
Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Met Asp Val
 1   5   10   15

<210> 297
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 297
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcagc 60
atcacttgtc gggcgagtca ggacattagc aattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcttccagtt tgcaaagtgg ggtcccatca 180
aaattcagcg gcagtggatc tgggatagaa ttcactctca ccatcagcag cctgcagcct 240
gaagattttt caacttatta ctgccatcaa tataatcgtt tcccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 298
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 298
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Ile Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ser Thr Tyr Tyr Cys His Gln Tyr Asn Arg Phe Pro Trp
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 299
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 299
caggacatta gcaattat 18

<210> 300
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 300
Gln Asp Ile Ser Asn Tyr
 1   5

<210> 301
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 301
gctgcttcc   9

<210> 302
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 302
Ala Ala Ser
 1

<210> 303
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 303
catcaatata atcgtttccc gtggacg   27

<210> 304
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 304
His Gln Tyr Asn Arg Phe Pro Trp Thr
 1   5

<210> 305
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 305
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgaggctc 60
tcatgtgcag cctctagatt cacctttact aactattgga tgagttgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtggccaaa ataaagcaag atggaagtga gaaatactat 180
ctggactctg tgaaggaccg attcaccatc tccagagaca acgccaagaa ctcactttat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagtagcagc 300
agctggtacg actactacta cggtatggac gtctggggcc acgggaccac ggtcaccgtc 360
tcctca 366

<210> 306
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 306
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Thr Asn Tyr
            20   25   30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Lys Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Leu Asp Ser Val
    50   55   60
Lys Asp 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 Val Tyr Tyr Cys
                85   90   95
Ala Ser Ser Ser Ser Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val Trp
            100   105   110
Gly His Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 307
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 307
agattcacct ttactaacta ttgg 24

<210> 308
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 308
Arg Phe Thr Phe Thr Asn Tyr Trp
 1   5

<210> 309
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 309
ataaagcaag atggaagtga gaaa 24

<210> 310
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 310
Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> 311
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 311
gcgagtagca gcagctggta cgactactac tacggtatgg acgtc 45

<210> 312
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 312
Ala Ser Ser Ser Ser Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 313
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 313
gaaattgtgt tgactcagtc tccagacttt cagtctgtga ctccaaaaga gaaagtcacc 60
atcacctgcc gggccagtca gagcattggt actaacttac actggtacca gcagagacca 120

gatcagtctc caaagctcct catcaagttt gcttcccagt ccttctcagg ggtcccctcg 180
aggttcagtg gcagtggatc tgggacagat ttcaccctca ccatcaatag cctggaagct 240
gaagatgctg caacgtatta ctgtcatcag actaactttt tacctcacac tttcggcgga 300
gggaccaagg tggaaatcaa acga 324

<210> 314
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 314
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
 1   5   10   15
Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20   25   30
Leu His Trp Tyr Gln Gln Arg Pro Asp Gln Ser Pro Lys Leu Leu Ile
        35   40   45
Lys Phe Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65   70   75   80
Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Thr Asn Phe Leu Pro His
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 315
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 315
cagagcattg gtactaac 18

<210> 316
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 316
Gln Ser Ile Gly Thr Asn
 1   5

<210> 317
<211> 9
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 317
tttgcttcc 9

<210> 318
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 318
Phe Ala Ser
1

<210> 319
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 319
catcagacta actttttacc tcacact 27

<210> 320
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 320
His Gln Thr Asn Phe Leu Pro His Thr
1 5

<210> 321
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 321
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgacattc atatcatatg atggaagtaa taaaaactat 180
gtagactcca tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagtctgag agttgaggac acggctgtat attactgtgc gaaagatcgt 300
ataagtggaa ctccatggta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 322

<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 322
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30
Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Thr Phe Ile Ser Tyr Asp Gly Ser Asn Lys Asn Tyr Val Asp Ser Met
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Asp Arg Ile Ser Gly Thr Pro Trp Tyr Gly Met Asp Val Trp
            100   105   110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 323
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 323
ggattcacct tcagtaacta tggc   24

<210> 324
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 324
Gly Phe Thr Phe Ser Asn Tyr Gly
 1   5

<210> 325
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 325
atatcatatg atggaagtaa taaa   24

<210> 326
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 326
Ile Ser Tyr Asp Gly Ser Asn Lys
 1   5

<210> 327
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 327
gcgaaagatc gtataagtgg aactccatgg tacggtatgg acgtc   45

<210> 328
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 328
Ala Lys Asp Arg Ile Ser Gly Thr Pro Trp Tyr Gly Met Asp Val
 1   5   10   15

<210> 329
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 329
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattgcc gattatttag cctggtttca acagaaacca 120
gggaaagccc ctaagtccct gatctttgct gcatccagtc tggaaagttg ggttccctta 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tatagtaggt tcccgatcac cttcggccaa 300
gggaccaagg tggaaatcaa a   321

<210> 330
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 330
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 Asp Ile Ala Asp Tyr
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35   40   45
Phe Ala Ala Ser Ser Leu Glu Ser Trp Val Pro Leu Lys Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Arg Phe Pro Ile
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 331
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 331
caggacattg ccgattat   18

<210> 332
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 332
Gln Asp Ile Ala Asp Tyr
 1   5

<210> 333
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 333
gctgcatcc   9

<210> 334
<211> 3
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 334
Ala Ala Ser
 1

<210> 335
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 335
caacagtata gtaggttccc gatcacc 27

<210> 336
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 336
Gln Gln Tyr Ser Arg Phe Pro Ile Thr
 1   5

<210> 337
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 337
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgacactc atagaacatg atggaagtaa taaaaactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagtctgag agttgaggac acggctgtat attactgtgc gaaagatcgt 300
ataactggaa ctccatggta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

<210> 338
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 338
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

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            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Thr Leu Ile Glu His Asp Gly Ser Asn Lys Asn Tyr Val Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Asp Arg Ile Thr Gly Thr Pro Trp 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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<210> 339
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 339
ggattcacct tcagtaacta tggc 24

<210> 340
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 340
Gly Phe Thr Phe Ser Asn Tyr Gly
 1   5

<210> 341
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 341
atagaacatg atggaagtaa taaa 24

<210> 342
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 342
Ile Glu His Asp Gly Ser Asn Lys

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 1               5


<210> 343
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 343
gcgaaagatc gtataactgg aactccatgg tacggtatgg acgtc                  45

<210> 344
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 344
Ala Lys Asp Arg Ile Thr Gly Thr Pro Trp Tyr Gly Met Asp Val
 1               5                  10                  15


<210> 345
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 345
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattgcc gattatttag cctggtttca acagaaacca 120
gggaaagccc ctaaatccct gatctttgcg gcatccagtc tggaaagttg ggttccctta 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataataggt tcccgatcac cttcggccaa 300
gggacacgac tggagattaa a                                            321

<210> 346
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 346
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 Asp Ile Ala Asp Tyr
            20                  25                  30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45
Phe Ala Ala Ser Ser Leu Glu Ser Trp Val Pro Leu Lys Phe Ser Gly
    50                  55                  60
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Arg Phe Pro Ile
                85                  90                  95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210> 347
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 347
caggacattg ccgattat                                                  18

<210> 348
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 348
Gln Asp Ile Ala Asp Tyr
 1               5


<210> 349
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 349
gcggcatcc                                                            9

<210> 350
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 350
Ala Ala Ser
 1


<210> 351
<211> 27
<212> DNA
<213> Artificial Sequence
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<220>
<223> Synthetic

<400> 351
caacagtata ataggttccc gatcacc 27

<210> 352
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 352
Gln Gln Tyr Asn Arg Phe Pro Ile Thr
1 5

<210> 353
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 353
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgaggctc 60
tcatgtgcag cctctagatt cacctttagt acctattgga tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtggccaaa ataaagcaag atggaagtga gaaatactat 180
ctggactctg tgaaggaccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaagac acggctgtgt attactgtgc gagtagcatt 300
acctggtacg actactacta cggtatggac gtctggggcc acgggaccac ggtcaccgtc 360
tcctca 366

<210> 354
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 354
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Thr Tyr
20 25 30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Lys Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Leu Asp Ser Val
50 55 60
Lys Asp 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 Val Tyr Tyr Cys
85 90 95
Ala Ser Ser Ile Thr Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly His Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 355
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 355
agattcacct ttagtaccta ttgg 24

<210> 356
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 356
Arg Phe Thr Phe Ser Thr Tyr Trp
1 5

<210> 357
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 357
ataaagcaag atggaagtga gaaa 24

<210> 358
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 358
Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> 359
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 359
gcgagtagca ttacctggta cgactactac tacggtatgg acgtc 45

<210> 360
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 360
Ala Ser Ser Ile Thr Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val
 1   5   10   15

<210> 361
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 361
gaaattgtgt tgacgcagtc tccagacttt cagtctgtga ctccaaaaga gaaagtcacc 60
atcacctgcc gggccagtca gagcattggt agtaacttac actggtacca gcagaaacca 120
gatcagtctc caaacctcct catcaagttt gcttcccagt ccttctcagg ggtcccctcg 180
aggttcagtg gcagtggatc tgggacagat ttcaccctca ccatcaatag cctggaagct 240
gaagatgctg caacgtatta ctgtcatcag actaattttt tacctcacac tttcggcgga 300
gggaccaagg tggaaatcaa a 321

<210> 362
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 362
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
 1   5   10   15
Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Asn
            20   25   30
Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Asn Leu Leu Ile
        35   40   45
Lys Phe Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65   70   75   80
Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Thr Asn Phe Leu Pro His
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 363
<211> 18
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 363
cagagcattg gtagtaac 18

<210> 364
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 364
Gln Ser Ile Gly Ser Asn
1 5

<210> 365
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 365
tttgcttcc 9

<210> 366
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 366
Phe Ala Ser
1

<210> 367
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 367
catcagacta attttttacc tcacact 27

<210> 368
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 368
His Gln Thr Asn Phe Leu Pro His Thr
 1   5

<210> 369
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 369
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt atctatggca tgaactgggt ccgccagggt 120
ccaggcaagg ggctggactg ggtggcagtt atttcagatg atggaagtaa taaagactat 180
gtagactccg tgaggggtcg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag cgctgaagac acggctgtct attactgtgc gaaagatcgt 300
atcactggca ctcattacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca   366

<210> 370
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 370
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
            20   25   30
Gly Met Asn Trp Val Arg Gln Gly Pro Gly Lys Gly Leu Asp Trp Val
        35   40   45
Ala Val Ile Ser Asp Asp Gly Ser Asn Lys Asp Tyr Val Asp Ser Val
    50   55   60
Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Met Asp Val Trp
            100   105   110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 371
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 371
ggattcacct tcagtatcta tggc 24

<210> 372
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 372
Gly Phe Thr Phe Ser Ile Tyr Gly
1 5

<210> 373
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 373
atttcagatg atggaagtaa taaa 24

<210> 374
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 374
Ile Ser Asp Asp Gly Ser Asn Lys
1 5

<210> 375
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 375
gcgaaagatc gtatcactgg cactcattac tacggtatgg acgtc 45

<210> 376
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 376
Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Met Asp Val
 1   5   10   15

<210> 377
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 377
gacatccaga tgacccagtc tccgtcctca ctgtctgcat ctgtcggaga cagaatcacc 60
atcacttgtc gggcgagtca ggacattgcc aattatttag cctggtttca gcagaaacca 120
ggtaatgccc ctacgtccct gatctatgct gcatccattt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcaccag cctgcagcca 240
gaagattttg caagttatta ctgccaacaa tataatagaa agccgtggac gttcggccga 300
gggaccaagg tggaaatcaa a   321

<210> 378
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 378
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Ile Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asn Tyr
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Asn Ala Pro Thr Ser Leu Ile
        35   40   45
Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Asn Arg Lys Pro Trp
                85   90   95
Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 379
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 379
caggacattg ccaattat   18

<210> 380
<211> 6
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 380
Gln Asp Ile Ala Asn Tyr
 1   5

<210> 381
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 381
gctgcatcc   9

<210> 382
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 382
Ala Ala Ser
 1

<210> 383
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 383
caacaatata atagaaagcc gtggacg   27

<210> 384
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 384
Gln Gln Tyr Asn Arg Lys Pro Trp Thr
 1   5

<210> 385
<211> 1210

<212> PRT
<213> Homo sapiens

<400> 385
Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
 1   5   10   15
Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
            20   25   30
Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
        35   40   45
Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
    50   55   60
Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
65   70   75   80
Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
                85   90   95
Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
            100   105   110
Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
        115   120   125
Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
    130   135   140
His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
145   150   155   160
Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
                165   170   175
Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
            180   185   190
Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
        195   200   205
Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
    210   215   220
Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
225   230   235   240
Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
                245   250   255
Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
            260   265   270
Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
        275   280   285
Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
    290   295   300
Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
305   310   315   320
Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
                325   330   335
Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
            340   345   350
Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
        355   360   365
Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
    370   375   380
Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
385   390   395   400
Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
                405   410   415
Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
            420   425   430
His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
        435   440   445

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Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
    450                 455                 460
Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
465                 470                 475                 480
Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
                485                 490                 495
Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
            500                 505                 510
Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
        515                 520                 525
Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
    530                 535                 540
Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
545                 550                 555                 560
Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
                565                 570                 575
Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
            580                 585                 590
Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
        595                 600                 605
Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
    610                 615                 620
Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
625                 630                 635                 640
Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
                645                 650                 655
Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
            660                 665                 670
Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
        675                 680                 685
Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
    690                 695                 700
Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
705                 710                 715                 720
Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
                725                 730                 735
Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
            740                 745                 750
Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
        755                 760                 765
Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
    770                 775                 780
Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
785                 790                 795                 800
Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
                805                 810                 815
Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
            820                 825                 830
Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
        835                 840                 845
Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
    850                 855                 860
Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
865                 870                 875                 880
Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
                885                 890                 895
Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
            900                 905                 910
Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
        915                 920                 925
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Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
    930                 935                 940
Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
945                 950                 955                 960
Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
                965                 970                 975
Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
            980                 985                 990
Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
        995                 1000                1005
Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe
    1010                1015                1020
Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala
1025                1030                1035                1040
Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln
                1045                1050                1055
Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp
            1060                1065                1070
Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro
        1075                1080                1085
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser
    1090                1095                1100
Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser
1105                1110                1115                1120
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro
                1125                1130                1135
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp
            1140                1145                1150
Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp
        1155                1160                1165
Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn
    1170                1175                1180
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val
1185                1190                1195                1200
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
                1205                1210


<210> 386
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 386
Leu Glu Glu Lys Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln
 1               5                  10                  15
Leu Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn
            20                  25                  30
Asn Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg
        35                  40                  45
Asn Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr
    50                  55                  60
Val Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu
65                  70                  75                  80
Gln Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala
                85                  90                  95
Val Leu Ser Asn Tyr Asp Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro
```

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            100                 105                 110
Met Arg Asn Leu Gln Glu Ile Leu His Gly Ala Val Arg Phe Ser Asn
        115                 120                 125
Asn Pro Ala Leu Cys Asn Val Glu Ser Ile Gln Trp Arg Asp Ile Val
    130                 135                 140
Ser Ser Asp Phe Leu Ser Asn Met Ser Met Asp Phe Gln Asn His Leu
145                 150                 155                 160
Gly Ser Cys Gln Lys Cys Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp
                165                 170                 175
Gly Ala Gly Glu Glu Asn Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala
            180                 185                 190
Gln Gln Cys Ser Gly Arg Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys
        195                 200                 205
His Asn Gln Cys Ala Ala Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys
    210                 215                 220
Leu Val Cys Arg Lys Phe Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys
225                 230                 235                 240
Pro Pro Leu Met Leu Tyr Asn Pro Thr Thr Tyr Gln Met Asp Val Asn
                245                 250                 255
Pro Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro
            260                 265                 270
Arg Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly
        275                 280                 285
Ala Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys
    290                 295                 300
Cys Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu
305                 310                 315                 320
Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys
                325                 330                 335
Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe
            340                 345                 350
Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu
        355                 360                 365
Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln
    370                 375                 380
Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu
385                 390                 395                 400
Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val
                405                 410                 415
Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile
            420                 425                 430
Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala
        435                 440                 445
Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr
    450                 455                 460
Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln
465                 470                 475                 480
Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro
                485                 490                 495
Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val
            500                 505                 510
Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn
        515                 520                 525
Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn
    530                 535                 540
Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His
545                 550                 555                 560
Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met
                565                 570                 575
Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val
```

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            580                 585                 590
Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly
        595                 600                 605
Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Cys
    610                 615                 620
Pro Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly Glu
625                 630                 635                 640
Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Gly His His His His His
                645                 650                 655
His Ser Ser Gly
            660


<210> 387
<211> 856
<212> PRT
<213> Homo sapiens

<400> 387
Leu Glu Glu Lys Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln
 1               5                  10                  15
Leu Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn
            20                  25                  30
Asn Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg
        35                  40                  45
Asn Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr
    50                  55                  60
Val Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu
65                  70                  75                  80
Gln Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala
                85                  90                  95
Val Leu Ser Asn Tyr Asp Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro
            100                 105                 110
Met Arg Asn Leu Gln Glu Ile Leu His Gly Ala Val Arg Phe Ser Asn
        115                 120                 125
Asn Pro Ala Leu Cys Asn Val Glu Ser Ile Gln Trp Arg Asp Ile Val
    130                 135                 140
Ser Ser Asp Phe Leu Ser Asn Met Ser Met Asp Phe Gln Asn His Leu
145                 150                 155                 160
Gly Ser Cys Gln Lys Cys Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp
                165                 170                 175
Gly Ala Gly Glu Glu Asn Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala
            180                 185                 190
Gln Gln Cys Ser Gly Arg Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys
        195                 200                 205
His Asn Gln Cys Ala Ala Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys
    210                 215                 220
Leu Val Cys Arg Lys Phe Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys
225                 230                 235                 240
Pro Pro Leu Met Leu Tyr Asn Pro Thr Thr Tyr Gln Met Asp Val Asn
                245                 250                 255
Pro Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro
            260                 265                 270
Arg Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly
        275                 280                 285
Ala Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys
    290                 295                 300
Cys Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu
305                 310                 315                 320
Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys
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                325                 330                 335
Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe
            340                 345                 350
Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu
        355                 360                 365
Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln
    370                 375                 380
Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu
385                 390                 395                 400
Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val
                405                 410                 415
Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile
            420                 425                 430
Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala
        435                 440                 445
Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr
    450                 455                 460
Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln
465                 470                 475                 480
Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro
                485                 490                 495
Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val
            500                 505                 510
Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn
        515                 520                 525
Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn
    530                 535                 540
Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His
545                 550                 555                 560
Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met
                565                 570                 575
Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val
            580                 585                 590
Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly
        595                 600                 605
Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Glu
    610                 615                 620
Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
625                 630                 635                 640
Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
                645                 650                 655
Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
            660                 665                 670
Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
        675                 680                 685
Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
    690                 695                 700
Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
705                 710                 715                 720
Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
                725                 730                 735
Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val
            740                 745                 750
Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
        755                 760                 765
Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
    770                 775                 780
Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr
785                 790                 795                 800
Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
```

```
                805                 810                 815
Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr
            820                 825                 830
Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
        835                 840                 845
Ser Phe Ser Arg Thr Pro Gly Lys
    850                 855
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<210> 388
<211> 227
<212> PRT
<213> Homo sapiens

<400> 388

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