

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 October 2002 (31.10.2002)

PCT

(10) International Publication Number
WO 02/086085 A2

(51) International Patent Classification⁷: **C12N**

(21) International Application Number: PCT/US02/12801

(22) International Filing Date: 24 April 2002 (24.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/285,683 24 April 2001 (24.04.2001) US

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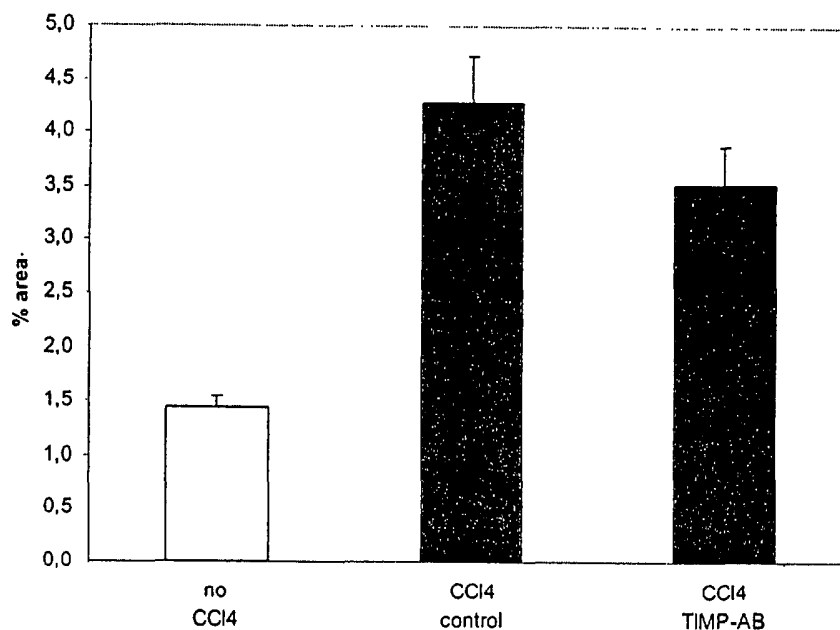
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,

[Continued on next page]

(54) Title: HUMAN TIMP-1 ANTIBODIES

Morphometry



(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.



GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *without international search report and to be republished upon receipt of that report*

HUMAN TIMP-1 ANTIBODIES

- [01] This application claims priority to and incorporates by reference co-pending provisional application Serial No. 60/285,683 filed April 24, 2001.

FIELD OF THE INVENTION

- [02] The invention relates to TIMP-1-binding human antibodies.

BACKGROUND OF THE INVENTION

- [03] Tissue inhibitors of metalloproteases (TIMPs) inhibit metalloproteases, a family of endopeptide hydrolases. Metalloproteases are secreted by connective tissue and hematopoietic cells, use Zn^{2+} or Ca^{2+} for catalysis, and may be inactivated by metal chelators as well as TIMP molecules. Matrix metalloproteases (MMPs) participate in a variety of biologically important processes, including the degradation of many structural components of tissues, particularly the extracellular matrix (ECM).
- [04] Degradation of extracellular matrix tissue is desirable in processes where destruction of existing tissues is necessary, *e.g.*, in embryo implantation (Reponen *et al.*, *Dev. Dyn.* 202, 388-96, 1995), embryogenesis, and tissue remodeling. Imbalance between synthesis and degradation of matrix proteins, however, can result in diseases such as liver fibrosis (Iredale *et al.*, *Hepatology* 24, 176-84, 1996). This imbalance can occur, for example, if levels of TIMPs are increased. Disorders in which TIMP-1 levels of increased include, for example, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer. *See, e.g.*, Inokubo

et al., *Am. Heart J.* 141, 211-17, 2001; Ylisirnio *et al.*, *Anticancer Res.* 20, 1311-16, 2000; Holten-Andersen *et al.*, *Clin. Cancer Res.* 6, 4292-99, 2000; Holten-Andersen *et al.*, *Br. J. Cancer* 80, 495-503, 1999; Peterson *et al.*, *Cardiovascular Res.* 46, 307-15, 2000; Arthur *et al.*, *Alcoholism: Clinical and Experimental Res.* 23, 840-43, 1999; Iredale *et al.*, *Hepatology* 24, 176-84, 1996.

- [06] There is a need in the art for reagents and methods of inhibiting TIMP-1 activity, which can be used to provide therapeutic effects.

BRIEF SUMMARY OF THE INVENTION

- [07] It is an object of the present invention to provide reagents and methods of inhibiting TIMP-1 activity. This and other objects of the invention are provided by one or more of the embodiments described below.
- [08] One embodiment of the invention is a purified preparation of a human antibody, wherein the antibody binds to a tissue inhibitor of metalloprotease-1 (TIMP-1) and neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.
- [09] Another embodiment of the invention is a purified preparation of a first human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.
- [10] Still another embodiment of the invention is a purified preparation of a first human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.
- [11] Yet another embodiment of the invention is a purified preparation of a first human antibody which has TIMP-1 binding and MMP-inhibiting activity characteristics of a second human antibody. The second antibody comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5

and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- [12] Even another embodiment of the invention is a purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ

ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- [13] A further embodiment of the invention is a purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101, SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NOS:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

- [14] Another embodiment of the invention is a pharmaceutical composition comprising a human antibody and a pharmaceutically acceptable carrier. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [15] Yet another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [16] Even another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [17] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [18] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [19] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID

NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- [20] Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- [21] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [22] Even another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- [23] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain

having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [24] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- [25] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [26] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [27] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- [28] A further embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- [29] Another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [30] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- [31] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human

antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [32] Even another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- [33] A further embodiment of the invention is a method of making a human antibody. The host cell of claim 43 is cultured under conditions whereby the antibody is expressed. The human antibody is purified from the host cell culture.
- [34] Another embodiment of the invention is a method of decreasing an MMP-inhibiting activity of a TIMP-1. The TIMP-1 is contacted with a human antibody that binds to the TIMP-1. The MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.
- [35] Still another embodiment of the invention is a method of ameliorating symptoms of a disorder in which TIMP-1 is elevated. An effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1 is administered to a patient having the disorder. Symptoms of the disorder are thereby ameliorated.
- [36] A further embodiment of the invention is a method of detecting a TIMP-1 in a test preparation. The test preparation is contacted with a human antibody that specifically binds to the TIMP-1. The test preparation is assayed for the presence of an antibody-TIMP-1 complex.

- [37] Even another embodiment of the invention is a method to aid in diagnosing a disorder in which a TIMP-1 level is elevated. A sample from a patient suspected of having the disorder is contacted with a human antibody that binds to TIMP-1. The sample is assayed for the presence of an antibody-TIMP-1 complex. Detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.
- [38] The invention thus provides human antibodies which bind to TIMP-1 and neutralize MMP-inhibiting activity of TIMP-1. These antibodies can be used, *inter alia*, in diagnostic and therapeutic methods.

BRIEF DESCRIPTION OF THE FIGURES

- [39] FIG. 1. Protein sequences encoded by the HuCAL[®] V_H and V_L Fab master genes. Seven V_H and V_L sequences are aligned, and the approximate location of restriction endonuclease sites introduced into the corresponding DNA sequences are indicated. The numbering is according to VBASE except for the gap in V_L position 9. In VBASE the gap is set at position 10. See also Chothia *et al.* (1992) *J. Mol. Biol.* 227, 776-798, Tomlinson *et al.* (1995) *EMBO J.* 14, 4628-4638 and Williams *et al.* (1996) *J. Mol. Biol.* 264, 220-232).
- [40] FIG. 2. Nucleotide sequences of the HuCAL[®] V_H and V_L Fab master genes.
- [41] FIG. 3. Fab display vector pMORPH[®] 18 Fab 1.
- [42] FIG. 4. Vector map of pMORPH[®] x9Fab1_FS.
- [43] FIG. 5. Sequence comparison between human and rat TIMP-1. Sequence regions in bold were used for peptide synthesis. Residues that make stronger direct contacts with MMP-3 are italicized, and residues that make weaker direct contacts with MMP-3 are underlined (Gomis-Ruth *et al.*, 1997).

- [44] FIG. 6. Activity of MS-BW-3 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 27% MMP-1 activity (in absence of antibody) as reference values.
- [45] FIG. 7. Activity of MS-BW-44 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 25% MMP-1 activity (in absence of antibody) as reference values.
- [46] FIG. 8. Activity of MS-BW-44, -44-2, 44-6 in human TIMP-1/ MMP-1 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM) and peptide substrate (final conc. 50 μ M) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 55% MMP-1 activity (in absence of antibody) as reference values.
- [47] FIG. 9. Activity of MS-BW-44, -44-2-4, 44-6-1 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM), and peptide substrate (final conc. 50 μ M) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in

material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 50% MMP-1 activity (in absence of antibody) as reference values.

- [48] FIG. 10. Binding of Fab fragments to human TIMP-1, -2, -3 and -4. TIMP-1, -2, -3, -4 proteins were immobilized on an ELISA plate, and binding of purified Fab fragments was measured by incubation with alkaline phosphatase conjugated anti-Fab antibody (Dianova) followed by development with Attophos substrate (Roche) and measurement at Ex405nm/Em535 nm.
- [49] FIG. 11. Activity of MS-BW-14, -17, -54 in rat TIMP-1/MMP-13 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (to final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 (in absence of TIMP-1) activity and 20% MMP-13 activity (in absence of antibody) as reference values.
- [50] FIG. 12. Activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in rat TIMP-1/ MMP-13 assay. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μ M) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 30% MMP-13 activity (in absence of antibody) as reference values.
- [51] FIG. 13. Activity of MS-BW-17-1 Fab and IgG₁ in rat TIMP-1/ MMP-13 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as

outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 15% MMP-13 activity (in absence of antibody) as reference values.

- [52] FIG. 14. Effect of the inhibitory effect of MS-BW-17-1 TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.
- [53] FIG. 15. Effect of anti-TIMP-1 antibody on fibrotic collagen as stained by Sirius Red in carbon tetrachloride-induced rat liver fibrosis model. Sirius Red-stained area as percent of total field in carbon tetrachloride-treated rats treated with PBS, control antibody, and MS-BW-14 anti-TIMP-1 antibody.

DETAILED DESCRIPTION OF THE INVENTION

- [54] The invention provides human antibodies that bind to TIMP-1. These antibodies are useful for a variety of therapeutic and diagnostic purposes.

Characteristics of Human TIMP-1 Antibodies

- [55] "Antibody" as used herein includes intact immunoglobulin molecules (*e.g.*, IgG₁, IgG_{2a}, IgG_{2b}, IgG₃, IgM, IgD, IgE, IgA), as well as fragments thereof, such as Fab, F(ab')₂, scFv, and Fv, which are capable of specific binding to an epitope of a human and/or rat TIMP-1 protein. Antibodies that specifically bind to TIMP-1 provide a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in an immunochemical assay. Preferably, antibodies that specifically bind to human and/or rat TIMP-1 do not detect other proteins in immunochemical assays and can immunoprecipitate the TIMP-1 from solution.
- [56] The K_d of human antibody binding to TIMP-1 can be assayed using any method known in the art, including technologies such as real-time Bimolecular Interaction Analysis (BIA) (Sjolander & Urbaniczky, *Anal. Chem.* 63, 2338-45, 1991, and Szabo *et al.*, *Curr. Opin. Struct. Biol.* 5, 699-705, 1995). BIA is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcoreTM).

Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

- [57] In a BIAcoreTM assay, some human antibodies of the invention specifically bind to human TIMP-1 with a K_d of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM. More preferred human antibodies specifically bind to human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 nM, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
- [58] Other human antibodies of the invention specifically bind to rat TIMP-1 with a K_d of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM. Preferred K_d s range from about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.
- [59] Preferably, antibodies of the invention neutralize an MMP-inhibiting activity of the TIMP-1. The MMP can be, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-19, MMP-20 or MMP-23.
- [60] IC_{50} for neutralizing MMP-inhibiting activity of TIMP-1 can be measured by any means known in the art. Preferably, IC_{50} is determined using the high throughput fluorogenic assay described in Bickett *et al.*, *Anal. Biochem.* 212, 58-64, 1993. In a typical fluorogenic assay, the IC_{50} of a human antibody for neutralizing human TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about

- 11 nM. The IC_{50} for neutralizing human TIMP-1 MMP-inhibiting activity of some human antibodies is about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.
- [61] A typical IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3 nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM. The IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity of some human antibodies is about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.
- [62] Preferred human antibodies of the invention are those for which the K_d for binding to TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the TIMP-1 are approximately equal.
- [63] A number of human antibodies having the TIMP-1 binding and MMP-inhibiting activity neutralizing characteristics described above have been identified by screening the MorphoSys HuCAL[®] Fab 1 library. The CDR cassettes assembled for the HuCAL[®] library were designed to achieve a length distribution ranging from 5 to 28 amino acid residues, covering the stretch from position 95 to 102. Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. Some clones, however, had shorter VHCDR3 regions. In fact, it is a striking feature of anti-human TIMP-1 human antibodies identified from this library that they all exhibit the combination VH312 and a relatively short VHCDR3 region, typically four amino acids.
- [64] In some embodiments of the invention, the VHCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:1-43. In other embodiments of the invention, the VLCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:44-86. See Tables 2, 3, and 7. Human antibodies which have TIMP-1

binding and MMP-inhibiting activity neutralizing characteristics of antibodies such as those described above and in Tables 2, 3, and 7 also are human antibodies of the invention.

Obtaining human antibodies

- [65] Human antibodies with the TIMP-1 binding and MMP-activity neutralizing characteristics described above can be identified from the MorphoSys HuCAL[®] library as follows. Human or rat TIMP-1, for example, is coated on a microtiter plate and incubated with the MorphoSys HuCAL[®] Fab phage library (see Example 1, below). Those phage-linked Fabs not binding to TIMP-1 can be washed away from the plate, leaving only phage which tightly bind to TIMP-1. The bound phage can be eluted, for example, by a change in pH or by elution with *E. coli* and amplified by infection of *E. coli* hosts. This panning process can be repeated once or twice to enrich for a population of antibodies that tightly bind to TIMP-1. The Fabs from the enriched pool are then expressed, purified, and screened in an ELISA assay. The identified hits are then screened in the enzymatic assay described in Bickett *et al.*, 1993, and Bodden *et al.*, 1994. Those Fabs that lead to the degradation of the peptide are likely the ones which bind to TIMP-1, thereby blocking its interaction to MMP-1.
- [66] The initial panning of the HuCAL[®] Fab 1 library also can be performed with TIMP-1 as the antigen in round one, followed in round 2 by TIMP-1 peptides fused to carrier proteins, such as BSA or transferrin, and in round 3 by TIMP-1 again. Human TIMP-1 peptides which can be used for panning include human TIMP-1 residues 2-12 (TCVPPHPQTAF, SEQ ID NO:87; CTSVPPHPQTAF, SEQ ID NO:88; STCVPPHPQTAF, SEQ ID NO:89; STSVPPHPQTAF, SEQ ID NO:90), 28-36 (CEVNQTTLYQ, SEQ ID NO:91), 64-75 (PAMESVCGYFHR, SEQ ID NO:92), 64-79 (PAMESVCGYFHRSHNR, SEQ ID NO:93; CPAMESVSGYFHRSHNR, SEQ ID NO:94; PAMESVSGYFHRSHNRC, SEQ ID NO:95), and 145-157 (CLWTDQLLQGSE, SEQ ID NO:96). These peptide sequences are selected from

regions of human TIMP-1 that are predicted to interact with MMPs. See Gomis-Ruth *et al.*, *Nature* 389, 77-81, 1997. Directing Fabs toward the MMP-interacting region of human TIMP-1 in round 2 should increase the chance of identifying Fabs that can block the ability of human TIMP-1 to inhibit human MMP-1 activity.

- [67] Another method that can be used to improve the likelihood of isolating neutralizing Fabs is the panning on human TIMP-1 and eluting the binding Fabs with human MMP-1. This strategy should yield higher affinity antibodies than would otherwise be obtained.
- [68] Details of the screening process are described in the specific examples, below. Other selection methods for highly active specific antibodies or antibody fragments can be envisioned by those skilled in the art and used to identify human TIMP-1 antibodies.
- [69] Human antibodies with the characteristics described above also can be purified from any cell that expresses the antibodies, including host cells that have been transfected with antibody-encoding expression constructs. The host cells are cultured under conditions whereby the human antibodies are expressed. A purified human antibody is separated from other compounds that normally associate with the antibody in the cell, such as certain proteins, carbohydrates, or lipids, using methods well known in the art. Such methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, and preparative gel electrophoresis. A preparation of purified human antibodies is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art, such as SDS-polyacrylamide gel electrophoresis. A preparation of purified human antibodies of the invention can contain more than one type of human antibody with the TIMP-1 binding and neutralizing characteristics described above.
- [70] Alternatively, human antibodies can be produced using chemical methods to synthesize its amino acid sequence, such as by direct peptide synthesis using solid-phase techniques (Merrifield, *J. Am. Chem. Soc.* 85, 2149-54, 1963; Roberge *et al.*, *Science* 269, 202-04,

1995). Protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Optionally, fragments of human antibodies can be separately synthesized and combined using chemical methods to produce a full-length molecule.

- [71] The newly synthesized molecules can be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, PROTEINS: STRUCTURES AND MOLECULAR PRINCIPLES, WH Freeman and Co., New York, N.Y., 1983). The composition of a synthetic polypeptide can be confirmed by amino acid analysis or sequencing (*e.g.*, using Edman degradation).

Assessment of therapeutic utility of human antibodies

- [72] To assess the ability of a particular antibody to be therapeutically useful to treat, liver fibrosis, for example, the antibody can be tested *in vivo* in a rat liver fibrosis model. Thus, preferred human antibodies of the invention are able to block both human and rat TIMP-1 activity. If desired, human Fab TIMP-1 antibodies can be converted into full immunoglobulins, for example IgG₁ antibodies, before therapeutic assessment. This conversion is described in Example 5, below.
- [73] To identify antibodies that cross-react with human and rat TIMP-1, an ELISA can be carried out using rat TIMP-1. Functional cross-reactivity can be confirmed in an enzymatic assay, as described in Bickett *et al.*, *Anal. Biochem.* 212, 58-64, 1993. The assay uses human or rat TIMP-1, human MMP-1 or rat MMP-13 (the rat counterpart of human MMP-1), and a synthetic fluorogenic peptide substrate. Enzyme activity of uncomplexed MMP-1 (or MMP-13) is assessed by observing an increase in a fluorescence signal.
- [74] Antibodies that block human and/or rat TIMP-1 activity can be screened in an ELISA assay that detects the decrease of TIMP-1/MMP-1 complex formation in cultures of

HepG2 cells. Antibodies that meet this criteria can then be tested in a rat liver fibrosis model to assess therapeutic efficacy and correlate this efficacy with the ability of the antibodies to block TIMP-1 inhibition of MMP-1 *in vitro*.

- [75] Antibodies that demonstrate therapeutic efficacy in the rat liver fibrosis model can then be tested for binding to and blockade of TIMP-2, -3, and -4 in an *in vitro* enzymatic assay. Blocking the minimum number of TIMPs necessary for efficacy in liver fibrosis or other TIMP-associated pathology is preferable to minimize potential side effects.

Polynucleotides encoding human TIMP-1 antibodies

- [76] The invention also provides polynucleotides encoding human TIMP-1 antibodies. These polynucleotides can be used, for example, to produce quantities of the antibodies for therapeutic or diagnostic use.
- [77] Polynucleotides that can be used to encode the VHCDR3 regions shown in SEQ ID NOS:1-43 are shown in SEQ ID NOS:226-268, respectively. Polynucleotides that can be used to encode the VLCDR3 region shown in SEQ ID NOS:44-86 are shown in SEQ ID NOS:183-225, respectively. Polynucleotides that encode heavy chains (SEQ ID NOS:140-182) and light chains (SEQ ID NOS:97-139) of human antibodies of the invention that have been isolated from the MorphoSys HuCAL[®] library are shown in SEQ ID NOS:269-311 and SEQ ID NOS:312-354, respectively.
- [78] Polynucleotides of the invention present in a host cell can be isolated free of other cellular components such as membrane components, proteins, and lipids. Polynucleotides can be made by a cell and isolated using standard nucleic acid purification techniques, or synthesized using an amplification technique, such as the polymerase chain reaction (PCR), or by using an automatic synthesizer. Methods for isolating polynucleotides are routine and are known in the art. Any such technique for obtaining a polynucleotide can be used to obtain isolated polynucleotides encoding antibodies of the invention. For example, restriction enzymes and probes can be used to

isolate polynucleotides which encode the antibodies. Isolated polynucleotides are in preparations that are free or at least 70, 80, or 90% free of other molecules.

- [79] Human antibody-encoding DNA molecules of the invention can be made with standard molecular biology techniques, using mRNA as a template. Thereafter, DNA molecules can be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook *et al.* (1989). An amplification technique, such as PCR, can be used to obtain additional copies of the polynucleotides.
- [80] Alternatively, synthetic chemistry techniques can be used to synthesize polynucleotides encoding antibodies of the invention. The degeneracy of the genetic code allows alternate nucleotide sequences to be synthesized that will encode an antibody having, for example, one of the VHCDR3, VLCDR3, light chain, or heavy chain amino acid sequences shown in SEQ ID NOS:1-43, 44-86, 97-139, or 140-182, respectively.

Expression of polynucleotides

- [81] To express a polynucleotide encoding a human antibody of the invention, the polynucleotide can be inserted into an expression vector that contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods that are well known to those skilled in the art can be used to construct expression vectors containing sequences encoding human antibodies and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook *et al.* (1989) and in Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, N.Y., 1995. See also Examples 1-3, below.
- [82] A variety of expression vector/host systems can be utilized to contain and express sequences encoding a human antibody of the invention. These include, but are not limited to, microorganisms, such as bacteria transformed with recombinant

bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors, insect cell systems infected with virus expression vectors (e.g., baculovirus), plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids), or animal cell systems.

- [83] The control elements or regulatory sequences are those non-translated regions of the vector -- enhancers, promoters, 5' and 3' untranslated regions -- which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the BLUESCRIPT phagemid (Stratagene, LaJolla, Calif.) or pSPORT1 plasmid (Life Technologies) and the like can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (e.g., heat shock, RUBISCO, and storage protein genes) or from plant viruses (e.g., viral promoters or leader sequences) can be cloned into the vector. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are preferable. If it is necessary to generate a cell line that contains multiple copies of a nucleotide sequence encoding a human antibody, vectors based on SV40 or EBV can be used with an appropriate selectable marker.

- [84] Large scale production of human TIMP-1 antibodies can be carried out using methods such as those described in Wurm *et al.*, *Ann. N.Y. Acad. Sci.* 782, 70-78, 1996, and Kim *et al.*, *Biotechnol. Bioengineer.* 58, 73-84, 1998.

Pharmaceutical compositions

- [85] Any of the human TIMP-1 antibodies described above can be provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier preferably is non-pyrogenic. The compositions can

be administered alone or in combination with at least one other agent, such as stabilizing compound, which can be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. A variety of aqueous carriers may be employed, *e.g.*, 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antibody of the invention in such pharmaceutical formulation can vary widely, *i.e.*, from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected. See U.S. Patent 5,851,525. If desired, more than one type of human antibody, for example with different K_d for TIMP-1 binding or with different IC_{50} s for MMP-inhibiting activity neutralization, can be included in a pharmaceutical composition.

- [86] The compositions can be administered to a patient alone, or in combination with other agents, drugs or hormones. In addition to the active ingredients, these pharmaceutical compositions can contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically. Pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means.
- [87] After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

Methods of decreasing MMP-inhibiting activity of human TIMP-1

- [88] The invention provides methods of decreasing an MMP-inhibiting activity of human or rat TIMP-1. Such methods can be used therapeutically, as described below, or in a research setting. Thus, the methods can be carried out in a cell-free system, in a cell culture system, or *in vivo*. *In vivo* methods of decreasing MMP-inhibiting activity of human or rat TIMP-1 are described below.
- [89] Human TIMP-1 is contacted with a human antibody that binds to the human TIMP-1, thereby decreasing the MMP-inhibiting activity of the human TIMP-1 relative to human TIMP-1 activity in the absence of the antibody. The antibody can be added directly to the cell-free system, cell culture system, or to an animal subject or patient, or can be provided by means of an expression vector encoding the antibody.

Diagnostic methods

- [90] The invention also provides diagnostic methods, with which human or rat TIMP-1 can be detected in a test preparation, including without limitation a sample of serum, lung, liver, heart, kidney, colon, a cell culture system, or a cell-free system (*e.g.*, a tissue homogenate). Such diagnostic methods can be used, for example, to diagnose disorders in which TIMP-1 is elevated. Such disorders include, but are not limited to, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis. When used for diagnosis, detection of an amount of the antibody-TIMP-1 complex in a test sample from a patient which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.
- [91] The test preparation is contacted with a human antibody of the invention, and the test preparation is then assayed for the presence of an antibody-TIMP-1 complex. If desired, the human antibody can comprise a detectable label, such as a fluorescent, radioisotopic,

chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase.

- [92] Optionally, the antibody can be bound to a solid support, which can accommodate automation of the assay. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach the antibody to the solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached to the antibody and the solid support. Binding of TIMP-1 and the antibody can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

Therapeutic methods

- [93] The invention also provides methods of ameliorating symptoms of a disorder in which TIMP-1 is elevated. These disorders include, without limitation, liver fibrosis alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, colon cancer, and scarring. *See, e.g., Inokubo et al., Am. Heart J. 141, 211-17, 2001; Ylisirnio et al., Anticancer Res. 20, 1311-16, 2000; Holten-Andersen et al., Clin. Cancer Res. 6, 4292-99, 2000; Holten-Andersen et al., Br. J. Cancer 80, 495-503, 1999; Peterson et al., Cardiovascular Res. 46, 307-15, 2000; Arthur et al., Alcoholism: Clinical and Experimental Res. 23, 840-43, 1999; Iredale et al., Hepatol. 24, 176-84, 1996.*
- [94] Human antibodies of the invention are particularly useful for treating liver fibrosis. All chronic liver diseases cause the development of fibrosis in the liver. Fibrosis is a programmed uniform wound healing response. Toxic damage or injury caused by foreign proteins cause the deposition of extracellular matrix such as collagen, fibronectin, and laminin. Liver fibrosis and cirrhosis can be caused by chronic degenerative diseases

of the liver such as viral hepatitis, alcohol hepatitis, autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis, hemochromatosis, Wilson's disease, and non-alcoholic steato-hepatitis, as well as chemical damage.

- [95] Altered degradation and synthesis of extracellular matrix (particularly collagens) play central roles in pathogenesis of liver fibrosis. In the early phases, hepatic stellate cells (HSC) are initially activated and release matrix metalloproteases with the ability to degrade the normal liver matrix. When HSC are fully activated, there is a net down-regulation of matrix degradation mediated by increased synthesis and extracellular release of tissue inhibitors of metalloprotease (TIMP)-1 and -2. The dynamic regulation of activity of metalloproteases during liver fibrosis makes them and their inhibitors targets for therapeutic intervention.
- [96] Human antibodies of the invention are also particularly useful for treating lung fibrosis. Lung airway fibrosis is a hallmark of airway remodeling in patients with chronic asthma, so human antibodies of the invention are also particularly useful for chronic asthma. Airway remodeling is a well-recognized feature in patients with chronic asthma. TIMP-1 but not TIMP-2 levels were significantly higher in untreated asthmatic subjects than in glucocorticoid-treated subjects or controls ($p < 0.0001$), and were far greater than those of MMP-1, MMP-2, MMP-3, and MMP-9 combined (Mautino *et al.*, Am J Respir Crit Care Med 1999 160:324-330). TIMP-1 mRNA and protein expression are selectively and markedly increased in a murine model of bleomycin-induced pulmonary fibrosis (Am. J. Respir. Cell Mol. Biol. 24:599-607, 2001). This specific elevation of TIMP-1 without increase in MMPs in asthma patients suggests that inhibition of TIMP-1 by an antibody can restore normal collagen degradation in the lung.
- [97] Human antibodies of the invention are also particularly useful for treating cancer. TIMP-1 protein has been found to be elevated in plasma of colon (Holten-Andersen *et al.*, Br J Cancer 1999, 80:495-503) and prostate (Jung *et al.*, Int J Cancer, 1997, 74:220-223) cancer patients, and high TIMP-1 plasma level correlates with poor clinical outcome of

colon cancer (Holten-Andersen et al., Clin Cancer Res 2000 6:4292-4299). TIMP-1 induces dose-dependent proliferation of breast tumorigenic clonal cell line and tyrosine phosphorylation (Luparello et al, Breast Cancer Res Treat, 1999, 54:235-244). Therefore, the use of antibody against TIMP-1 may block its ability to induce cancer.

- [98] Human TIMP-1 antibodies can be used to prevent or diminish scar formation, such as scar formation after surgery (particularly ophthalmic surgery) or injury (such as a burn, scrape, crush, cut or tear injury).
- [99] In one embodiment of the invention, a therapeutically effective dose of a human antibody of the invention is administered to a patient having a disorder in which TIMP-1 is elevated, such as those disorders described above. Symptoms of the disorder, including deposition of extracellular matrix, as well as loss of tissue or organ function, are thereby ameliorated.

Determination of a Therapeutically Effective Dose

- [100] The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of human antibody that reduces MMP-inhibiting activity of the TIMP-1 relative to the activity which occurs in the absence of the therapeutically effective dose.
- [101] The therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. A rat liver fibrosis model is described in Example 6.
- [102] Therapeutic efficacy and toxicity, e.g., ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population) of a human antibody, can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀.

- [103] Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.
- [104] The exact dosage will be determined by the practitioner, in light of factors related to the patient who requires treatment. Dosage and administration are adjusted to provide sufficient levels of the human antibody or to maintain the desired effect. Factors that can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.
- [105] Polynucleotides encoding human antibodies of the invention can be constructed and introduced into a cell either *ex vivo* or *in vivo* using well-established techniques including, but not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and DEAE- or calcium phosphate-mediated transfection.
- [106] Effective *in vivo* dosages of an antibody are in the range of about 5 mg to about 50 mg/kg, about 50 mg to about 5 mg/kg, about 100 mg to about 500 mg/kg of patient body weight, and about 200 to about 250 mg/kg of patient body weight. For administration of polynucleotides encoding the antibodies, effective *in vivo* dosages are in the range of

about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA.

- [107] The mode of administration of human antibody-containing pharmaceutical compositions of the invention can be any suitable route which delivers the antibody to the host. Pharmaceutical compositions of the invention are particularly useful for parenteral administration, *i.e.*, subcutaneous, intramuscular, intravenous, or intranasal administration.
- [108] All patents, patent applications, and references cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

Construction of a Human Combinatorial Antibody Library (HuCAL[®] Fab 1)

- [109] *Cloning of HuCAL[®] Fab 1.* HuCAL[®] Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL[®] Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL[®]-scFv; Knappik *et al.*, *J. Mol. Biol.* 296, 55, 2000). HuCAL[®] Fab 1 was cloned into a phagemid expression vector pMORPH[®] 18 Fab1 (FIG. 3). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C_H1, C_H2, and C_H3 are synthetic genes fully compatible with the modular system of HuCAL[®] (Knappik *et al.*, 2000).
- [110] First, the V_H and V_L libraries were isolated from HuCAL[®]-scFv. V_H fragments were amplified by 15 PCR cycles (Pwo polymerase) with primers 5'-

GTGGTGGTTCCGATATC-3' (SEQ ID NO:380) and 5'- AGCGTCACA-CTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO:381). PCR-products were digested with EcoRV / DraIII and gel-purified. VL?-chains were obtained by restriction digest with EcoRV / BsiWI and gel-purified. These V? and V? libraries were cloned into pMORPH® 18 FabI cut with *EcoRV* / *DraIII* and *EcoRV* / *BsiWI*, respectively. After ligation and transformation in *E. coli* TG-1, library sizes of 4.14×10^8 and 1.6×10^8 , respectively, were obtained, in both cases exceeding the V? diversity of HuCAL®-scFv.

- [111] Similarly, the VH library was isolated from HuCAL®-scFv by restriction digest using *StyI* / *MunI*. This VH library was cloned into the pMORPH® 18-V? and V? libraries cut with *StyI* / *MunI*. After ligation and transformation in *E. coli* TG-1, a total library size of 2.09×10^{10} was obtained, with 67% correct clones (as identified by sequencing of 207 clones).
- [112] *Phagemid rescue, phage amplification and purification.* HuCAL® Fab was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD₆₀₀ of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol/ 50 µg/ml kanamycin, cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel *et al.*, 1998), resuspended in PBS/20% glycerol, and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C, colonies were scraped off and adjusted to an OD₆₀₀ of 0.5. Helper phage were added as described above.

EXAMPLE 2

Solid phase panning

- [113] Wells of MaxiSorp™ microtiter plates (Nunc) were coated with rat- or human TIMP protein diluted to 50 µg/ml dissolved in PBS (2 µg/well). After blocking with 5% non-fat dried milk in PBS, $1-5 \times 10^{12}$ HuCAL® Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phage were eluted by pH-elution with 100 mM triethylamine and subsequent neutralization with 1M TRIS-Cl pH 7.0. See Krebs *et al.*, *J. Immunol. Meth.* 254, 67, 2001. Two to three rounds of panning were performed with phage amplification conducted between each round as described above.

EXAMPLE 3

Solution panning

- [114] Biotinylated antigen was diluted to 40 nM in PBS, 1013 HuCAL®-Fab 1 phage were added and incubated for 1 h at 20°C. Phage-antigen complexes were captured on Neutravidin plates (Pierce). After several washing steps, bound phages were eluted by different methods (Krebs *et al.*, 2001). Two rounds of panning were routinely performed.

EXAMPLE 4

Subcloning of selected Fab fragments for expression

- [115] The Fab-encoding inserts of the selected HuCAL® Fab 1 fragments were subcloned into the expression vector pMORPH® x7_FS (Knappik *et al.*, *J. Mol. Biol.* 296, 55, 2000) to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL® Fab 1 clones was digested with *Xba*I / *Eco*RI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *Xba*I / *Eco*RI cut vector pMORPH® x7, previously carrying a scFv insert, produces a Fab expression vector designated pMORPH® x9_Fab1_FS (FIG. 4). Fabs expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tagII) for detection and purification.

EXAMPLE 5

Identification of TIMP-binding Fab fragments by ELISA

- [116] The wells of 384-well Maxisorp ELISA plates were coated with 20 µl/well solutions of rat TIMP or human TIMP at a concentration of 5 µg/ml diluted in coating buffer. Expression of individual Fab in *E. coli* TG-1 from expression vector pMORPH[®] x9_FS was induced with 0.5 mM IPTG for 12 h at 30°C. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used in an ELISA. The Fab fragment was detected after incubation with alkaline phosphatase-conjugated anti-Fab antibody (Dianova), followed by development with Attophos substrate (Roche) and measurement at Ex450 nm / Em535 nm. Values at 370 nm were read out after addition of horseradish peroxidase-conjugated anti-mouse IgG antibody and POD soluble substrate (Roche Diagnostics).

EXAMPLE 6

Expression and purification of HuCAL[®]-Fab 1 antibodies in E. coli

- [117] Expression of Fab fragments encoded by pMORPH[®] x9_FS in TG-1 cells was carried out in shaker flask cultures with 1 liter of 2xTY medium supplemented with 34 µg/ml chloramphenicol. After induction with 0.5 mM IPTG, cells were grown at 22°C for 16 h. Periplasmic extracts of cell pellets were prepared, and Fab fragments were isolated by Strep-tactin[®] chromatography (IBA, Goettingen, Germany). The apparent molecular weights were determined by size exclusion chromatography (SEC) with calibration standards. Concentrations were determined by UV-spectrophotometry.

EXAMPLE 7

Construction of HuCAL[®] immunoglobulin expression vectors

- [118] *Heavy chain cloning.* The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*NheI* / *ApaI*), and a stuffer compatible with the restriction sites used for HuCAL[®] design

was inserted for the ligation of the leader sequences (*NheI* / *EcoRI*), VH-domains (*EcoRI* / *BlnI*), and the immunoglobulin constant regions (*BlnI* / *ApaI*). The leader sequence (EMBL M83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG₁ (PIR J00228), IgG₄ (EMBL K01316), and serum IgA₁ (EMBL J00220) were dissected into overlapping oligonucleotides with lengths of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL[®] design. The oligonucleotides were spliced by overlap extension-PCR.

[119] *Light chain cloning.* The multiple cloning site of pcDNA3.1/Zeo⁺ (Invitrogen) was replaced by two different stuffers. The λ -stuffer provided restriction sites for insertion of a λ -leader (*NheI* / *EcoRV*), HuCAL[®]-scFv V λ -domains (*EcoRV* / *BsiWI*), and the λ -chain constant region (*BsiWI* / *ApaI*). The corresponding restriction sites in the λ -stuffer were *NheI* / *EcoRV* (λ -leader), *EcoRV* / *HpaI* (V λ - domains), and *HpaI* / *ApaI* (λ -chain constant region). The λ -leader (EMBL Z00022) as well as the λ -leader (EMBL L27692) were both equipped with Kozak sequences. The constant regions of the human λ - (EMBL J00241) and λ -chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

[120] *Generation of IgG-expressing CHO-cells.* CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 μ g/ml G418 and 300 μ g/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA (see below). Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

EXAMPLE 8

Design of the CDR3 libraries

- [121] *V? positions 1 and 2.* The original HuCAL[®] master genes were constructed with their authentic N-termini: V?11: QS (CAGAGC), V?12: QS (CAGAGC), and V?13: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL[®] library construction, the first two amino acids were changed to DI to facilitate library cloning (*EcoRI* site). All HuCAL[®] libraries contain V?1 genes with the *EcoRV* site GATATC (DI) at the 5'-end. All HuCAL[®] kappa genes (master genes and all genes in the library) contain DI at the 5'-end.
- [122] *VH position 1.* The original HuCAL[®] master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. In the HuCAL[®] Fab 1 library, all VH chains contain Q (=CAG) at the first position.
- [123] *V?1/V?3 position 85.* Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000), position 85 of V?1 and V?3 can be either T or V. Thus, during HuCAL[®] scFv 1 library construction, position 85 of V?1 and V?3 was varied as follows: V?1 original, 85T (codon ACC); V?1 library, 85T or 85V (TRIM codons ACT or GTT); V?3 original, 85V (codon GTG); V?3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL[®] Fab1.
- [124] *CDR3 design.* All CDR3 residues which were kept constant are indicated in FIG. 1.
- [125] *CDR3 length.* The designed CDR3 length distribution is as follows. Residues which were varied are shown in brackets (x) in FIG. 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7 residues), with Q90 fixed; V lambda CDR3, 8 to 10 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and

D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

EXAMPLE 9

Chronic carbon tetrachloride-induced liver fibrosis

[126] Sprague Dawley rats (200-220 g) are used in an *in vivo* model of liver fibrosis. To maximally induce microsomal metabolism of carbon tetrachloride metabolism, animals receive 1 g/l isoniazid with their drinking water starting one week before the administration of carbon tetrachloride. Carbon tetrachloride (1:1 in mineral oil) is administered orally every fifth day at a dose of 0.2 ml/100 g body weight. A human TIMP-1 antibody is administered intravenously, either once or repeatedly, during the period of carbon tetrachloride treatment. Necropsy is performed after 5-7 weeks of treatment. McLean *et al.*, *Br. J. Exp. Pathol.* 50, 502-06, 1969.

[127] Transverse cylinders of liver tissue are cut from the right liver lobe, fixed in formaldehyde, and embedded in paraffin. The amount of fibrosis in the liver is indicated by the picrosirius red-stained fibrotic areas. Picrosirius-positive areas are determined in several centrilobular fields in each section. Parameters of color detection are standardized and kept constant throughout the experiment. The field are selected using a standardized grid which covers an area of 31 mm². A Leica Quantimed 500 MC system is used for morphometry.

EXAMPLE 10

Hydroxyproline determination

[128] The method of Prockop & Udenfried, *Anal. Biochem.* 1, 228-39, 1960, can be used to determine hydroxyproline in liver tissues, with the following modifications. Liver specimens of 60-90 mg wet weight are dried and hydrolyzed in 6 N HCl at 100 °C for 17 h. The hydrolyzed material is dried and reconstituted in 5 ml of deionized water. Two

hundred microliters of this hydrolysate are mixed with 200 ml of ethanol and 200 ml chloramin T solution (0.7 % in citrate buffer [5.7 g sodium acetate, 3.75 g trisodium citrate, 0.55 g citric acid, 38.5 ml ethanol, made up to 100 ml with water]) and allowed to oxidize for 20 min at room temperature. Four hundred microliters of Ehrlich's reagent (12 g p-dimethylaminobenzaldehyde in 40 ml ethanol and 2.7 ml H₂SO₄) are added. After incubation for 3 h at 35 °C, absorbance at 573 nm is measured.

EXAMPLE 11

Affinity determination by surface plasmon resonance measurements (BIAcore™)

- [129] For affinity determination, monomeric fractions of affinity and SEC purified Fab fragments or purified IgG1 molecules were used. All experiments were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 5.0 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 3-4 µl of 5 µg/ml TIMP-1 typically resulted in 500 resonance units for kinetic measurements. All sensograms were fitted globally using BIA evaluation software. For monovalent Fab fragments a monovalent fit (Langmuir binding) and for IgGs a bivalent fit was applied.

EXAMPLE 12

IC₅₀ determination in human TIMP-1/human MMP-1 and rat TIMP-1/rat MMP-13 assay

- [130] Purified Fab fragments or IgGs were used for IC₅₀ determination. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), MMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), and peptide substrate (final conc. 50 µM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em430 nm was measured.

[131] The following controls were included in the assay and used as reference values for IC₅₀ determination:

A: MMP + substrate: this value was defined as 100% MMP activity in absence of antibody and TIMP.

B: MMP + TIMP + substrate: this value was defined as maximum inhibition achieved in the assay and calculated as a % of total MMP activity.

[132] To define the concentration of antibody that resulted in 50% reversal of inhibition (IC₅₀), the following procedure was used:

- The value for 50% reversal of inhibition (expressed as % activity MMP) was calculated as: $Y = [(A - B)/2] + B$.
- MMP activity was plotted against concentration of antibody in the assay.
- The concentration of antibody that results in 50% reversal of inhibition (Y) was read on the x-axis and defined as IC₅₀.
- Error bars in the graphs were derived from triplicate wells in one assay.
- Standard deviations for IC₅₀ values were calculated from 3 independent assays.

EXAMPLE 13

Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

[133] To increase affinity and biological activity of selected antibody fragments, CDR regions were optimized by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekäs *et al.*, 1994). Fab fragments in expression vector pMORPH[®] x9 were cloned into phagemid vector pMORPH[®] _18 using *EcoRI* / *XbaI* restriction sites. CDR cassettes containing several diversified positions were synthesized and cloned into Fab fragments in pMORPH[®] _18 using unique restriction sites (Knappik *et al.*, 2000). Affinity

maturation libraries were generated by transformation into *E. coli* TOP10F, and phage were prepared as described above. Phage displaying Fab fragments with improved affinity were selected by 2-3 rounds solution panning using stringent washing conditions (e.g., competition with 1 μ M non-biotinylated antigen or washing for up to 48 h with frequent buffer exchange) and limited amounts of antigen (0.04 – 4 nM). Seventeen human TIMP-1 antibodies were tested for affinity to human TIMP-1 (with some tested for affinity to rat TIMP-1) using a BIAcoreTM assay. The K_d of these antibodies for human TIMP-1 and rat TIMP-1 are shown in Table 1.

Table 1. Overview of species cross-reactive Fab

Fab	Monovalent K _D human TIMP-1	Monovalent K _D rat TIMP-1	IC ₅₀ in human protease assay	IC ₅₀ in rat protease assay
MS-BW-25	25+/- 16 nM*	4517 +/- 2400 nM	115 +/- 15 nM	> 300 nM
MS-BW-27	~74 nM	~ 3200 nM	Non blocking	
MS-BW-21	520+/- 20 nM	36 +/- 2 nM	> 300 nM	67 +/- 5nM
MS-BW-38	~3 nM	~353 nM	~11 nM	> 300 nM
MS-BW-39	~7500 nM	~108 nM	> 100 nM	> 100 nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 14

Screening for Fab with improved off-rates by koff ranking using surface plasmon resonance

- [134] Phage eluted after solution panning were used to infect *E. coli* TG-1 and plated on agar plates containing 34 µg/ml chloramphenicol. Clones were picked into 96 well plates and used to produce Fab fragments. On the same plate, parental clones were inoculated as controls. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used for koff ranking in BIAcore™.
- [135] All measurements were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 4.5 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 10 µl of 25 µg/ml TIMP-1 typically resulted in 5000 resonance units for koff ranking. All sensograms were fitted using BIA evaluation software. Clones with improved off rate were selected by comparison to parental clones.

EXAMPLE 15

Generation of species cross-reactive antibodies

- [136] To maximize the likelihood of obtaining blocking antibodies that are cross-reactive between human and rat TIMP-1, alternating pannings were carried out on rat and human protein. Additionally, all antibodies selected by pannings on solely the human or rat TIMP-1 protein were analyzed for cross-reactivity in order to check for cross-reactive antibodies that might be selected by chance. Antibodies selected from these pannings were analyzed for cross-reactivity in ELISA using crude *E. coli* extracts. Cross-reactive antibodies in this assay were subjected to expression in 1-liter scale followed by purification. Purified antibodies were tested for cross-reactivity in BIAcore™ and protease assays (Table 1).

- [137] As shown in Table 1, a total of five different Fab cross-reactive with human and rat TIMP-1 were generated. BIAcore™ measurements revealed that although these antibodies clearly bind to human and rat TIMP-1, affinities for both species differ by at least a factor of 50. An antibody used for human therapy or in an animal model should have an affinity to the target protein in the low nanomolar, preferably in the sub-nanomolar range. As none of the above-described antibodies had affinities in this range for both species, these antibodies were not considered useful for further experiments or development.

EXAMPLE 16

Generation of blocking antibodies against human TIMP-1

- [138] To generate blocking antibodies against human TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on purified TIMP-1 protein followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, TIMP-1/MMP-1 assay and BIAcore™. A total of 6100 clones were analyzed in AutoScreen®, 670 of them showed binding to human TIMP-1. Sequence analysis revealed that in total seven unique antibody clones had been selected (Table 2). For these seven Fab clones, the affinities measured in BIAcore™ were in the range of 10 – 180 nM (Table 4). When tested in the human protease assay, five of them were able to block the interaction between human TIMP-1 and MMP-1. The concentration of monovalent Fab needed to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% (IC₅₀) was in the range of 11 - 100 nM (Table 2). The most active Fab clones are MS-BW-3 (K_d 13 nM; IC₅₀ 11 nM) and MS-BW-28 (K_d 10 nM; IC₅₀ 22 nM).
- [139] A striking feature of antibodies selected against human TIMP-1 is that they all exhibit the combination VH312 and a relatively short VH-CDR3 region, predominantly four amino acids (see Table 2). The HCDR3 cassettes assembled for the HuCAL®-Fab 1 library

were designed to achieve a length distribution ranging from 5 to 28 amino acid residues. A four amino acid HCDR3 can occur in the library due to TRIM deletion, but is considered a very rare event. Another remarkable feature was the high degree of sequence homology among the selected LCDR3 sequences.

Table 2. Overview of anti-human TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K _D to human TIMP-1	IC ₅₀ in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-1	H3	FMDI, SEQ ID NO:1	?2	QSYDYQQFT, SEQ ID NO:44	65+/-13 nM*	>100 nM
MS-BW-2	H3	GFDY, SEQ ID NO:2	?2	QSYDFKTYL, SEQ ID NO:45	180+/-28 nM	>100 nM
MS-BW-3	H3	FLDI, SEQ ID NO:3	?2	QSYDFLRFS, SEQ ID NO:46	13+/-2 nM	11+/-2nM
MS-BW-25	H3	TFPIDADS, SEQ ID NO:4	?2	QSYDFINVI, SEQ ID NO:47	25+/-16nM	115+/-15 nM
MS-BW-26	H3	GHVDY, SEQ ID NO:5	?2	QSYDFVRFM, SEQ ID NO:48	~100 nM	non blocking
MS-BW-27	H3	YWRGLSFDI, SEQ ID NO:6	?2	QSYDFYKFN, SEQ ID NO:49	~74	non blocking
MS-BW-28	H3	FFDY, SEQ ID NO:7	?2	QSYDFRRFS, SEQ ID NO:50	10+/-1 nM	22+/-2nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 17

Increasing the affinity of selected anti-human TIMP-1 antibodies

- [140] In order to increase the affinity of monovalent anti-human TIMP-1 Fab fragments to the sub-nanomolar range, a step-wise affinity maturation approach was applied, by optimizing CDR sequences and keeping framework regions constant.

Affinity maturation by light chain cloning

- [141] The CDR3 sequences of the two antibody fragments with highest affinity (MS-BW-3 and MS-BW-28) had the remarkable feature of an unusually short four amino acid HCDR3 sequence. Furthermore, each Fab had a very similar LCDR3 sequence. This indicates that MS-BW-3 and MS-BW-28 bind to the same epitope and that this epitope might tolerate only a very small subset of CDR3 sequences. As a four amino acid HCDR3 is a very rare event in the library, it can be anticipated that in the initial library not all possible combinations of the short HCDR3 and the preferred LCDR3 are present. Therefore, it was considered that another combination of the selected HCDR3 and LCDR3 sequences might increase the affinity. For this approach, the heavy chain of MS-BW-3 and MS-BW-28 were paired with the light chains of MS-BW-1, -2, -3, -25, -26, -27, and -28 by cloning.
- [142] The resulting constructs were transformed into *E. coli* and expressions/purifications in 1-liter scale were performed. Of the 12 new constructs, 10 resulted in functional Fab molecules. These were analyzed in BIAcore™ and human protease assay as summarized in Table 3. The best antibody named MS-BW-44 had a monovalent affinity of 2 nM and an IC₅₀ of 4 nM (FIG. 7) and was thus improved by a factor of 6.5 (K_d) or 2.75 (IC₅₀).

Table 3. Overview of Fab derived from light chain cloning

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC ₅₀ * in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-40	H3	FLDI, SEQ ID NO:3	?2	QSYDYQQFT, SEQ ID NO:44	~49 nM	> 100 nM
MS-BW-41	H3	FLDI, SEQ ID NO:3	?2	QSYDFKTYL, SEQ ID NO:45	~6 nM	29+/-6nM
MS-BW-43	H3	FLDI, SEQ ID NO:3	?2	QSYDFINVI, SEQ ID NO:47	~65 nM	> 100 nM
MS-BW-44	H3	FLDI, SEQ ID NO:3	?2	QSYDFVRFM, SEQ ID NO:48	2 +/- 0.4 nM*	4+/-1 nM
MS-BW-45	H3	FLDI, SEQ ID NO:3	?2	QSYDFYKFN, SEQ ID NO:49	8 +/- 5 nM	9+/-3 nM
MS-BW-46	H3	FLDI, SEQ ID NO:3	?2	QSYDFRRFS, SEQ ID NO:50	6 +/- 3 nM	4+/-0.5 nM
MS-BW-47	H3	FFDY, SEQ ID NO:7	?2	QSYDYQQFT, SEQ ID NO:44	~152 nM	> 100 nM
MS-BW-49	H3	FFDY, SEQ ID NO:7	?2	QSYDFKTYL, SEQ ID NO:45	~21 nM	> 100 nM
MS-BW-51	H3	FFDY, SEQ ID NO:7	?2	QSYDFINVI, SEQ ID NO:47	~7 nM	7+/-1 nM
MS-BW-52	H3	FFDY, SEQ ID NO:7	?2	QSYDFVRFM, SEQ ID NO:48	~11 nM	9+/-1 nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

Affinity maturation by optimizing HCDR1 and HCDR2

- [143] In the HuCAL[®]-Fab 1 library, only the CDRs HCDR3 and LCDR3 are diversified to a high extent. Although it is known from crystallographic studies that amino acids from these two CDRs make most of the antibody antigen contacts, the residual four CDRs are also important for antigen binding. However, their contribution to the binding energy can vary from antibody to antibody. In the HuCAL[®]-Fab 1 library those CDRs exhibit only a limited variability due to the presence of the different master frameworks (Knappik *et al.*, 2000). In order to improve the affinity of the selected antibodies, an affinity maturation approach by randomizing HCDR1 and HCDR2 was applied. For this approach two affinity maturation libraries based on MS-BW-44 cloned into phage display vector pMORPH[®] 18 were created. In library 1, only HCDR2 of MS-BW-44 was diversified using "TRIM technology" as described in Virnekäs *et al.*, *Nucl. Acids. Res.* 22, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. In library 2, both HCDR1 and HCDR2 were diversified using the TRIM technology. In both cases, phage antibody libraries comprising 1×10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan[®] procedure. In order to select antibodies having an increased affinity to human TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied. Antibody off rates were ranked by BIAcore[™] using crude *E. coli* extracts of selected antibodies. Clones with slower off rate than parental clone MS-BW-44 were subjected to 1-liter scale expression and purification. Purified Fab were analyzed in BIAcore[™] and human protease assay (Table 4).

Table 4. Comparison of Fab derived from HCDR1 and HCDR2 optimization with parental clone MS-BW-44

Fab	Monovalent K_D to human TIMP-1	IC_{50} in human protease assay*
MS-BW-44	2 +/- 0.4 nM	2 +/- 0.5 nM
MS-BW-44-2	0.5 +/- 0.2 nM	0.4 +/- 0.3 nM
MS-BW-44-6	0.6 +/- 0.2 nM	0.2 +/- 0.1 nM

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1 (0.4 nM each).

[144] Clone MS-BW-44-2 was derived from library 1 thus having a modified HCDR2 cassette. Its affinity measured by BIAcore™ was 0.5 nM. Clone MS-BW-44-6 was derived from library 2 having a modified HCDR 1 and HCDR 2 cassette and the affinity measured by BIAcore™ was 0.6 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8.

Table 8: Overview and sequence comparison of affinity matured Fab fragments against human TIMP-1. Sequence changes compared to parental Fab fragments (**bold**) are italicized

Clone	VH			VL				Monov. K _D to human TIMP-1 (nM)	IC ₅₀ in human protease assay (nM)
	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Framework	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)	
MS-BW-									
3	VH3	GFTFSSYAMS (355)	AISGGSGSTYYADSVK G (357)	FLDI (3)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF LRFS (47)	13 +/- 2
44	VH3	GFTFSSYAMS (355)	AISGGSGSTYYADSVK G (357)	FLDI (3)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	2 +/- 0.4
44-6	VH3	GFTFSSYAMS (355)	VISGNGSNTYYADSVK G (358)	FLDI (3)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	0.6 +/- 0.2
44-2	VH3	GFTFSSYAMS (355)	GISGNGVLIFYADSVK G (359)	FLDI (3)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	0.5 +/- 0.2
44-2-4	VH3	GFTFSSYAMS (355)	GISGNGVLIFYADSVK G (359)	GLMDY (360)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	0.2 +/- 0.02
44-2-15	VH3	GFTFSSYAMS (355)	GISGNGVLIFYADSVK G (359)	WFDH (361)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	0.3 +/- 0.1
44-2-16	VH3	GFTFSSYAMS (355)	GISGNGVLIFYADSVK G (359)	WFDV (362)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (48)	0.5 +/- 0.2
44-6-1	VH3	GFTFSSYAMS (355)	VISGNGSNTYYADSVK G (358)	FLDI (3)	VL2	TGTSSDVG GGYNYVS (363)	DVSNRPS (364)	QSYDF VREFM (365)	0.2 +/- 0.04

* IC₅₀ values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1; IC₅₀ of MS-BW-44 is 2 nM under these conditions

- [145] When initially analyzed in the human TIMP-1/MMP-1 assay, it was not possible to distinguish a Fab with a sub-nanomolar affinity from a Fab with 1 nM affinity, most likely because the concentration of Fab required to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% was below the concentration of total TIMP-1 in the assay. When a modified assay was used with concentrations of TIMP-1 and MMP-1 decreased from 1.2 nM to 0.4 nM, it was possible to distinguish a 2 nM Fab from a sub-nanomolar Fab (Table 4, FIG. 8). Using this modified protease assay, MS-BW-44-2 and MS-BW-44-6 had IC_{50} values of 0.4 nM and 0.2 nM respectively. Parental clone MS-BW-44 had an IC_{50} of 2 nM under these conditions. Thus, by this affinity maturation approach, an affinity gain of a factor of 5 (K_d) or 5-10 (IC_{50}) was achieved.

Affinity maturation by optimizing HCDR3

- [146] As mentioned above, amino acid residues in HCDR3 and LCDR3 are considered the most important for antigen binding. Taking into account that a four amino acid HCDR3 was not planned in the design of HuCAL[®]-Fab 1 and thus only occurs as a rare case due to a TRIM deletion, probably not all possible combinations of the four amino acids in HCDR3 were represented in the original HuCAL[®]-Fab 1 library. Therefore, an affinity maturation library was constructed with four and five amino acid HCDR3 maturation cassettes inserted into Fab derived from the previous maturation cycle (among them MS-BW-44-2 and MS-BW-44-6). The obtained affinity maturation library had a diversity of 1×10^8 clones, therefore theoretically covering all possible four and five amino acid HCDR3 variations. Applying very stringent panning conditions, the best antibody identified, MS-BW-44-2-4, had an affinity measured by BIAcore[™] of 0.2 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8. The improvement factor gained by this affinity maturation approach is 2.5 with respect to the affinity and 2 with respect to the IC_{50} .

Affinity maturation by optimizing LCDR3

- [147] As an alternative approach, a maturation strategy was used to further optimize the light chain CDR3 sequence. This was due to the fact that in the first maturation cycle where light chain exchange cloning between selected antibodies was applied, only a very limited subset of sequence variation had been exploited. Therefore, a maturation library was constructed in which, using TRIM technology, a diversified LCDR3 cassette was inserted into Fab derived from HCDR1 and HCDR2 optimization (among them MS-BW-44-2 and MS-BW-44-6). The best Fab identified with this maturation strategy was MS-BW-44-6-1 with an affinity measured by BIAcore™ of 0.15 nM and an IC₅₀ in a human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibody and its parental clones is shown in Table 8. The improvement factor gained by this maturation approach is 4 with respect to affinity. A further improvement of the IC₅₀ in the protease assay could not be measured due to limitations in the assay.
- [148] As a result of a step-wise affinity maturation approach using four different maturation strategies, the monovalent affinity of an anti-human TIMP-1 specific Fab fragment was improved by a factor of 87 and its activity in human TIMP-1/MMP-1 assay by a factor of 55. The decision for defining the best Fab fragment has been made on the basis of K_d measurements using BIAcore™, as this method proved to be reliable for ranking antibodies with sub-nanomolar affinities, whereas the sensitivity of the human TIMP-1/MMP-1 assay was considered not suitable to rank activity of the best Fabs in the sub-nanomolar range with respect to each other.
- [149] The best Fab MS-BW-44-6-1 has an affinity measured by BIAcore™ of 0.15 nM and an IC₅₀ in human TIMP-1/MMP-1 assay of 0.2 nM. Compared to its parental clone, MS-BW-3, it has optimized LCDR3, HCDR1 and HCDR2 sequences.

EXAMPLE 18

Cross reactivity of selected anti-human TIMP-1 Fab with TIMP-2, TIMP-3, and TIMP-4

- [150] TIMP-1 belongs to a family of closely related protease inhibitors all binding to various members of the MMP family of proteases. To date there are four human TIMP proteins described. To investigate potential cross-reactivity of antibody fragments selected against human TIMP-1 with other members of the human TIMP family, an ELISA was performed in which binding of antibody fragments to immobilized purified human TIMP-1, -2, -3 or -4 was analyzed (FIG. 10). Antibody fragments binding to immobilized human TIMP-1 showed no binding to human TIMP-2, -3, -4 above background level when compared to unrelated control protein BSA.

EXAMPLE 19

Generation of blocking antibodies against rat TIMP-1

- [151] To generate blocking antibodies against rat TIMP-1, the HuCAL[®]-Fab 1 library was used for antibody selection (AutoPan[®]) on immobilized rat TIMP-1 followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen[®]). Purified Fab proteins were subjected to further characterization in ELISA, protease assays, and BIAcore[™]. Of the 8,450 selected clones were analyzed in AutoScreen[®], 750 of them showed binding to rat TIMP-1. Sequence analysis revealed that in total 36 unique Fab clones specific for rat TIMP-1 were enriched during selection (Table 7). Their affinities were measured by BIAcore[™] and were found to be in the range of 9 – 1000 nM (Table 7). When tested in the rat protease assay, all but one of them were able to block the interaction between rat TIMP-1 and rat MMP-13 (Table 7). The concentration of monovalent Fab needed to reverse the inhibitory effect of rat TIMP-1 on rat MMP-13 activity by 50% (IC₅₀) was in the range of 7 - 300 nM. The most active Fab

clones are MS-BW-14 (K_d 10 nM; IC_{50} 14 nM), MS-BW-17 (K_d 13 nM; IC_{50} 11 nM), and MS-BW-54 (K_d 9 nM; IC_{50} 7 nM).

Table 7. Overview of anti-rat TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K _D to rat TIMP-1	IC ₅₀ * in rat protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-5	H1A	GLYWAVYPYFDF, SEQ ID NO:8	?1	QSRDFNRGP, SEQ ID NO:51	~210 nM	non blocking
MS-BW-6	H3	LDTYYPDLEFY, SEQ ID NO:9	?1	QSYDQQRKW, SEQ ID NO:52	~68 nM	~100 nM
MS-BW-7	H1A	TYYYFDS, SEQ ID NO:10	?3	QQLYGTVS, SEQ ID NO:53	~168 nM	> 300 nM
MS-BW-9	H3	YMAYMAEAIDV, SEQ ID NO:11	?1	QSYDGGFKTH, SEQ ID NO:54	~256 nM	> 300 nM
MS-BW-10	H1B	LVGIVGYKPDLELYFDV, SEQ ID NO:12	?3	QSYDYSL, SEQ ID NO:55	~200 nM	~30 nM
MS-BW-11	H3	YGAYFGLDY, SEQ ID NO:13	?3	QSYDFNFH, SEQ ID NO:56	~200 nM	>300 nM
MS-BW-12	H6	GYADISFDY, SEQ ID NO:14	?2	QSYDMIARYP, SEQ ID NO:57	~419 nM	>300 nM
MS-BW-13	H3	YYLLLDY, SEQ ID NO:15	?3	QSWDIHPFDV, SEQ ID NO:58	~939 nM	not tested
MS-BW-14	H1A	WSDQSYHYWHPYFDV, SEQ ID NO:16	?1	QSWDLEPY, SEQ ID NO:59	10 +/- 5 nM	14 +/- 3 nM
MS-BW-15	H3	LIGYFDL, SEQ ID NO:17	?2	QSYDVLDS, SEQ ID NO:60	~80 nM	~200 nM
MS-BW-17	H5	LTNYFDSIYYDH, SEQ ID NO:18	?2	QSYDPSHPSK, SEQ ID NO:61	13 +/- 3 nM	11 +/- 3 nM
MS-BW-18	H5	LVGGGYDLMFDS, SEQ ID NO:19	?2	QSYDDMQF, SEQ ID NO:62	~153 nM	> 300 nM
MS-BW-19	H5	YVITYGYDDYHFDY, SEQ ID NO:20	?2	QSWDINHAI, SEQ ID NO:63	~187 nM	> 300 nM
MS-BW-20	H1A	SGYLDY, SEQ ID NO:21	?2	QSYDYDYDG, SEQ ID NO:64	~70 nM	> 300 nM

MS-BW-21	H1A	YIGYTNVMDIRPGYFLDY, SEQ ID NO:22	? 3	QQANDFPI, SEQ ID NO:65	36 +/- 2 nM	67 +/- 5 nM
MS-BW-22	H5	FRAYGDDDFYFDV, SEQ ID NO:23	? 2	QSWDNLKMPPV, SEQ ID NO:66	35 nM	65 +/- 11 nM
MS-BW-23	H1B	JMWSDYGQLVKGGDI, SEQ ID NO:24	? 2	QSYDVFPINR, SEQ ID NO:67	~207 nM	> 300 nM
MS-BW-24	H5	YYVTDTAIFYDY, SEQ ID NO:25	? 2	QSDLYFP, SEQ ID NO:68	23 nM	20 +/- 1 nM
MS-BW-29	H5	HDFDGSIFMDF, SEQ ID NO:26	? 2	QSYDVTPR, SEQ ID NO:69	~214 nM	> 100 nM
MS-BW-30	H5	YAGHQYEFFDF, SEQ ID NO:27	? 3	QSRDPVGFP, SEQ ID NO:70	~36 nM	> 100 nM
MS-BW-31	H5	LYADADIYFDY, SEQ ID NO:28	? 2	QSYDLSRP, SEQ ID NO:71	~13 +/- 9 nM	> 100 nM
MS-BW-32	H1A	TKYVGSEDV, SEQ ID NO:29	? 2	QSYDFSHYFF, SEQ ID NO:72	~92 nM	> 100 nM
MS-BW-36	H5	YRYPHMDF, SEQ ID NO:30	? 3	QSYDLRYSH, SEQ ID NO:73	~42 nM	~75 nM
MS-BW-37	H5	LFAGLELYFDY, SEQ ID NO:31	? 2	QSYDLRNR, SEQ ID NO:74	10 +/- 9 nM	> 100 nM
MS-BW-38	H3	GGFFNMDY, SEQ ID NO:32	? 2	QSYDFTYGS, SEQ ID NO:75	~353 nM	> 300 nM
MS-BW-39	H1A	GYIPYHLFDY, SEQ ID NO:33	? 3	QQFNDSFY, SEQ ID NO:76	~108 nM	> 100 nM
MS-BW-54	H5	YYGFEYDLLFDN, SEQ ID NO:34	? 2	QSYDISGYP, SEQ ID NO:77	9 +/- 1 nM	7 nM
MS-BW-55	H1B	ITYIGYDF, SEQ ID NO:35	? 2	QSRDLYYVYY, SEQ ID NO:78	~23 nM	~ 100 nM
MS-BW-56	H1A	QEWYMDY, SEQ ID NO:36	? 3	QSYDRSMW, SEQ ID NO:79	~170 nM	> 100 nM
MS-BW-57	H5	LYPEDLIYFDY, SEQ ID NO:37	? 2	QSWDVQTDK, SEQ ID NO:80	~39 nM	~60 nM
MS-BW-58	H6	WMTTPGHYYGYTFDV, SEQ ID NO:38	? 3	QSWDPSHY, SEQ ID NO:81	~138 nM	not tested
MS-BW-59	H5	LRVHDYAMYFDL, SEQ ID NO:39	? 2	QSYDIMP, SEQ ID NO:82	~15 nM	30 +/- 5 nM

MS-BW-60	H5	FVSYNGSVPYFDY, SEQ ID NO:40	? 2	QSMDFRLMH, SEQ ID NO:83	~30 nM	> 100 nM
MS-BW-61	H5	IIGDYVIFFDV, SEQ ID NO:41	? 2	QSFDMIHPY, SEQ ID NO:84	~51 nM	> 100 nM
MS-BW-62	H5	LFTYPFLYFDV, SEQ ID NO:42	? 2	QSDFPVM, SEQ ID NO:85	~36 nM	19 +/- 2
MS-BW-63	H5	ILTGHVLLFDY, SEQ ID NO:43	? 2	QSDNPYL, SEQ ID NO:86	~14 nM	20 +/- 1nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 20

Increasing the affinity of selected anti-rat TIMP-1 antibodies

- [152] Affinity maturation was applied to increase the affinity of monovalent anti-rat TIMP-1 Fab fragments to the sub-nanomolar range. No clear sequence homology could be identified among the light chain CDR3 sequences of the selected antibody fragments, indicating that an optimal light chain CDR3 sequence was probably not present or had not been selected from the original HuCAL[®]-Fab 1 library. We therefore started with modification of LCDR3 to increase the affinity of Fabs.
- [153] Two affinity maturation libraries based on MS-BW-14, -17, and -54 cloned into phage display vector pMORPH[®] 18 were created. In library 1, only LCDR3 was diversified using TRIM technology, as described in Virnekäs *et al.*, *Nucl. Acids. Res.* 22, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. In library 2, LCDR1, LCDR2, and LCDR3 were diversified simultaneously using the TRIM technology, while the connecting framework regions were kept constant. In both cases, phage antibody libraries comprising 3×10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan[®] procedure. To select antibodies having an increased affinity to rat TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied.
- [154] Antibody-off-rates were ranked by BIAcore[™] using crude *E. coli* extracts. Clones with slower off rate than parental clones MS-BW-14, -17, or -54 were subjected to expression and purification in 1-liter scale. Purified Fab were analyzed in BIAcore[™] and rat protease assays (Table 6). MS-BW-17-1 (K_d 0.8 nM, IC_{50} 1.6 nM), MS-BW-17-2 (K_d 1.3 nM, IC_{50} 1.1 nM), and MS-BW-17-3 (K_d 1.9 nM, IC_{50} 3 nM) were derived from affinity maturation library 1 having an optimized LCDR3 sequence, whereas MS-BW-

54-1 (K_d 2 nM, IC_{50} 3 nM) was derived from affinity maturation library 2 having an optimized LCDR1, -2, and -3 sequence (Table 9).

Table 9. Overview and sequence comparison of affinity matured Fab fragments against rat TIMP-1. Sequence changes compared to parental Fab fragments (**bold**) are italicized.

Clone (MS- BW-)	VH				VL				Monov. K _D to rat TIMP-1 (nM)	IC ₅₀ in rat protease assay (nM)
	Frame- work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Frame- work	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
14	VH1A	G GF SS Y ALS (366)	GIIFIFGTANYA Q K F Q G (368)	WSDQSYHYWH P Y F D V (370)	VL1	SGSSSNIGSN I YVS (371)	LM I YDNNQ R PS (373)	Q S WD L EPY (59)	10 +/- 5	14 +/- 3
17	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	L T NYFDSI Y YDH (18)	VL2	TGTSSDVGGY N YVS (363)	LM I YDVSNRPS (374)	Q S YD P SHPS K (61)	13 +/- 3	11 +/- 3
54	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	Y IG F E D LL F DN (34)	VL2	TGTSSDVGGY N YVS (363)	LM I YDVSNRPS (374)	Q S YD I SGYP (77)	9 +/- 1	7
17-1	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	L T NYFDSI Y YDH (18)	VL2	TGTSSDVGGY N YVS (363)	LM I YDVSNRPS (374)	Q A F D V A PNG K (376)	0.8	1.6
17-2	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	L T NYFDSI Y YDH (18)	VL2	TGTSSDVGGY N YVS (363)	LM I YDVSNRPS (374)	Q A F A V M P N V E (377)	1.3	1.1
17-3	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	L T NYFDSI Y YDH (18)	VL2	TGTSSDVGGY N YVS (363)	LM I YDVSNRPS (374)	Q S FTV S P G A D (378)	1.9	3
54-1	VH5	G S FTSYWIG (367)	IIYPGDS D TRYSP S FQ G (369)	Y IG F E D LL F DN (34)	VL2	TGTSSD L GGY N YVS (372)	LM I Y A GNRPS (375)	Q A YD S SGYP (379)	2	3

- [155] The improvement gained by these different one-step maturation strategies was up to a factor of 16.3 with regard to affinity and 10 with regard to functional activity in the protease assay.

EXAMPLE 21

Conversion of anti-TIMP-1 Fab fragments into human IgG₁ molecules for use in the rat model of chronic carbon tetrachloride-induced liver fibrosis

- [156] Anti-TIMP-1 Fab fragments were converted into human IgG₁ molecules to create antibody molecules with prolonged *in vivo* half-lives for the use in the rat model of chronic carbon tetrachloride-induced liver fibrosis. This was done by cloning the heavy and light chain variable regions of the Fab into two separate vectors for mammalian IgG₁ expression (Krebs *et al.*, 2001)
- [157] Anti-rat TIMP-1 clone MS-BW-14 was chosen for the first *in vivo* study, and IgG₁ protein was produced by transient expression. Anti-human TIMP-1 clone MS-BW-3 was selected as a negative control IgG₁ and was also produced by transient expression. Purified IgG₁ proteins MS-BW-14 and MS-BW-3 were subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays. Bivalent affinity for rat TIMP-1 measured in BIAcore™ (chip density 500 RU, fitting model for bivalent analyte) is 0.2 nM for MS-BW-14, compared to 13 nM for the corresponding monovalent Fab fragment. This increase in affinity for the IgG₁ is due to the avidity effects caused by binding of bivalent IgG₁ to immobilized rat TIMP-1 protein on the BIAcore™ chip. As expected, the negative control IgG₁ MS-BW-3 showed no binding to rat TIMP-1 but bound to human TIMP-1 with a bivalent affinity of approximately 0.4 nM.
- [158] FIG. 12 shows the activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in a rat TIMP-1/rat MMP-13 assay. The IC₅₀ of MS-BW-14 Fab and IgG₁ are nearly identical. The avidity effect seen in BIAcore™ does not occur in this assay because, in contrast to

the BIAcore™ experiment, this assay is based on a monovalent interaction in solution between TIMP-1 and the IgG₁. As expected, MS-BW-3 has no effect on rat TIMP-1 binding to rat MMP-13 and thus is a suitable negative control for a rat *in vivo* study.

- [159] Affinity matured clone MS-BW-17-1 was then converted from a monovalent Fab fragment to a bivalent IgG₁. Protein was produced by stable transfection. Purified protein was subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays (FIG. 13). In BIAcore™ an increased bivalent affinity (avidity) of 0.04 nM for IgG₁ compared to 0.8 nM for monovalent Fab fragment was seen, whereas the activity in the rat TIMP-1/rat MMP-13 assay was comparable for IgG₁ and Fab as expected.

EXAMPLE 22

Cross-reactivity of anti-rat TIMP-1 IgG₁ MS-BW-17-1 with mouse TIMP-1

- [160] Species cross-reactivity of MS-BW-17-1 IgG₁ and Fab with mouse TIMP-1 was determined by BIAcore™ to investigate the feasibility of alternative *in vivo* models that use mice instead of rats. Although MS-BW-17-1 clearly bound to mouse TIMP-1 immobilized to the chip surface, the affinity of both Fab (180 nM) and IgG₁ (9 nM) was 225-fold weaker than the affinity to rat TIMP-1. As the interaction between mouse TIMP-1 and BW-17-1 IgG₁ in serum is most likely monovalent, the affinity of BW-17-1 Fab probably reflects the “real” affinity of this interaction. Therefore, the Fab affinity value should be considered when calculating the feasibility of using BW-17-1 IgG₁ in a mouse *in vivo* study.

EXAMPLE 23

Effect of Timp-1 antibody on the development of bleomycin-induced pulmonary fibrosis

- [161] The following example demonstrates the ability of a human anti-rat Timp-1 antibody (BW17.1) to prevent fibrotic collagen deposition in a bleomycin-induced rat lung fibrosis model.
- [162] Male Lewis rats (6 weeks of age) received a single intratracheal challenge with bleomycin (0.3 mg/rat, in saline) or vehicle (saline) on day 0. Fourteen days later, animals were euthanized, the lung excised, fixed, and processed for evaluation of lung fibrosis. Lung tissue sections were cut, and quantitative assessment by image analysis of lung collagen in lung tissue sections stained with Mason Trichrome stain performed.
- [163] Antibody administration: A 20 mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered subcutaneously on day -1. Subsequently, a 10mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered s.c. on days 2, 5, 8, and 11. The following five groups of animals were studied: Saline i.t. challenge + antibody vehicle (PBS); Saline i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + antibody vehicle (PBS); Bleomycin i.t. challenge + control antibody.
- [164] FIG. 14 shows the effect of the inhibitory effect of TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.

EXAMPLE 24

Effect of BW-14 anti-TIMP-1 antibody in a rat model with CCl₄-induced liver fibrosis

- [165] Carbon tetrachloride (CCl₄) was used to induce liver fibrosis as described in Example 9. A single intravenous dose of 3 mg/kg BW-14 or control antibody BW-3, respectively,

was administered on day 19. At this time, total liver collagen (hydroxyproline determined according to Prockop and Udenfried) is already significantly increased by CCl₄, and fibrotic collagen rapidly accumulates during the following weeks. The rats were sacrificed on day 28. The treatment groups were: no CCl₄ + control antibody BW 3 (n=10 rats), CCl₄ + control antibody BW 3 (n=20 rats), and CCl₄ + BW 14 (n=20 rats).

- [166] The effect of control vs. TIMP-1 antibody as reflected in morphometric measurements of fibrous collagen (Sirius Red stained area as percentage of the total field) is shown in FIG. 15. Comparison of both control antibody treated groups shows that CCl₄ caused an approximately three-fold increase in collagen area. BW-14 antibody treatment reduced the pathological collagen increment by 26%. The lower fibrous collagen value of the CCl₄ + BW-14 group compared to the CCl₄ + BW-3 group was statistically significant ($p < 0.05$, Kolmogorow-Smirnow test).

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CLAIMS

1. A purified preparation of a human antibody, wherein the antibody:
binds to a tissue inhibitor of metalloprotease-1 (TIMP-1); and
neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.
2. The preparation of claim 1 wherein the MMP is human MMP-1.
3. The preparation of claim 2 wherein the MMP is rat MMP-13.
4. The preparation of claim 1 wherein the TIMP-1 is a human TIMP-1.
5. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM.
6. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
7. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about 11 nM.

8. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

9. The preparation of claim 4 wherein the K_d for binding to human TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the human TIMP-1 are approximately equal.

10. The preparation of claim 1 wherein the TIMP-1 is a rat TIMP-1.

11. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM.

12. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.

13. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3

nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM.

14. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.

15. The preparation of claim 10 wherein the K_d for binding to rat TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the rat TIMP-1 are approximately equal.

16. A purified preparation of a human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

17. A purified preparation of a human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

18. A purified preparation of a human antibody which comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10

and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

19. A purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID

NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

20. The purified preparation of claim 19 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

21. The purified preparation of claim 19 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

22. A purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101,

SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

23. A pharmaceutical composition comprising:
 - a human antibody which (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1; and
 - a pharmaceutically acceptable carrier.
24. The pharmaceutical composition of claim 23 wherein the MMP is human MMP-1.
25. The pharmaceutical composition of claim 23 wherein the MMP is rat MMP-13.
26. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a human TIMP-1.

27. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a rat TIMP-1.
28. The pharmaceutical composition of claim 23 wherein a K_d for binding to the TIMP-1 and an IC_{50} for neutralizing the MMP-1-inhibiting activity of the TIMP-1 are approximately equal.
29. A purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
30. The purified polynucleotide of claim 31 wherein the VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
31. A purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
32. The purified polynucleotide of claim 31 wherein the VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
33. The purified polynucleotide of claim 31 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
34. The purified polynucleotide of claim 33 wherein the heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

35. The purified polynucleotide of claim 33 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

36. The purified polynucleotide of claim 35 wherein the light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

37. An expression vector comprising the polynucleotide of claim 29.

38. An expression vector comprising the polynucleotide of claim 30.

39. An expression vector comprising the polynucleotide of claim 31.

40. An expression vector comprising the polynucleotide of claim 32.

41. An expression vector comprising the polynucleotide of claim 33.

42. An expression vector comprising the polynucleotide of claim 34.

43. An expression vector comprising the polynucleotide of claim 35.

44. An expression vector comprising the polynucleotide of claim 36.

45. A host cell comprising the expression vector of claim 37.

46. A host cell comprising the expression vector of claim 38.

47. A host cell comprising the expression vector of claim 39.

48. A host cell comprising the expression vector of claim 40.

49. A host cell comprising the expression vector of claim 41.

50. A host cell comprising the expression vector of claim 42.

51. A host cell comprising the expression vector of claim 43.

52. A host cell comprising the expression vector of claim 44.

53. A method of making a human antibody, comprising the steps of:
- culturing the host cell of claim 45 under conditions whereby the antibody is expressed; and
- purifying the human antibody from the host cell culture.
54. The method of claim 55 wherein the expression vector comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:183-357.
55. A method of decreasing an MMP-inhibiting activity of a TIMP-1, comprising the step of:
- contacting the TIMP-1 with a human antibody that binds to the TIMP-1, whereby the MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.
56. The method of claim 55 wherein the MMP is human MMP-1.
57. The method of claim 55 wherein the MMP is rat MMP-13.
58. The method of claim 55 wherein the TIMP-1 is a human TIMP-1.
59. The method of claim 55 wherein the TIMP-1 is a rat TIMP-1.
60. The method of claim 55 wherein the step of contacting is carried out in a cell-free system.
61. The method of claim 55 wherein the step of contacting is carried out in a cell culture system.
62. The method of claim 55 wherein the step of contacting is carried out *in vivo*.

63. The method of claim 55 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS:27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

64. A method of ameliorating symptoms of a disorder in which TIMP-1 is elevated, comprising the step of:

administering to a patient having the disorder an effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1, whereby symptoms of the disorder are ameliorated.

65. The method of claim 64 wherein the MMP is human MMP-1.

66. The method of claim 64 wherein the MMP is rat MMP-13.

67. The method of claim 64 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer.

68. The method of claim 64 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71,

SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

69. A method of detecting a TIMP-1 in a test preparation, comprising the steps of:
contacting the test preparation with a human antibody that specifically binds to the TIMP-1; and
assaying the test preparation for the presence of an antibody-TIMP-1 complex.

70. The method of claim 69 wherein the antibody comprises a detectable label.

71. The method of claim 69 wherein the antibody is bound to a solid support.

72. The method of claim 69 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID

NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, and SEQ ID NOS:43 and 86.

73. A method to aid in diagnosing a disorder in which a TIMP-1 level is elevated, comprising the steps of:

contacting a sample from a patient suspected of having the disorder with a human antibody that binds to TIMP-1; and

assaying for the presence of an antibody-TIMP-1 complex, whereby detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

74. The method of claim 73 wherein the antibody comprises a detectable label.

75. The method of claim 73 wherein the antibody is bound to a solid support.

76. The method of claim 73 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID

NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

77. The method of claim 73 wherein the sample is obtained from a tissue selected from the group consisting of colon, liver, heart, kidney, prostate, serum, and lung.

78. The method of claim 73 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome,

lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

Position	Framework 1																				CDR 1																																							
	1																				2																				3																			
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	a	b	c	d	e	f	1	2	3	4																														
	EcoRV																				PstI																																							
VLK1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	G	I	S	-	-	-	S	Y	L	A																							
VLK2	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	Q	S	L	L	H	S	-	N	G	Y	N	Y	L	D																				
VLK3	D	I	V	L	T	Q	S	P	A	T	L	S	L	S	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	V	S	S	-	-	-	S	Y	L	A																						
VLK4	D	I	V	M	T	Q	S	P	D	S	L	A	V	S	L	G	E	R	A	T	I	N	C	R	S	S	Q	S	V	L	Y	S	S	N	N	K	N	Y	L	A																				
VL1	D	I	V	L	T	Q	P	P	-	S	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	S	N	I	G	S	-	-	-	N	Y	V	S																					
VL2	D	I	A	L	T	Q	P	A	-	S	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	S	D	V	G	G	Y	-	-	-	N	Y	V	S																				
VL3	D	I	E	L	T	Q	P	P	-	S	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	L	G	D	-	-	-	-	-	-	K	Y	A	S																				
	EcoRV																				BssSI																				SexAI																			

VH

Position	Framework 1										CDR 1																													
	1										2										3																			
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	a	b	2	3	4	5	6	7	8										
	MfeI										BspEI																													
WH1A	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	V	K	V	S	C	K	A	S	G	G	T	F	S	-	-	Y	A	I	S	W	V	R		
WH1B	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	S	-	-	Y	Y	M	H	W	V	R
WH2	Q	V	Q	L	K	E	S	G	P	A	L	V	K	P	T	Q	T	L	T	L	T	C	T	F	S	G	F	S	L	S	T	S	G	V	G	V	W	I	R	
WH3	Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	S	L	R	L	S	C	A	S	G	A	S	G	F	T	F	S	-	-	Y	A	M	S	W	V	R	
WH4	Q	V	Q	L	V	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S	G	G	S	I	S	S	-	-	Y	Y	W	S	W	I	R
WH5	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	C	K	G	S	G	Y	S	F	T	S	-	-	Y	W	I	G	W	V	R
WH6	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	Q	T	L	S	L	T	C	A	I	S	G	D	S	V	S	S	N	S	A	A	W	N	W	I	R

Fig. 1

Framework 2										CDR 2										Framework 3																			
4										5										6										7									
5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9					
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[illegible]

Fig. 1, cont.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

Framework 1																			
CDR 1																			
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
VLK1	EcoRV	GAT	ATC	CAG	ATG	ACC	CAG	CGC	TCT	AGC	CTG	AGC	GCG	AGC	GTG	GGT	GAT	CGT	GTG
VLK2	EcoRV	GAT	ATC	GTG	ATG	ACC	CAG	AGC	CGA	CTG	AGC	CTG	CCA	GTG	ACT	CCG	GCG	GAG	CCT
VLK3	EcoRV	GAT	ATC	GTG	CTG	ACC	CAG	CGC	GCG	AGC	CTG	AGC	CTG	CCA	GTG	ACT	CCG	GCG	GAA
VLK4	EcoRV	GAT	ATC	GTG	ATG	ACC	CAG	CGC	GAT	AGC	CTG	GCG	GTG	AGC	CTG	GCG	GAA	CGT	GCG
VLK1	EcoRV	GAT	ATC	GTG	CTG	ACC	CAG	CGC	CCT	TCA	GTG	AGT	GCG	GGA	CCA	GGT	CAG	CGT	GTG
VLK2	EcoRV	GAT	ATC	GCA	CTG	ACC	CAG	CCA	GCT	TCA	GTG	AGC	GCG	TGA	CCA	GGT	CAG	AGC	ATT
VLK3	EcoRV	GAT	ATC	GAA	CTG	ACC	CAG	CGC	CCT	TCA	GTG	AGC	GTT	GGA	CCA	GGT	CAG	ACC	GCG

VH

Framework 1																			
CDR 1																			
Position	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
VH1A	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	TCT	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH1B	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH2	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH3	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH4	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH5	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	AGC	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG
VH6	EcoRV	CAG	GTG	CAA	TTG	GTT	CAG	TCT	GCG	GCG	GAA	GTG	AAA	AAA	CCG	GCG	AGC	AGC	GTG

Fig. 2

Framework 2										CDR 2										Framework 3																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
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FIG. 2, cont.

[illegible]

Fig. 2, cont.

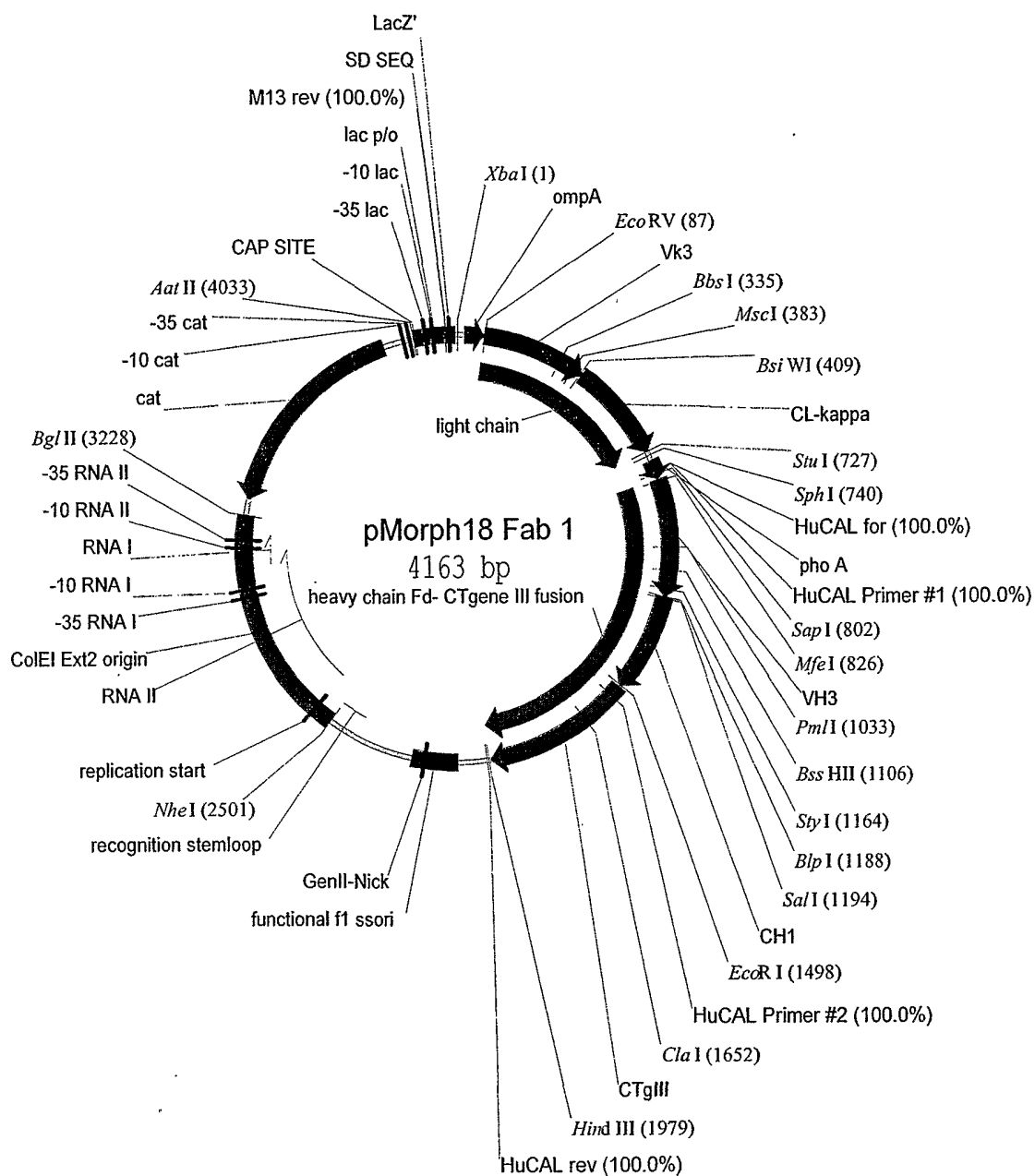


FIG. 3

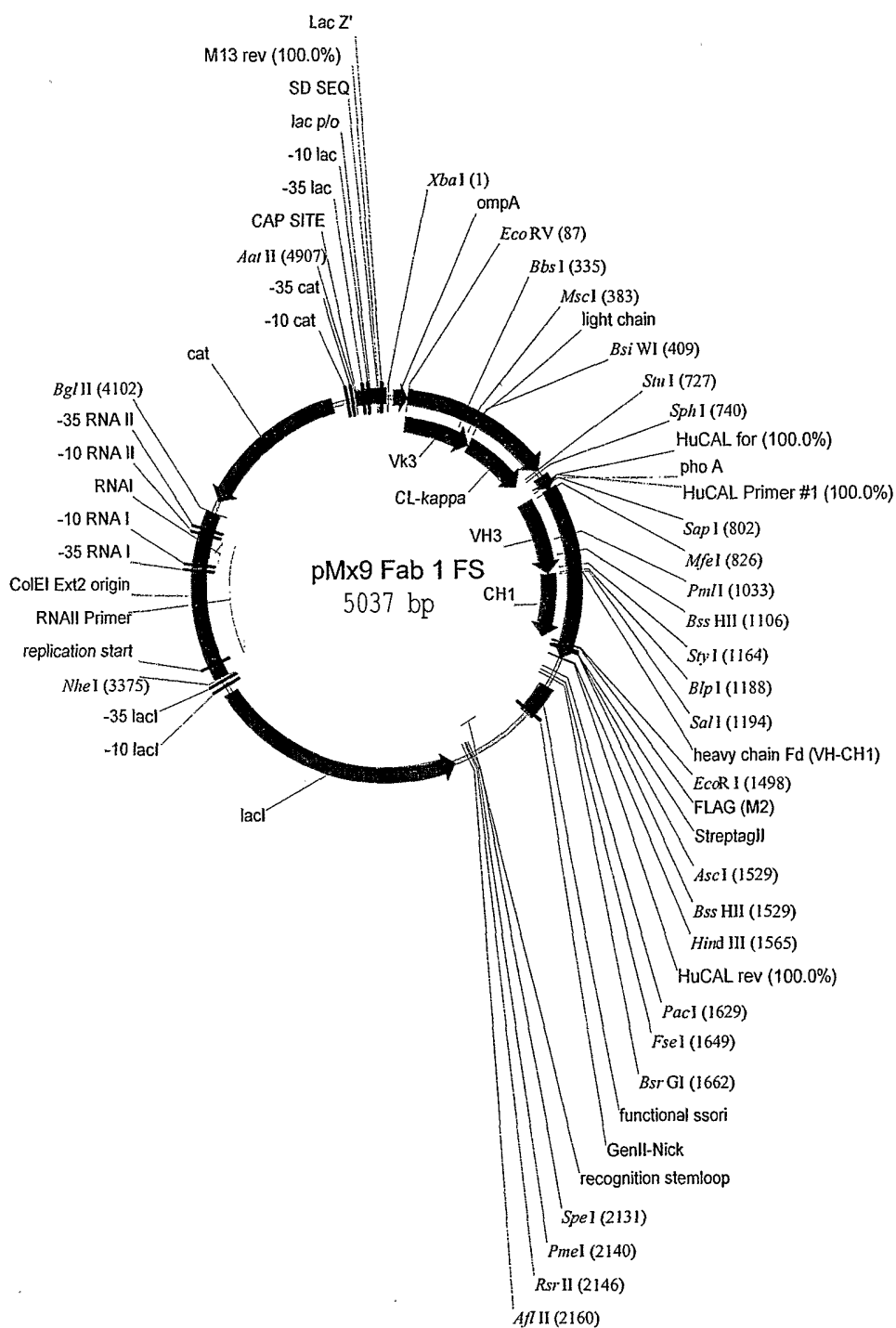


FIG. 4

TIMP1_human	135850		1	C T C V P H P Q T A F C N S D L V I R A K F V G T P E V N Q T T L Y Q R Y E I K M T K M Y K G F Q	50
TIMP1_rat	1174697		1	C S C A P T H P Q T A F C N S D L V I R A K F M G S P E I I E T T L Y Q R Y E I K M T K M L K G F D	50
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
TIMP1_human	135850		51	A L G D A A D I R F V Y T P A M E S V C G Y F H R S H N R S E E F L I A G K L Q D G L L H I T C S	100
TIMP1_rat	1174697		51	A V G N A T G F R F A Y T P A M E S L C G Y V H K S Q N R S E E F L I A G R L R N G N L H I T A C S	100
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
TIMP1_human	135850		101	F V A P W N S L S L A Q R R G F T K Y T V G C E E C T V F P C L S I P C K L Q S G T H C L W T D Q	150
TIMP1_rat	1174697		101	F L V P W H N L S P A O Q K A F V K T Y S A G C G V C T V F P C S A I P C K L E S D S H C L W T D Q	150
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
			*	* * * * *	**
TIMP1_human	135850		151	I L Q G S E K G F Q S R H L A C L P R E P G L C T W Q S L R S Q I A	184
TIMP1_rat	1174697		151	I L M G S E K G Y Q S D H F A C L P R N P D L C T W Q Y L G V S M T R S L P L A K A E A	194
			*	* * * * *	**
			*	* * * * *	**
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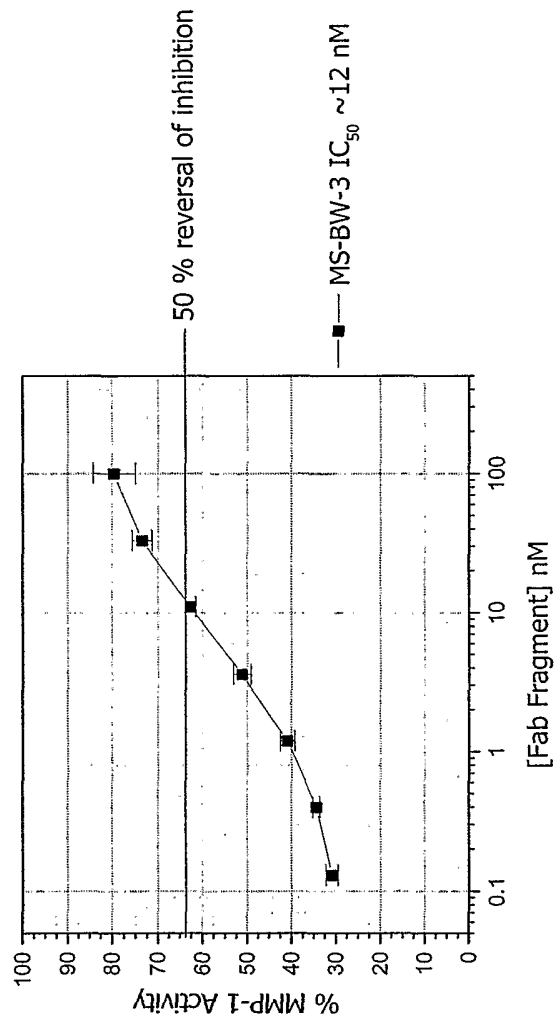


FIG. 6

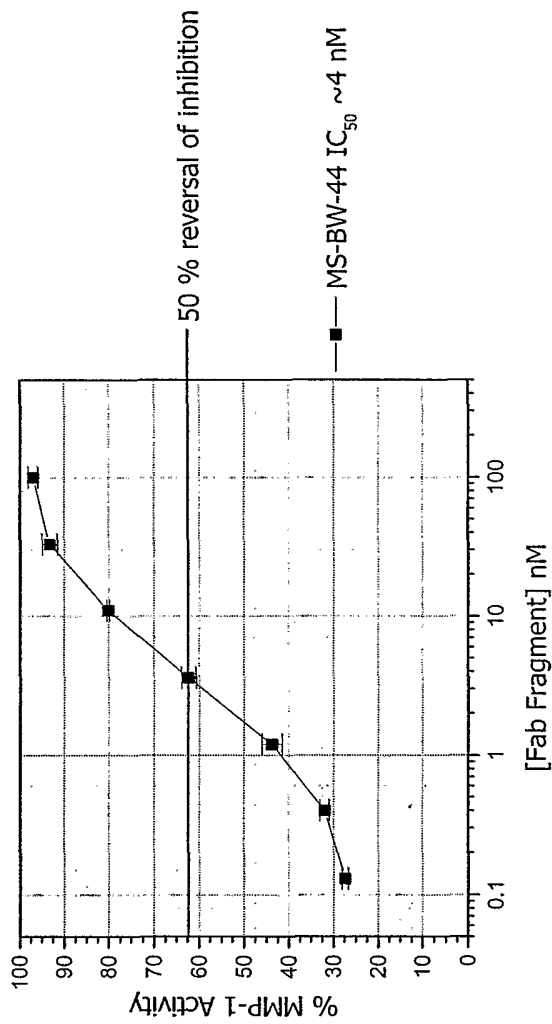


FIG. 7

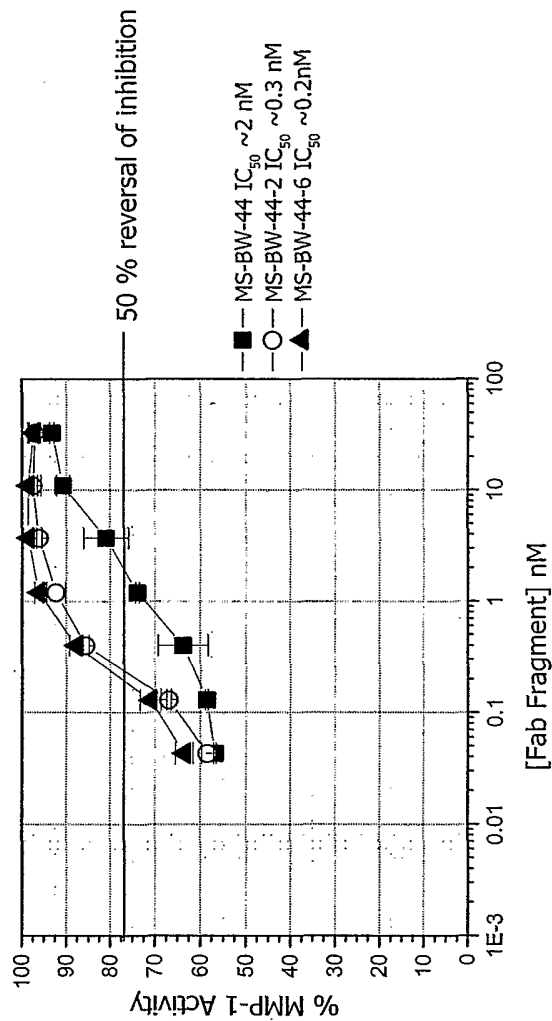


FIG. 8

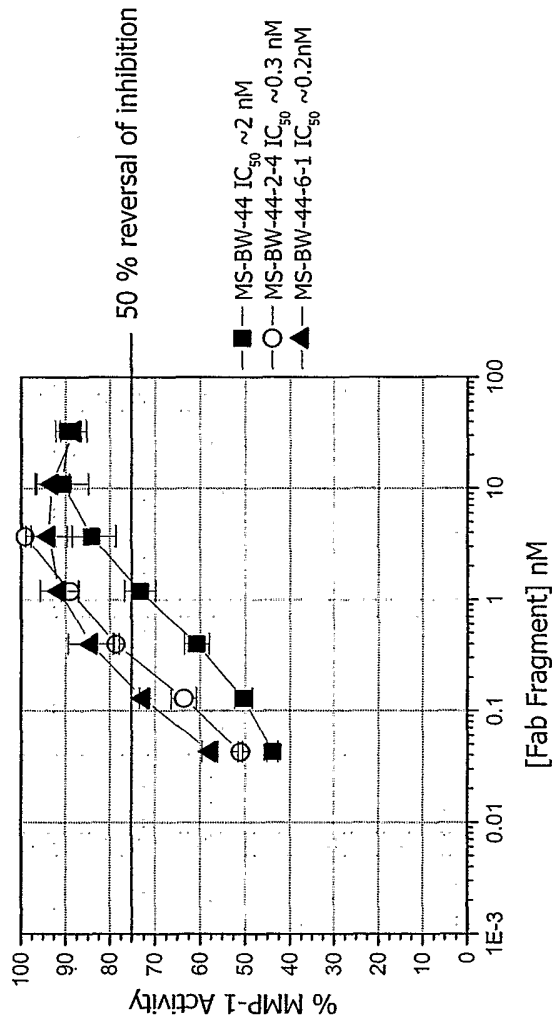


FIG. 9

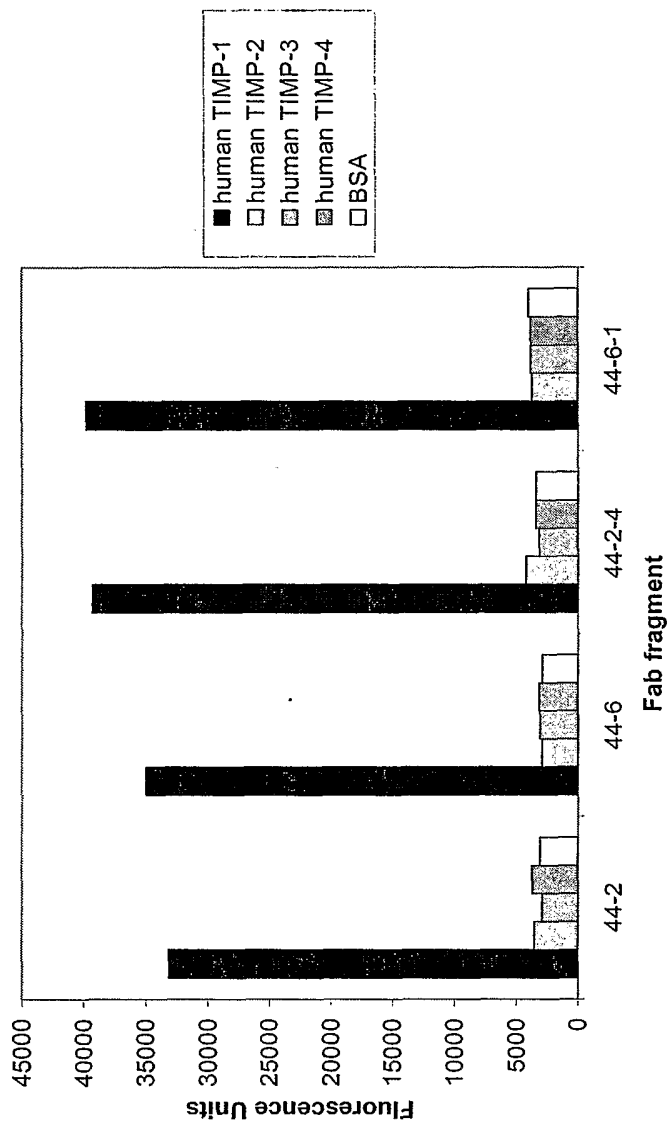


FIG. 10

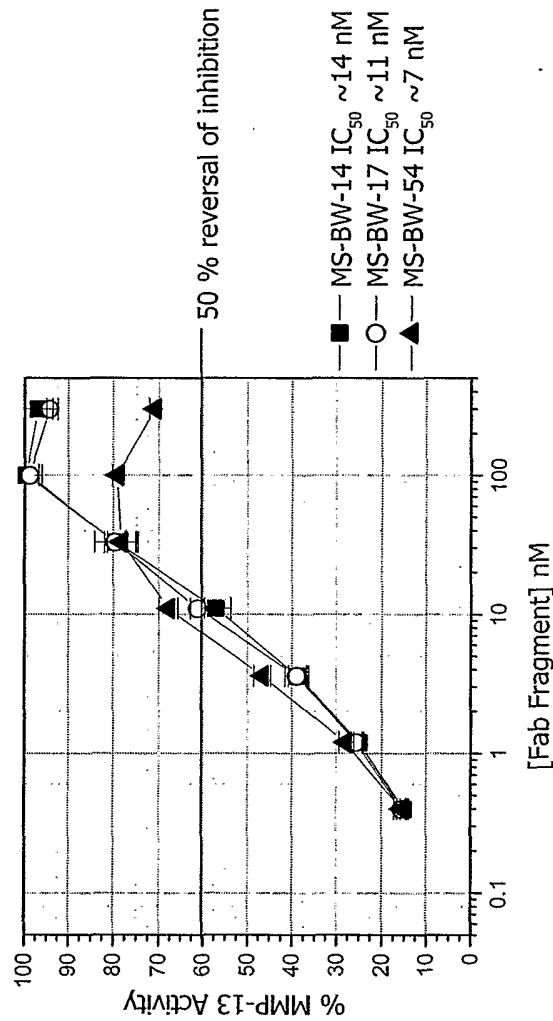


FIG. 11

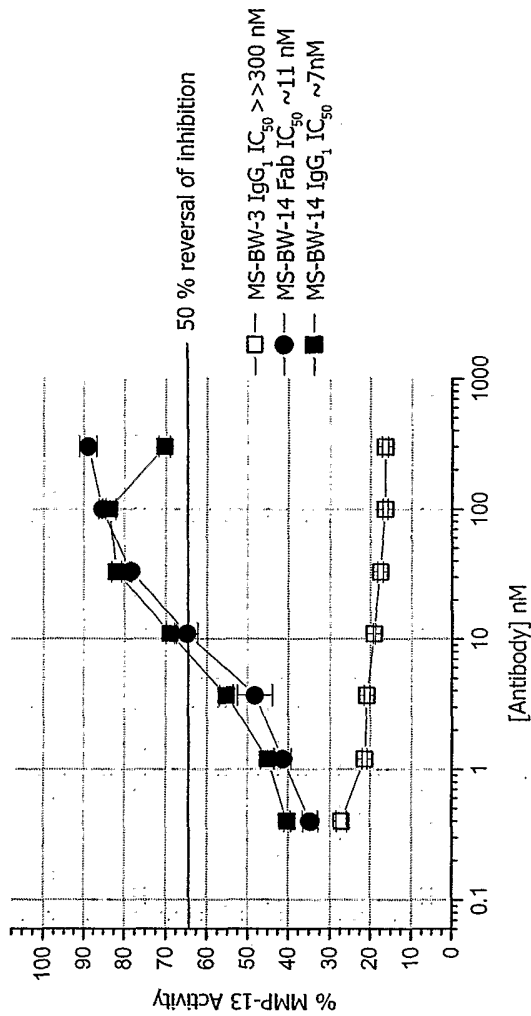


FIG. 12

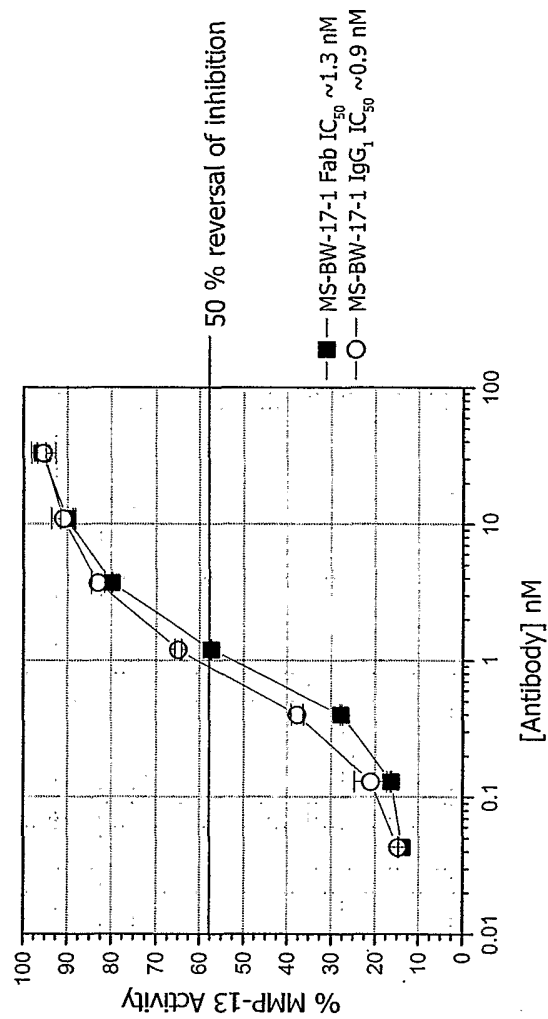


FIG. 13

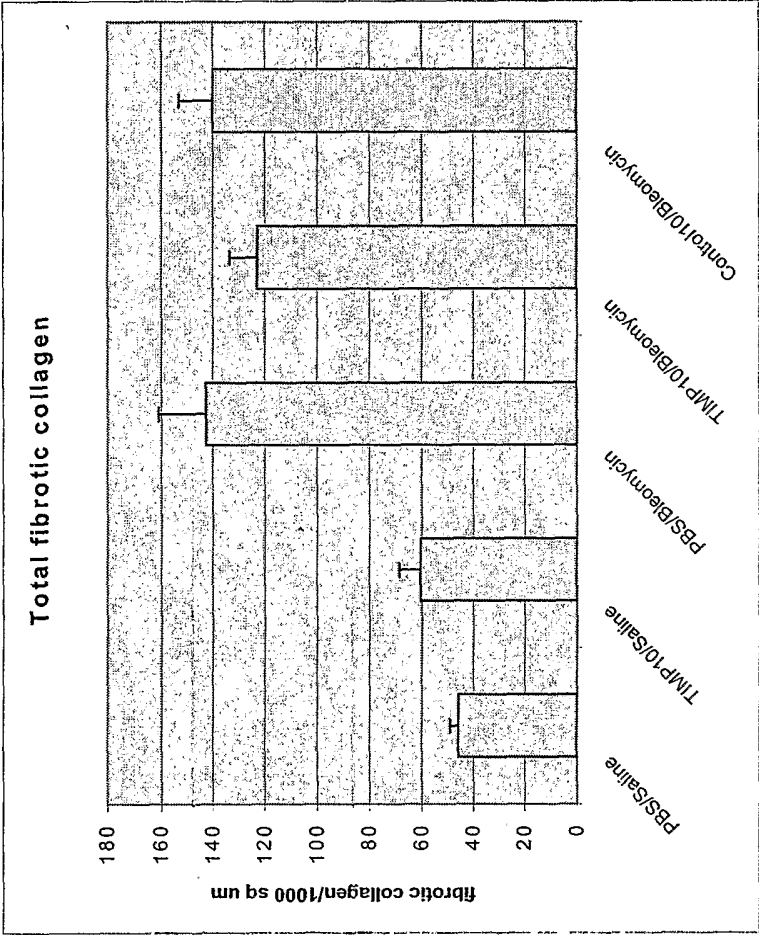
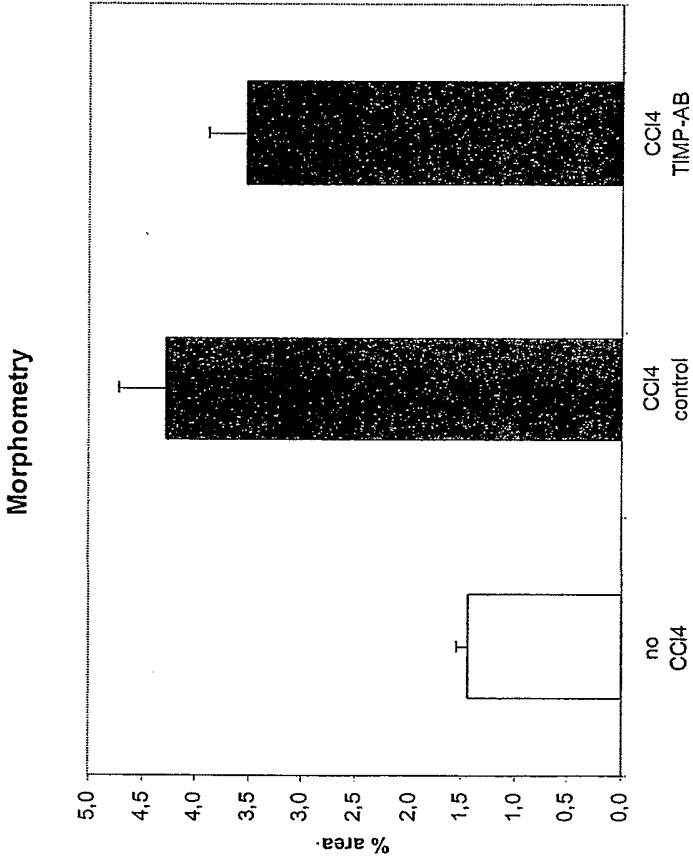


FIG. 14

FIG. 15



SEQUENCE LISTING

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MorphoSys AG

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<151> 2001-04-24

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Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser
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Gly Gly Phe Phe Asn Met Asp Tyr
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Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn
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Ile Thr Tyr Ile Gly Tyr Asp Phe
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Gln Glu Trp Tyr Met Asp Tyr
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Gln Ser Tyr Asp Phe Lys Thr Tyr Leu
1 5

<210> 46
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Gln Ser Tyr Asp Phe Leu Arg Phe Ser
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Gln Gln Leu Tyr Gly Thr Val Ser
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Gln Ser Tyr Asp Gly Phe Lys Thr His
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Gln Ser Tyr Asp Tyr Ser Leu Leu
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<210> 56

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Gln Ser Tyr Asp Phe Asn Phe His
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Gln Ser Tyr Asp Met Ile Ala Arg Tyr Pro
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<213> Homo sapiens

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Gln Ser Trp Asp Ile His Pro Phe Asp Val
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<210> 59

<211> 8
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Gln Ser Trp Asp Leu Glu Pro Tyr
1 5

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<400> 60
Gln Ser Tyr Asp Val Leu Asp Ser Glu
1 5

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Gln Ser Tyr Asp Pro Ser His Pro Ser Lys
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<400> 62
Gln Ser Tyr Asp Asp Met Gln Phe
1 5

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<400> 63
Gln Ser Trp Asp Ile Asn His Ala Ile
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Gln Ser Tyr Asp Tyr Tyr Asp Tyr Gly
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Gln Gln Ala Asn Asp Phe Pro Ile
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Gln Ser Trp Asp Asn Leu Lys Met Pro Val
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Gln Ser Tyr Asp Leu Ser Pro Arg
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Gln Ser Tyr Asp Phe Ser His Tyr Phe Phe
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Gln Ser Tyr Asp Leu Arg Tyr Ser His
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<400> 74

Gln Ser Tyr Asp Leu Arg Asn Arg
1 5

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Gln Ser Tyr Asp Phe Thr Tyr Gly Ser

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Gln Gln Phe Asn Asp Ser Pro Tyr
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Gln Ser Tyr Asp Ile Ser Gly Tyr Pro
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Gln Ser Arg Asp Leu Tyr Tyr Val Tyr Tyr
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Gln Ser Tyr Asp Arg Ser Met Trp
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Gln Ser Trp Asp Val Gln Thr Asp Lys
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Gln Ser Trp Asp Pro Ser His Tyr Tyr
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Gln Ser Tyr Asp Ile Met Pro Glu Arg
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Gln Ser Met Asp Phe Arg Leu Met His
1 5

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Gln Ser Phe Asp Met Ile His Pro Tyr
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Gln Ser Asp Phe Pro Val Met
1 5

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Gln Ser Asp Asn Pro Tyr Leu
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Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
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Cys Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

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Ser Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

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Ser Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe Cys
1 5 10

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1 5 10

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Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg
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<213> Homo sapiens

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1 5 10 15

Arg

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<212> PRT

<213> Homo sapiens

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Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn Arg
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Cys

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<213> Homo sapiens

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Cys Leu Trp Thr Asp Gln Leu Leu Gln Gly Ser Glu
1 5 10

<210> 97

<211> 215

<212> PRT

<213> Homo sapiens

<400> 97

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

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<210> 98

<211> 215

<212> PRT

<213> Homo sapiens

<400> 98

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

```

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 99

<211> 211

<212> PRT

<213> Homo sapiens

<400> 99

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

<210> 100
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 100
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ile
 85 90 95
 Asn Val Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 101
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 101
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Val
      85          90          95
Arg Phe Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145          150          155          160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
      195          200          205
Thr Val Ala Pro Thr Glu Ala
      210          215

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<210> 102
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 <213> Homo sapiens

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<400> 102
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
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Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20          25          30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Tyr
      85          90          95
Lys Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145          150          155          160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180          185          190

```

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 103
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 103
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
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 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Arg
 85 90 95
 Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 104
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 104
 Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1 5 10 15
 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30

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

<210> 105
 <211> 213
 <212> PRT
 <213> Homo sapiens

<400> 105
 Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1 5 10 15
 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30
 Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gln Arg Lys
 85 90 95
 Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly

145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 106
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 106
 Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Gly Thr Ser
 85 90 95
 Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Ala
 210 215

<210> 107
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 107

```

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

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<210> 108

<211> 211

<212> PRT

<213> Homo sapiens

<400> 108

```

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

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Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
    115                      120                      125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
    130                      135                      140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
    145                      150                      155                      160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
    165                      170                      175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
    180                      185                      190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
    195                      200                      205
Thr Glu Ala
    210

```

<210> 109

<211> 211

<212> PRT

<213> Homo sapiens

<400> 109

```

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

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<210> 110
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 110
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Met Ile
 85 90 95
 Ala Arg Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 111
 <211> 213
 <212> PRT
 <213> Homo sapiens

<400> 111
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

```

65              70              75              80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile His Pro Phe Asp
85              90              95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100            105            110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115            120            125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130            135            140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145            150            155            160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165            170            175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180            185            190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195            200            205
Ala Pro Thr Glu Ala
210

```

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<210> 112
<211> 213
<212> PRT
<213> Homo sapiens

```

```

<400> 112
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1              5              10              15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20            25            30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35            40            45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50            55            60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65            70            75            80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Leu Glu Pro
85            90            95
Tyr Val Phe Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100           105           110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115           120           125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130           135           140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145           150           155           160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165           170           175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180           185           190

```

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 113
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 113
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Leu
 85 90 95
 Asp Ser Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 114
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 114
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30

```

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

```

<210> 115

<211> 214

<212> PRT

<213> Homo sapiens

<400> 115

```

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

```


<400> 117

```

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

```

<210> 118

<211> 215

<212> PRT

<213> Homo sapiens

<400> 118

```

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

```

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Ala
 210 215

<210> 119
 <211> 216
 <212> PRT
 <213> Homo sapiens

.
 <400> 119
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asn Leu
 85 90 95
 Lys Met Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 120
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 120
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Phe
 85 90 95
 Pro Ile Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 121
 <211> 213
 <212> PRT
 <213> Homo sapiens

<400> 121
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Leu Tyr Phe
      85          90          95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
      100          105          110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
      115          120          125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
      130          135          140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145          150          155          160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
      165          170          175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
      180          185          190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
      195          200          205
Ala Pro Thr Glu Ala
      210

```

<210> 122

<211> 214

<212> PRT

<213> Homo sapiens

<400> 122

```

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

```

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
 195 200 205
 Val Ala Pro Thr Glu Ala
 210

<210> 123
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 123
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Pro Val Gly Phe Pro
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
 100 105 110
 Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
 115 120 125
 Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
 130 135 140
 Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
 145 150 155 160
 Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
 165 170 175
 Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
 180 185 190
 Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
 195 200 205
 Pro Thr Glu Ala
 210

<210> 124
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 124
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30

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

<210> 125

<211> 216

<212> PRT

<213> Homo sapiens

<400> 125

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

```

145          150          155          160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
          165          170          175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
          180          185          190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
          195          200          205
Lys Thr Val Ala Pro Thr Glu Ala
          210          215

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<210> 126
<211> 212
<212> PRT
<213> Homo sapiens

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```

<400> 126
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1          5          10          15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
          20          25          30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
          35          40          45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
          50          55          60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
          65          70          75          80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg Tyr Ser His
          85          90          95
Val Phe Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
          100          105          110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
          115          120          125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
          130          135          140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
          145          150          155          160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
          165          170          175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
          180          185          190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
          195          200          205
Pro Thr Glu Ala
          210

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<210> 127
<211> 214
<212> PRT
<213> Homo sapiens

```

<400> 127

```

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

```

<210> 128

<211> 215

<212> PRT

<213> Homo sapiens

<400> 128

```

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

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Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205
Thr Val Ala Pro Thr Glu Ala
210 215

```

<210> 129

<211> 215

<212> PRT

<213> Homo sapiens

<400> 129

```

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

```

<210> 130
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 130
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Ser
 85 90 95
 Gly Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 131
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 131
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Leu Tyr
85          90          95
Tyr Val Tyr Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100        105        110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115        120        125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130        135        140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145        150        155        160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165        170        175
Tyr Ala Ala Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180        185        190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195        200        205
Lys Thr Val Ala Pro Thr Glu Ala
210        215

```

<210> 132

<211> 211

<212> PRT

<213> Homo sapiens

<400> 132

```

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

```

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
 195 200 205
 Thr Glu Ala
 210

<210> 133
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 133
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Val Gln
 85 90 95
 Thr Asp Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 134
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 134
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30

```

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

```

<210> 135
 <211> 215
 <212> PRT
 <213> Homo sapiens

```

<400> 135
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
   1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
   20          25          30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
   35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
   50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
   65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Met
   85          90          95
Pro Glu Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
  100         105         110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
  115         120         125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
  130         135         140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys

```

145					150					155				160	
Ala	Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr
				165					170					175	
Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His
			180					185					190		
Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys
		195					200					205			
Thr	Val	Ala	Pro	Thr	Glu	Ala									
	210					215									

<210> 136
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 136															
Asp	Ile	Ala	Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln
1				5					10					15	
Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
		20					25					30			
Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu
		35				40						45			
Met	Ile	Tyr	Asp	Val	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe
	50					55					60				
Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
65					70					75				80	
Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Met	Asp	Phe	Arg
			85						90					95	
Leu	Met	His	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln
			100					105					110		
Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu
		115					120					125			
Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr
	130					135					140				
Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys
145					150					155					160
Ala	Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr
				165					170					175	
Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His
		180						185					190		
Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys
		195					200					205			
Thr	Val	Ala	Pro	Thr	Glu	Ala									
	210					215									

<210> 137
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 137

```

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

```

<210> 138

<211> 213

<212> PRT

<213> Homo sapiens

<400> 138

```

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

```

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
 145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 139

<211> 213

<212> PRT

<213> Homo sapiens

<400> 139

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

<210> 140
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 140
 Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Phe Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 141
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 141
 Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
      100        105        110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
      115        120        125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
      130        135        140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
      165        170        175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
      180        185        190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
      195        200        205
Lys Lys Val Glu Pro Lys Ser Glu Phe
      210        215

```

<210> 142

<211> 217

<212> PRT

<213> Homo sapiens

<400> 142

```

Gln 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
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35          40          45
Ser Ala Ile Ser Gly Ser 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 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 Phe Leu Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
      100        105        110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
      115        120        125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
      130        135        140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
      165        170        175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
      180        185        190

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Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 143
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 143
 Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Thr Phe Pro Ile Asp Ala Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 144
 <211> 218
 <212> PRT
 <213> Homo sapiens

<400> 144
 Gln 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

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Gly His Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110
 Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
 115 120 125
 Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
 130 135 140
 Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 145 150 155 160
 Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 165 170 175
 Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 180 185 190
 Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
 195 200 205
 Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 145

<211> 222

<212> PRT

<213> Homo sapiens

<400> 145

Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Tyr Trp Arg Gly Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

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145          150          155          160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
          165          170          175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
          180          185          190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
          195          200          205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215          220

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<210> 146

<211> 217

<212> PRT

<213> Homo sapiens

<400> 146

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Gln 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
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Ala Ile Ser Gly Ser 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 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 Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100          105          110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
          115          120          125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
          130          135          140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
          165          170          175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
          180          185          190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
          195          200          205
Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215

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<210> 147

<211> 225

<212> PRT

<213> Homo sapiens

<400> 147

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

<210> 148

<211> 224

<212> PRT

<213> Homo sapiens

<400> 148

Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Leu Asp Thr Tyr Tyr Pro Asp Leu Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 149

<211> 220

<212> PRT

<213> Homo sapiens

<400> 149

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

210

215

220

<210> 150
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 150
 Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Tyr Met Ala Tyr Met Ala Glu Ala Ile Asp Val Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 151
 <211> 230
 <212> PRT
 <213> Homo sapiens

<400> 151
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe

50					55					60					
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Val	Gly	Ile	Val	Gly	Tyr	Lys	Pro	Asp	Glu	Leu	Leu	Tyr
			100					105					110		
Phe	Asp	Val	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser
		115					120					125			
Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr
	130					135					140				
Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro
145					150					155					160
Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val
				165					170					175	
His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser
			180					185					190		
Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile
		195					200					205			
Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val
	210				215					220					
Glu	Pro	Lys	Ser	Glu	Phe										
225					230										

<210> 152
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 152

Gln	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			
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35				40						45			
Ser	Ala	Ile	Ser	Gly	Ser	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	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	Tyr	Gly	Ala	Tyr	Phe	Gly	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115						120				125			
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205
 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 153
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 153
 Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30
 Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60
 Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg Gly Tyr Ala Asp Ile Ser Phe Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 154
 <211> 220
 <212> PRT
 <213> Homo sapiens

<400> 154

Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Tyr Tyr Leu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 155

<211> 229

<212> PRT

<213> Homo sapiens

<400> 155

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

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      100      105      110
Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
      115      120      125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
      130      135      140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145      150      155      160
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
      165      170      175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
      180      185      190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
      195      200      205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
      210      215      220
Pro Lys Ser Glu Phe
225

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<210> 156
 <211> 220
 <212> PRT
 <213> Homo sapiens

```

<400> 156
Gln 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
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35      40      45
Ser Ala Ile Ser Gly Ser 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 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 Leu Ile Gly Tyr Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
      100      105      110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
      115      120      125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
      130      135      140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145      150      155      160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
      165      170      175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
      180      185      190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
      195      200      205

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Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 157
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 157
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 158
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 158
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30

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

<210> 159

<211> 226

<212> PRT

<213> Homo sapiens

<400> 159

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

130 135 140
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190
 Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 195 200 205
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
 210 215 220
 Glu Phe
 225

<210> 160
 <211> 219
 <212> PRT
 <213> Homo sapiens

<400> 160
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110
 Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 115 120 125
 Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 130 135 140
 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 145 150 155 160
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 165 170 175
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 180 185 190
 Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 195 200 205
 Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 161

<211> 231
 <212> PRT
 <213> Homo sapiens

<400> 161
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Phe
 100 105 110
 Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
 115 120 125
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 130 135 140
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 145 150 155 160
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 165 170 175
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 180 185 190
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 195 200 205
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 210 215 220
 Val Glu Pro Lys Ser Glu Phe
 225 230

<210> 162
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 162
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 163
 <211> 228
 <212> PRT
 <213> Homo sapiens

<400> 163
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ile Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp
 100 105 110
 Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125
 Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
 130 135 140
 Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160
 Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

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      165      170      175
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
      180      185      190
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
      195      200      205
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
      210      215      220
Lys Ser Glu Phe
225

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<210> 164
 <211> 224
 <212> PRT
 <213> Homo sapiens

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<400> 164
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
  1      5      10      15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
      20      25      30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
      35      40      45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
      50      55      60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
      65      70      75      80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85      90      95
Ala Arg Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr Trp Gly Gln
      100      105      110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115      120      125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130      135      140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
      145      150      155      160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165      170      175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180      185      190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195      200      205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
      210      215      220

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<210> 165
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 165

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

<210> 166

<211> 225

<212> PRT

<213> Homo sapiens

<400> 166

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

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 167
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 167
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe

210

215

220

<210> 168
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 168
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Lys Tyr Val Gly Ser Glu Asp Val Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 145 150 155 160
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205
 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 169
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 169
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

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

<210> 170

<211> 224

<212> PRT

<213> Homo sapiens

<400> 170

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

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 171
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 171
 Gln 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
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser 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 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 Gly Gly Phe Phe Asn Met Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 172
 <211> 223
 <212> PRT
 <213> Homo sapiens

<400> 172
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

<210> 173
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 173
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

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      130              135              140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145              150              155              160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
      165              170              175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
      180              185              190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
      195              200              205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
      210              215              220
Phe
225

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<210> 174
<211> 221
<212> PRT
<213> Homo sapiens

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<400> 174
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1              5              10              15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
      20              25              30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35              40              45
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
      50              55              60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
      65              70              75              80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85              90              95
Ala Arg Ile Thr Tyr Ile Gly Tyr Asp Phe Trp Gly Gln Gly Thr Leu
      100              105              110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
      115              120              125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
      130              135              140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
      145              150              155              160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
      165              170              175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
      180              185              190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
      195              200              205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
      210              215              220

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<210> 175

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<211> 220
 <212> PRT
 <213> Homo sapiens

<400> 175
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gln Glu Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 176
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 176
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Tyr	Pro	Glu	Asp	Leu	Ile	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
			115				120					125			
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
			130			135					140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
		195				200						205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Glu	Phe
		210				215					220				

<210> 177

<211> 231

<212> PRT

<213> Homo sapiens

<400> 177

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

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

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
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Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
	130					135					140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
	195					200						205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Glu	Phe
	210					215					220				

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

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

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<210> 251

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<400> 257
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<210> 258
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<210> 265
<211> 39
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<210> 268
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 <212> DNA
 <213> Homo sapiens

<400> 269
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 cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat 180
 gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
 ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttttatg 300
 gatatttggg gccaaaggcac cctggtgacg gttagctcag cgtcgaccaa aggtccaagc 360
 gtgtttccgc tggctccgag cagcaaaagc accagcggcg gcacggctgc cctgggctgc 420
 ctggttaaag attatttccc ggaaccagtc accgtgagct ggaacagcgg ggcgctgacc 480
 agcggcgtgc atacctttcc ggcggtgctg caaagcagcg gcctgtatag cctgagcagc 540
 gttgtgaccg tgccgagcag cagcttaggc actcagacct atatttgcaa cgtgaaccat 600
 aaaccgagca acaccaaagt ggataaaaaa gtggaaccga aaagc 645

<210> 270
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 270
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 agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc 120
 cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat 180

gcggatagcg	tgaaaggccg	ttttaccatt	tcacgtgata	attcgaaaaa	caccctgtat	240
ctgcaaatga	acagcctgcg	tgcggaagat	acggccgtgt	attattgcg	gcgtgggttt	300
gattattggg	gccaaggcac	cctggtgacg	gttagctcag	cgtcgaccaa	aggtccaagc	360
gtgtttccgc	tggctccgag	cagcaaaagc	accagcggcg	gcacggctgc	cctgggctgc	420
ctgggttaaag	attattttccc	ggaaccagtc	accgtgagct	ggaacagcgg	ggcgtgacc	480
agcggcgtgc	atacctttcc	ggcgggtgctg	caaagcagcg	gcctgtatag	cctgagcagc	540
gttgtgaccg	tgccgagcag	cagcttaggc	actcagacct	atatttgcaa	cgtgaaccat	600
aaaccgagca	acaccaaagt	ggataaaaaa	gtggaaccga	aaagc		645

<210> 271
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 271	
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cctgggaagg	gtctcgagt
gcggatagcg	tgaaaggccg
ctgcaaatga	acagcctgcg
gatatattggg	gccaaggcac
gtgtttccgc	tggctccgag
ctgggttaaag	attattttccc
agcggcgtgc	atacctttcc
gttgtgaccg	tgccgagcag
aaaccgagca	acaccaaagt
cgccggcggc	ctggtgcaac
agctatgcga	tgagctgggt
attagcggta	gcggcggcag
tcacgtgata	attcgaaaaa
acggccgtgt	attattgcg
gttagctcag	cgtcgaccaa
accagcggcg	gcacggctgc
ggaaccagtc	accgtgagct
ggcgggtgctg	caaagcagcg
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	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	645

<210> 272
 <211> 657
 <212> DNA
 <213> Homo sapiens

<400> 272	
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cctgggaagg	gtctcgagt
gcggatagcg	tgaaaggccg
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cctattgatg	ctgattcttg
aaaggtccaa	gcgtgtttcc
gccctgggct	gcctgggtta
ggggcgctga	ccagcggcgt
agcctgagca	gcgttgtagc
aacgtgaacc	ataaaccgag
cgccggcggc	ctggtgcaac
agctatgcga	tgagctgggt
attagcggta	gcggcggcag
tcacgtgata	attcgaaaaa
acggccgtgt	attattgcg
cctggtgta	cggttagctc
agcagcaaaa	gcaccagcgg
ccggaaccag	tcaccgtgag
ccggcgggtgc	tgcaaaagcag
agcagcttag	gcactcagac
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	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	657

<210> 273
 <211> 648
 <212> DNA
 <213> Homo sapiens

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<400> 273
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agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc      120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat      180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat      240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgggtcat      300
gttgattatt ggggccaaagg caccctgggt acggttagct cagcgtcgac caaagggtcca      360
agcgtgtttc cgctggctcc gagcagcaaa agcaccagcg gcggcacggc tgccctgggc      420
tgccctggtta aagattatct cccggaacca gtcaccgtga gctggaacag cggggcgctg      480
accagcggcg tgcatacctt tccggcgggt ctgcaaagca gcggcctgta tagcctgagc      540
agcgttgtga ccgtgccgag cagcagctta ggcaactcaga cctatatattg caacgtgaac      600
cataaaccga gcaacaccaa agtgataaaa aaagtggaac cgaaaagc      648

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<210> 274
<211> 660
<212> DNA
<213> Homo sapiens

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<400> 274
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cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat      180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat      240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtttattgg      300
cgtggtcttt cttttgatat ttggggccaa ggcaaccctgg tgacggttag ctacagctcg      360
accaaaggct caagcgtgtt tccgctggct ccgagcagca aaagcaccag cggcggcacg      420
gctgccctgg gctgcctggg taaagattat ttcccggaac cagtcaccgt gagctggaac      480
agcggggcgc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg      540
tatagcctga gcagcgttgt gaccgtgccg agcagcagct taggcactca gacctatatt      600
tgcaacgtga accataaacc gagcaacacc aaagtggata aaaaagtgga accgaaaagc      660

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<210> 275
<211> 645
<212> DNA
<213> Homo sapiens

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<400> 275
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agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc      120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat      180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat      240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttttttt      300
gattattggg gccaaggcac cctggtgacg gttagctcag cgtcgaccaa aggtccaagc      360
gtgtttccgc tggctccgag cagcaaaagc accagcggcg gcacggctgc cctgggctgc      420
ctgggttaaag attatttccc ggaaccagtc accgtgagct ggaacagcgg ggcgctgacc      480
agcggcgtgc atacctttcc ggcggtgctg caaagcagcg gcctgtatag cctgagcagc      540
gttggtgacc tgccgagcag cagcttaggc actcagacct atatttgcaa cgtgaaccat      600
aaaccgagca acaccaaagt ggataaaaaa gtggaaccga aaagc      645

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<210> 276

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<211> 669
 <212> DNA
 <213> Homo sapiens

<400> 276
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 agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc 120
 cctgggcagg gtctcgagt gatgggcggc attattccga tttttggcac ggcgaaactac 180
 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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 tattgggctg tttatcctta ttttgatttt tggggccaag gcaccctggg gacgggttagc 360
 tcagcgtcga ccaaagggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420
 ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccgggaacc agtcaccgtg 480
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 agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcaactcag 600
 acctatattt gcaacgtgaa ccataaacgg agcaacacca aagtggataa aaaagtggaa 660
 ccgaaaagc 669

<210> 277
 <211> 666
 <212> DNA
 <213> Homo sapiens

<400> 277
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 agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc 120
 cctgggaagg gtctcgagt ggtgagcgcg attagcggta gcggcggcag cacctattat 180
 gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
 ctgcaaataa acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcttgat 300
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 ggctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
 tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaaccg 660
 aaaagc 666

<210> 278
 <211> 654
 <212> DNA
 <213> Homo sapiens

<400> 278
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 agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc 120
 cctgggcagg gtctcgagt gatgggcggc attattccga tttttggcac ggcgaaactac 180
 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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 tattattttg attcttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgacaaaa 360
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ctgggctgcc	tggttaaaga	ttatttccc	gaaccagtca	ccgtgagctg	gaacagcggg	480
gcgctgacca	gcggcgtgca	tacctttccg	gcggtgctgc	aaagcagcgg	cctgtatagc	540
ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagacct	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagt	gataaaaaag	tggaaccgaa	aagc	654

<210> 279

<211> 666

<212> DNA

<213> Homo sapiens

<400> 279

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cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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gcttatatgg	ctgaggctat	tgatgtttgg	ggccaaggca	ccctggtgac	ggttagctca	360
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tggaacagcg	gggcgctgac	cagcggcgtg	catacctttc	cggcggtgct	gcaaaagcagc	540
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tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tgataaaaaa	agtgaaccg	660
aaaagc						666

<210> 280

<211> 684

<212> DNA

<213> Homo sapiens

<400> 280

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cctgggcagg	gtctcgagtg	gatgggctgg	attaaccgga	atagcggcgg	cacgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatg	acccgtgata	ccagcattag	caccgcgtat	240
atggaactga	gcagcctgcg	tagcgaagat	acggccgtgt	attattgcgc	gcgtcttgtt	300
ggtattgttg	gttataagcc	tgatgagctt	ctttattttg	atgtttgggg	ccaaggcacc	360
ctggtgacgg	ttagctcagc	gtcgaccaaa	ggtccaagcg	tgtttccgct	ggctccgagc	420
agcaaaagca	ccagcggcgg	cacggctgcc	ctgggctgcc	tggttaaaga	ttatttccc	480
gaaccagtca	ccgtgagctg	gaacagcggg	gcgctgacca	gcggcgtgca	tacctttccg	540
gcggtgctgc	aaagcagcgg	cctgtatagc	ctgagcagcg	ttgtgaccgt	gccgagcagc	600
agcttaggca	ctcagacct	tatttgcaac	gtgaaccata	aaccgagcaa	caccaaagt	660
gataaaaaag	tggaaccgaa	aagc				684

<210> 281

<211> 660

<212> DNA

<213> Homo sapiens

<400> 281

caggtgcaat	tggtgaaaag	cggcggcggc	ctggtgcaac	cgggcggcag	cctgcgtctg	60
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agctgcgcg	cctccggatt	taccttttagc	agctatgcga	tgagctgggt	gcgccaagcc	120
cctgggaagg	gtctcgagt	ggtgagcgcg	attagcggt	gcggcggcag	cacctattat	180
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tatagcctga	gcagcggtgt	gaccgtgccg	agcagcagct	taggcactca	gacctatatt	600
tgcaacgtga	accataaacc	gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	660

<210> 282

<211> 669

<212> DNA

<213> Homo sapiens

<400> 282

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acctgtgcga	tttccggaga	tagcgtgagc	agcaacagcg	cggcgtggaa	ctggattcgc	120
cagtctcctg	ggcgtggcct	cgagtggctg	ggcgtacct	attatcgtag	caaatggat	180
aacgattatg	cggtgagcgt	gaaaagccgg	attaccatca	acccggatac	ttcgaaaaac	240
cagtttagcc	tgcaactgaa	cagcgtgacc	ccggaagata	cggccgtgta	ttattgcgcg	300
cgtgggttatg	ctgatatttc	ttttgattat	tggggccaag	gcaccctggt	gacggttagc	360
tcagcgtcga	ccaaaggtcc	aagcgtgttt	ccgctggctc	cgagcagcaa	aagcaccagc	420
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agcggcctgt	atagcctgag	cagcgttgtg	accgtgccga	gcagcagctt	aggcactcag	600
acctatattt	gcaacgtgaa	ccataaacgg	agcaacacca	aagtggataa	aaaagtggaa	660
ccgaaaagc						669

<210> 283

<211> 654

<212> DNA

<213> Homo sapiens

<400> 283

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cctgggaagg	gtctcgagt	ggtgagcgcg	attagcggt	gcggcggcag	cacctattat	180
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ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagacct	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	654

<210> 284

<211> 681

<212> DNA

<213> Homo sapiens

<400> 284

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cctgggcagg	gtctcgagt	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatt	accgcggatg	aaagcaccag	caccgcgtat	240
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gatcagtcct	atcattatta	ttggcatcct	tattttgatg	tttggggcca	aggcaccctg	360
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ttaggcactc	agacctatat	ttgcaacgtg	aaccataaac	cgagcaaacac	caaagtggat	660
aaaaaagtgg	aaccgaaaag	c				681

<210> 285

<211> 654

<212> DNA

<213> Homo sapiens

<400> 285

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cctgggaagg	gtctcgagt	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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ggtccaagcg	tgtttccgct	ggctccgagc	agcaaaagca	ccagcggcgg	cacggctgcc	420
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ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagacctt	tattttgcaac	600
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<210> 286

<211> 669

<212> DNA

<213> Homo sapiens

<400> 286

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cctgggaagg	gtctcgagt	gatgggcatt	atttatccgg	gcgatagcga	tacccggtat	180
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aattattttt	attctattta	ttatgatcat	tggggccaag	gcaccctggg	gacgggttagc	360
tcagcgtcga	ccaaaggtcc	aagcgtgttt	ccgctggctc	cgagcagcaa	aagcaccagc	420
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agctggaaca	gcggggcgct	gaccagcggc	gtgcatacct	ttccggcggt	gctgcaaagc	540

agcggcctgt	atagcctgag	cagcgttgtg	accgtgccga	gcagcagctt	aggcactcag	600
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ccgaaaagc						669

<210> 287
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 287						
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cctgggaagg	gtctcgagt	gatgggcatt	atttatccgg	gcgatagcga	taccggttat	180
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ggtggtggtt	atgatcttat	gtttgattct	tggggccaag	gcacctgggt	gacggttagc	360
tcagcgtcga	ccaaaggtcc	aagcgtgttt	ccgctggctc	cgagcagcaa	aagcaccagc	420
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ccgaaaagc						669

<210> 288
 <211> 672
 <212> DNA
 <213> Homo sapiens

<400> 288						
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agctcagcgt	cgaccaaagg	tccaagcgtg	tttccgctgg	ctccgagcag	caaaagcacc	420
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agcagcggcc	tgtatagcct	gagcagcgtt	gtgaccgtgc	cgagcagcag	cttaggcact	600
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gaaccgaaaa	gc					672

<210> 289
 <211> 651
 <212> DNA
 <213> Homo sapiens

<400> 289						
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cctgggcagg	gtctcgagt	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
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agcagcgttg	tgaccgtgcc	gagcagcagc	ttaggcactc	agacctatat	ttgcaacgtg	600
aaccataaac	cgagcaacac	caaagtggat	aaaaaagtgg	aaccgaaaag	c	651

<210> 290
 <211> 687
 <212> DNA
 <213> Homo sapiens

<400> 290						
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cctgggcagg	gtctcgagt	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatt	accgcggatg	aaagcaccag	caccgcgtat	240
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ccggaaccag	tcaccgtgag	ctggaacagc	ggggcgctga	ccagcggcgt	gcataacctt	540
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gtggataaaa	aagtggaacc	gaaaagc				687

<210> 291
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 291						
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acctatattt	gcaacgtgaa	ccataaaccg	agcaacacca	aagtggataa	aaaagtggaa	660
ccgaaaagc						669

<210> 292
 <211> 678

<212> DNA
 <213> Homo sapiens

<400> 292
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 agctgcaaag cctccggata tacctttacc agctattata tgcactgggt ccgccaagcc 120
 cctgggcagg gtctcgagt gatgggctgg attaaccgga atagcggcgg caccgaactac 180
 gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat 240
 atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtattatg 300
 tggctctgatt atggtcagct tgttaaggtt ggtgatattt ggggccaagg caccctggtg 360
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 gtcaccgtga gctggaacag cggggcgctg accagcggcg tgcatacctt tccggcggtg 540
 ctgcaaagca gcggcctgta tagcctgagc agcgttgtga ccgtgccgag cagcagctta 600
 ggcactcaga cctatatttg caacgtgaac cataaaccga gcaacaccaa agtgataaa 660
 aaagtggaac cgaaaagc 678

<210> 293
 <211> 666
 <212> DNA
 <213> Homo sapiens

<400> 293
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 cctgggaagg gtctcgagt gatgggcatt atttatccgg gcgatagcga taccctgtat 180
 tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
 cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttattat 300
 gttactgata ctgcttattt tgattattgg ggccaaggca ccctggtgac ggtagctca 360
 gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420
 ggcaacagcg ccctgggctg cctgggttaa gattatttcc cggaaccagt caccgtgagc 480
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 ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
 tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaaccg 660
 aaaagc 666

<210> 294
 <211> 666
 <212> DNA
 <213> Homo sapiens

<400> 294
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 cctgggaagg gtctcgagt gatgggcatt atttatccgg gcgatagcga taccctgtat 180
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 cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcatgat 300
 tttgatggtt ctatttttat ggatttttgg ggccaaggca ccctggtgac ggtagctca 360
 gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420
 ggcacggctg ccctgggctg cctgggttaa gattatttcc cggaaccagt caccgtgagc 480

tggaacagcg	gggcgctgac	cagcggcgtg	catacctttc	cggcggtgct	gcaaagcagc	540
ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatattgca	acgtgaacca	taaaccgagc	aacaccaaag	tggataaaaa	agtggaaccg	660
aaaagc						666

<210> 295
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 295						
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agctgcaaag	gttcgagata	ttcctttacg	agctattgga	ttggctgggt	gcgccagatg	120
cctgggaagg	gtctcgagtg	gatgggcatt	atttatccgg	gcgatagcga	taccggttat	180
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ccgaaaagc						669

<210> 296
 <211> 614
 <212> DNA
 <213> Homo sapiens

<400> 296						
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gccagatgcc	tgggaagggt	ctcgagtgga	tgggcattat	ttatccgggc	gatagcgata	120
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ccgcgtatct	tcaatggagc	agcctgaaag	cgagcgatac	ggccatgata	tattgcgcgc	240
gtctttatgc	tgatgctgat	atttattttg	attattgggg	ccaaggcacc	ctggtgacgg	300
ttagctcagc	gtcgacaaa	ggtccaagcg	tgtttccgct	ggctccgagc	agcaaaagca	360
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ccgtgagctg	gaacagcggg	gcgctgacca	gcggcgtgca	tacctttccg	gcggtgctgc	480
aaagcagcgg	cctgtatagc	ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	540
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tggaaccgaa	aagc					614

<210> 297
 <211> 660
 <212> DNA
 <213> Homo sapiens

<400> 297						
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agctgcaaag	cctccggagg	cacttttagc	agctatgcga	ttagctgggt	gcgccaagcc	120

cctgggcagg	gtctcgagtg	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
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atggaactga	gcagcctgcg	tagcgaagat	acggccgtgt	attattgcgc	gcgtactaag	300
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accaaaggtc	caagcgtggt	tccgctggct	ccgagcagca	aaagcaccag	cggcggcacg	420
gctgccctgg	gctgcctggt	taaagattat	ttcccggaac	cagtcaccgt	gagctggaac	480
agcggggcgc	tgaccagcgg	cgtgcatacc	tttccggcgg	tgctgcaaag	cagcggcctg	540
tatagcctga	gcagcgttgt	gaccgtgccg	agcagcagct	taggcactca	gacctatatt	600
tgcaacgtga	accataaacc	gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	660

<210> 298

<211> 660

<212> DNA

<213> Homo sapiens

<400> 298

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cctgggaagg	gtctcgagtg	gatgggcatt	atttatccgg	gcgatagcga	taccgcgttat	180
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tatagcctga	gcagcgttgt	gaccgtgccg	agcagcagct	taggcactca	gacctatatt	600
tgcaacgtga	accataaacc	gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	660

<210> 299

<211> 666

<212> DNA

<213> Homo sapiens

<400> 299

caggtgcaat	tggttcagag	cggcgcggaa	gtgaaaaaac	cgggcgaaag	cctgaaaatt	60
agctgcaaag	gttccggata	ttcctttacg	agctattgga	ttggctgggt	gcgccagatg	120
cctgggaagg	gtctcgagtg	gatgggcatt	atttatccgg	gcgatagcga	taccgcgttat	180
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ggcacggctg	ccctgggctg	cctgggttaa	gattatttcc	cggaaccagt	caccgtgagc	480
tggaacagcg	gggcgctgac	cagcggcgtg	catacctttc	cggcggtgct	gcaaagcagc	540
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tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tggataaaaa	agtggaaccg	660
aaaagc						666

<210> 300

<211> 657

<212> DNA

<213> Homo sapiens

<400> 300

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cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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gccctgggct	gcctgggttaa	agattatttc	ccggaaccag	tcaccgtgag	ctggaacagc	480
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agcctgagca	gcgttgtgac	cgtgccgagc	agcagcttag	gcactcagac	ctatatttgc	600
aacgtgaacc	ataaaccgag	caacacccaa	gtggataaaa	aagtggaacc	gaaaagc	657

<210> 301

<211> 663

<212> DNA

<213> Homo sapiens

<400> 301

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cctgggcagg	gtctcgagtg	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
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atttgcaacg	tgaaccataa	accgagcaac	accaaagtgg	ataaaaaagt	ggaaccgaaa	660
agc						663

<210> 302

<211> 669

<212> DNA

<213> Homo sapiens

<400> 302

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cctgggaagg	gtctcgagtg	gatgggcatt	atttatccgg	gcgatagcga	taccggttat	180
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acctatatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 303

<211> 657

<212> DNA

<213> Homo sapiens

<400> 303

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cctgggcagg	gtctcgagt	gatgggctgg	attaaccgga	atagcggcgg	cacgaactac	180
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tatattgggt	atgatttttg	gggccaaggc	accctggtga	cggttagctc	agcgtcgacc	360
aaaggtccaa	gcgtgtttcc	gctggctccg	agcagcaaaa	gcaccagcgg	cggcacggct	420
gccctgggct	gcctgggtta	agattatttc	ccggaaccag	tcaccgtgag	ctggaacagc	480
ggggcgctga	ccagcggcgt	gcataccttt	ccggcggtgc	tgcaaagcag	cggcctgtat	540
agcctgagca	gcgttgtgac	cgtgccgagc	agcagcttag	gcactcagac	ctatatattgc	600
aacgtgaacc	ataaaccgag	caacaccaaa	gtggataaaa	aagtggaacc	gaaaagc	657

<210> 304

<211> 654

<212> DNA

<213> Homo sapiens

<400> 304

caggtgcaat	tggttcagtc	tggcgcgga	gtgaaaaaac	cgggcagcag	cgtgaaagt	60
agctgcaaag	cctccggagg	cacttttagc	agctatgcga	ttagctgggt	gcgccaagcc	120
cctgggcagg	gtctcgagt	gatgggctgg	attattccga	tttttggcac	ggcgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatt	acgcgggatg	aaagcaccag	caccgcgtat	240
atggaactga	gcagcctgcg	tagcgaagat	acggccgtgt	attattgcgc	gcgtcaggag	300
tggtatatgg	attattgggg	ccaaggcacc	ctggtgacgg	ttagctcagc	gtcgacccaa	360
ggtccaagcg	tgtttccgct	ggctccgagc	agcaaaagca	ccagcggcgg	cacggctgcc	420
ctgggctgcc	tggttaaaga	ttattttccc	gaaccagtca	ccgtgagctg	gaacagcggg	480
gcgctgacca	gcggcgtgca	tacctttccc	gcggtgctgc	aaagcagcgg	cctgtatagc	540
ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagaccta	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagt	gataaaaaag	tggaaccgaa	aagc	654

<210> 305

<211> 666

<212> DNA

<213> Homo sapiens

<400> 305

caggtgcaat	tggttcagag	cggcgcggaa	gtgaaaaaac	cgggcgaaag	cctgaaaatt	60
agctgcaaag	gttccggata	ttcctttacg	agctattgga	ttggctgggt	gcgccagatg	120
cctgggaagg	gtctcgagt	gatgggcatt	atttatccgg	gcgatagcga	taccggttat	180
tctccgagct	ttcagggcca	ggtgaccatt	agcgcggata	aaagcattag	caccgcgtat	240
cttcaatgga	gcagcctgaa	agcgagcgat	acggccatgt	attattgcgc	gcgtctttat	300

cctgaggatc	ttattttattt	tgattatttg	ggccaaggca	ccctgggtgac	ggttagctca	360
gcgtcgacca	aaggtccaag	cgtgtttccg	ctggctccga	gcagcaaaaag	caccagcggc	420
ggcacggctg	ccctgggctg	cctgggttaa	gattattttcc	cggaaccagt	caccgtgagc	480
tggaacagcg	gggcgctgac	cagcggcgctg	catacctttc	cggcggtgct	gcaaagcagc	540
ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tggataaaaa	agtgaaccg	660
aaaagc						666

<210> 306
 <211> 687
 <212> DNA
 <213> Homo sapiens

<400> 306	
caggtgcaat	tgcaacagtc
acctgtgcga	tttccggaga
cagtctcctg	ggcgtggcct
aacgattatg	cggtgagcgt
cagtttagcc	tgcaactgaa
cgttgatga	ctcctcctgg
accctggatga	cggttagctc
agcagcaaaa	gcaccagcgg
ccggaaccag	tcaccgtgag
ccggcggtgc	tgcaaagcag
agcagcttag	gcactcagac
gtggataaaa	aagtgaacc
	gaaaagc
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	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	687

<210> 307
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 307	
caggtgcaat	tggttcagag
agctgcaaag	gttccggata
cctgggaagg	gtctcgagt
tctccgagct	ttcagggcca
cttcaatgga	gcagcctgaa
gttcatgatt	atgctatgta
tcagcgtcga	ccaaaggtcc
ggcggcacgg	ctgccctggg
agctggaaca	gcggggcgct
agcggcctgt	atagcctgag
acctatattt	gcaacgtgaa
ccgaaaagc	
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	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	669

<210> 308
 <211> 672
 <212> DNA
 <213> Homo sapiens

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<400> 308
caggtgcaat tggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt      60
agctgcaaag gttccggata ttcttttacg agctattgga ttggctgggt gcgccagatg      120
cctgggaagg gtctcgagt gatgggcatt atttatccgg gcgatagcga taccggttat      180
tctccgagct ttcagggcca ggtgaccatt agcgcgata aaagcattag caccgcgtat      240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttttggt      300
tcttataatg gttctgttcc ttattttgat tattggggcc aaggcaccct ggtgacgggt      360
agctcagcgt cgaccaaagg tccaagcgtg tttccgctgg ctccgagcag caaaagcacc      420
agcgcgcgca cggctgccct gggctgcctg gttaaagatt atttcccgga accagtcacc      480
gtgagctgga acagcggggc gctgaccagc ggctgcata cctttccggc ggtgctgcaa      540
agcagcggcc tgtatagcct gagcagcgtt gtgaccgtgc cgagcagcag cttaggcact      600
cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg      660
gaaccgaaaa gc                                         672

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```

<210> 309
<211> 666
<212> DNA
<213> Homo sapiens

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```

<400> 309
caggtgcaat tggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt      60
agctgcaaag gttccggata ttcttttacg agctattgga ttggctgggt gcgccagatg      120
cctgggaagg gtctcgagt gatgggcatt atttatccgg gcgatagcga taccggttat      180
tctccgagct ttcagggcca ggtgaccatt agcgcgata aaagcattag caccgcgtat      240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtattatt      300
ggtgattatg ttattttttt tgatgtttgg ggcaaggca ccctggtgac ggtagctca      360
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc      420
ggcacggctg ccctgggctg cctgggttaaa gattatttcc cggaaccagt caccgtgagc      480
tggaacagcg gggcgctgac cagcgcgctg catacctttc cggcggtgct gcaaagcagc      540
ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc      600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaaccg      660
aaaagc                                         666

```

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<210> 310
<211> 609
<212> DNA
<213> Homo sapiens

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<400> 310
attagctgca aaggttccgg atattccttt acgagctatt ggattggctg ggtgcgccag      60
atgcctggga aggtctcga gtggatgggc attattttatc cgggcgatag cgataccggt      120
tattctccga gctttcagg ccaggtgacc attagcgcg ataaaaagcat tagcaccgcg      180
tatcttcaat ggagcagcct gaaagcgagc gatacggcca tgtattattg cgcgcgctctt      240
tttacttatc cttttcttta ttttgatgtt tggggccaag gcaccctggt gacggttagc      300
tcagcgtcga ccaaaggctc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc      360
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaaacc agtcaccgtg      420
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc      480
agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag      540
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa      600

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ccgaaaagc

609

<210> 311

<211> 666

<212> DNA

<213> Homo sapiens

<400> 311

caggtgcaat	tggttcagag	cggcgcggaa	gtgaaaaaac	cgggcgaaaag	cctgaaaatt	60
agctgcaaag	gttccggata	ttcctttacg	agctattgga	ttggctgggt	gcgccagatg	120
cctgggaagg	gtctcgagt	gatgggcatt	atztatccgg	gcgatagcga	taccgcgttat	180
tctccgagct	ttcagggcca	ggtgaccatt	agcgcggata	aaagcattag	caccgcgtat	240
cttcaatgga	gcagcctgaa	agcgagcgat	acggccatgt	attattgcgc	gcgtattctt	300
actggtcacg	ttcttctttt	tgattattgg	ggccaaggca	ccctggtgac	ggttagctca	360
gcgtcgacca	aaggtccaag	cgtgtttccg	ctggctccga	gcagcaaaaag	caccagcggc	420
ggcacggctg	ccctgggctg	cctgggttaa	gattatttcc	cggaaccagt	caccgtgagc	480
tggaacacg	gggcgctgac	cagcggcgtg	catacctttc	cggcggtgct	gcaaagcagc	540
ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tgataaaaa	agtggaaccg	660
aaaagc						666

<210> 312

<211> 645

<212> DNA

<213> Homo sapiens

<400> 312

gatatgcac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actatcagca	gtttactgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtggtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 313

<211> 645

<212> DNA

<213> Homo sapiens

<400> 313

gatatgcac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttaagac	ttatcttgtg	300

tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtgg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 314

<211> 645

<212> DNA

<213> Homo sapiens

<400> 314

gatatcgcac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttcttcg	tttttctgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtgg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 315

<211> 638

<212> DNA

<213> Homo sapiens

<400> 315

gatatcgcac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttattaa	tgttattgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtgg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 316

<211> 645

<212> DNA

<213> Homo sapiens

<400> 316

gatatcgcac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
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tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggtac	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttgttcg	ttttatggtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 317

<211> 638

<212> DNA

<213> Homo sapiens

<400> 317

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggtac	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acttttataa	gtttaatgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 318

<211> 638

<212> DNA

<213> Homo sapiens

<400> 318

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggtac	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttcgtcg	ttttctgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 319

<211> 642

<212> DNA

<213> Homo sapiens

<400> 319

gatatcgtgc	tgacccagcc	gccttcagtg	agtggcgcac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	agggcgtgccg	180
gatcgtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agccgtgact	ttaatcgtgg	tcctgtgttt	300
ggcggcgcca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgccga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctgggtgtg	cctgattagc	420
gacttttatc	cgggagccgt	gacagtggcc	tggaaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgcctgagca	gtggaagtcc	cacagaagct	acagctgccg	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 320

<211> 639

<212> DNA

<213> Homo sapiens

<400> 320

gatatcgtgc	tgacccagcc	gccttcagtg	agtggcgcac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	agggcgtgccg	180
gatcgtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctatgacc	agcgttaagt	ggtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tgggtgtgcct	gatttagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcgagg	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtcccac	agaagctaca	gctgccagggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgccggc	actgaggcc			639

<210> 321

<211> 672

<212> DNA

<213> Homo sapiens

<400> 321

gatatcgtgc	tgacccagag	cccggcgacc	ctgagcctgt	ctccggggcg	acgtgcgacc	60
ctgagctgca	gagcgagcca	gagcgtgagc	agcagctatc	tggcgtggta	ccagcagaaa	120
ccaggtcaag	caccgcgtct	attaatttat	ggcgcgagca	gccgtgcaac	tgggggtccc	180
gcgcgtttta	gcggctctgg	atccggcacg	gatttttacc	tgaccattag	cagcctggaa	240
cctgaagact	ttgcgactta	ttattgccag	cagcttttatg	gtacttctgt	tacctttggc	300
cagggtagca	aagttgaaat	taaacgtacg	gtggctgctc	cgagcgtgtt	tattttttccg	360
ccgagcgatg	aacaactgaa	aagcggcacg	gcgagcgtgg	tgtgcctgct	gaacaacttt	420
tatccgcgtg	aagcgaaagt	tcagtggaaa	gtagacaacg	cgtcgaaaag	cggcaacagc	480
caggaaagcg	tgaccgaaca	ggatagcaaa	gatagcacct	attctctgag	cagcacccctg	540
accctgagca	aagcggatta	tgaaaaacat	aaagtgtatg	cgtgcgaagt	gacccatcaa	600
ggtctgagca	gcccggtgac	taaatctttt	aatcgtggcg	aggcctgata	agcatgcgta	660

ggagaaaata aa

672

<210> 322

<211> 642

<212> DNA

<213> Homo sapiens

<400> 322

gatatcgtgc	tgaccagcc	gccttcagt	agtggcgac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gatcggttta	gcgatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctatgacg	gttttaagac	tcatgtgttt	300
ggcggcgcca	cgaagttaac	cggtcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttcgccgca	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tggaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgcctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 323

<211> 633

<212> DNA

<213> Homo sapiens

<400> 323

gatatcgaac	tgaccagcc	gccttcagt	agcgttgac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240
gacgaagcgg	attattattg	ccagagctat	gactattctc	ttcttgtgtt	tggcggcggc	300
acgaagttaa	ccgttcttgg	ccagccgaaa	gccgcaccga	gtgtgacgct	gtttccgccc	360
agcagcgaag	aattgcaggc	gaacaaagcg	accctggtgt	gcctgattag	cgacttttat	420
ccgggagccg	tgacagtggc	ctggaaggca	gatagcagcc	ccgtcaaggc	gggagtggag	480
accaccacac	cctccaaaca	aagcaacaac	aagtacgcgg	ccagcagcta	tctgagcctg	540
acgcctgagc	agtgggaagtc	ccacagaagc	tacagctgcc	aggtcacgca	tgagggggagc	600
accgtggaaa	aaaccgttgc	gccgactgag	gcc			633

<210> 324

<211> 633

<212> DNA

<213> Homo sapiens

<400> 324

gatatcgaac	tgaccagcc	gccttcagt	agcgttgac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240
gacgaagcgg	attattattg	ccagagctat	gactttaatt	ttcatgtgtt	tggcggcggc	300
acgaagttaa	ccgttcttgg	ccagccgaaa	gccgcaccga	gtgtgacgct	gtttccgccc	360

agcagcgaag	aattgcaggc	gaacaaagcg	accctgggtgt	gcctgattag	cgacttttat	420
ccgggagccg	tgacagtggc	ctggaaggca	gatagcagcc	ccgtcaaggc	gggagtggag	480
accaccacac	cctccaaaca	aagcaacaac	aagtacgcgg	ccagcagcta	tctgagcctg	540
acgcctgagc	agtggaagtc	ccacagaagc	tacagctgcc	aggtcacgca	tgagggggagc	600
accgtggaaa	aaaccgttgc	gccgactgag	gcc			633

<210> 325
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 325						
gatatcgac	tgacccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acatgattgc	tcgttatcct	300
gtgtttggcg	gcggcacgaa	gttaaccgtt	cttggccagc	cgaaagccgc	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaac	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtgg	aagtcacaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaacc	gttgcgccga	ctgaggcc		648

<210> 326
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 326						
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tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcgga	240
gacgaagcgg	attattattg	ccagagctgg	gacattcatc	cttttgatgt	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgcgccg	actgaggcc			639

<210> 327
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 327						
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tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120

cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gatcgtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctgggacc	ttgagcctta	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tgggtgtgct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtcccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgcgccg	actgaggcc			639

<210> 328
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 328	
gatatcgcac	tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
tcgtgtacgg	gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
catcccggga	aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
agcaaccgtt	ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
caagcggaag	acgaagcgga ttattattgc cagagctatg acgttcttga ttctgaggtg 300
tttggcggcg	gcacgaagt aaccgttctt ggccagccga aagccgcacc gagtgtgacg 360
ctgtttccgc	cgagcagcga agaattgcag gcgaacaaag cgacctggt gtgcctgatt 420
agcgactttt	atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag 480
gcgggagtg	agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
tatctgagcc	tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600
catgagggga	gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 329
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 329	
gatatcgcac	tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
tcgtgtacgg	gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
catcccggga	aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
agcaaccgtt	ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
caagcggaag	acgaagcgga ttattattgc cagagctatg acccttctca tccttctaag 300
gtgtttggcg	gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
acgctgtttc	cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420
attagcgact	tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480
aaggcgggag	tggagaccac cacaccctcc aaacaaagca acaacaagta cgcgccagc 540
agctatctga	gcctgacgcc tgagcagtg aagtcccaca gaagctacag ctgccaggtc 600
acgcatgagg	ggagcaccgt ggaaaaaac gttgcgccga ctgaggcc 648

<210> 330
 <211> 642
 <212> DNA
 <213> Homo sapiens

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<400> 330
gatatcgac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc      60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag      120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg      180
agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg      240
caagcggaag acgaagcgga ttattattgc cagagctatg acgatatgca gtttgtgttt      300
ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg      360
tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctgggtgtg cctgattagc      420
gacttttatc cgggagccgt gacagtggcc tggaaaggcag atagcagccc cgtcaaggcg      480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat      540
ctgagcctga cgctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat      600
gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc                                642

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<210> 331

<211> 645

<212> DNA

<213> Homo sapiens

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<400> 331
gatatcgac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc      60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag      120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg      180
agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg      240
caagcggaag acgaagcgga ttattattgc cagagctggg acattaatca tgctattgtg      300
tttggcggcg gcacgaagt aaccgttctt ggccagccga aagccgcacc gagtgtgacg      360
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggg gtgcctgatt      420
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag      480
gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc      540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg      600
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc                                645

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<210> 332

<211> 645

<212> DNA

<213> Homo sapiens

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<400> 332
gatatcgac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc      60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag      120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg      180
agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg      240
caagcggaag acgaagcgga ttattattgc cagagctatg actattatga ttatgggtgtg      300
tttggcggcg gcacgaagt aaccgttctt ggccagccga aagccgcacc gagtgtgacg      360
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggg gtgcctgatt      420
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag      480
gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc      540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg      600
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc                                645

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<210> 333
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 333
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc 60
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 ccagggtcaag caccgctctc attaatattat ggcgcgagca gccgtgcaac tgggggtccc 180
 gcgcgttttta gcggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag caggctaattg attttcctat tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg 360
 ccgagcgatg aacaactgaa aagcggcacg gcgagcgtgg tgtgctgct gaacaacttt 420
 tatccgctg agcgaaagt tcagtggaaa gtagacaacg cgctgcaaag cggcaacagc 480
 caggaaagcg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcacctg 540
 accctgagca aagcggatta tgaaaaacat aaagtgtatg cgtgcgaagt gacccatcaa 600
 ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc 645

<210> 334
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 334
 gatatcgac tgaccagcc agcttcagt agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctccaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagctggg acaatcttaa gatgcctgtt 300
 gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
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 attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480
 aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcgccagc 540
 agctatctga gcctgacgcc tgagcagtgg aagtcaccaca gaagctacag ctgccaggtc 600
 acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc 648

<210> 335
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 335
 gatatcgac tgaccagcc agcttcagt agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctccaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagctatg acgtttttcc tattaatcgt 300
 gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
 acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420
 attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480

aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtgg	aagtcccaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaacc	gttgcgccga	ctgaggcc		648

<210> 336
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 336						
gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagcgatc	tttattttcc	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttgggcag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcgga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagt	gaagtccac	agaagctaca	gctgccagg	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgcgccg	actgaggcc			639

<210> 337
 <211> 642
 <212> DNA
 <213> Homo sapiens

<400> 337						
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tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acgttactcc	tcgtgtgttt	300
ggcggcggca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgcgga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tggaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgcctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 338
 <211> 636
 <212> DNA
 <213> Homo sapiens

<400> 338						
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tcgtgtagcg	gcgatgcgct	ggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcgga	240

gacgaagcgg	attattattg	ccagagccgt	gaccctgttg	gttttcctgt	gtttggcggc	300
ggcacgaagt	taaccgttct	tggccagccg	aaagccgcac	cgagtgtgac	gctgtttccg	360
ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	cacctccaa	acaaagcaac	aacaagtacg	cgcccgagcag	ctatctgagc	540
ctgacgcctg	agcagtggaa	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
agcacctggt	aaaaaacctg	tgcgccgact	gaggcc			636

<210> 339
 <211> 642
 <212> DNA
 <213> Homo sapiens

<400> 339						
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catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggtatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acctttctcc	tcgtgtgttt	300
ggcggcgcca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgccga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tggaaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggtcacgcac	600
gaggggagca	ccgtggaaaa	aaccgttgcc	ccgactgagg	cc		642

<210> 340
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 340						
gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggtatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acttttctca	ttattttttt	300
gtgtttggcg	gcggcacgaa	gttaaccggt	cttggccagc	cgaaagccgc	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaca	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtgg	aagtcccaca	gaagctacag	ctgccagggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaacc	gttgcgccga	ctgaggcc		648

<210> 341
 <211> 636
 <212> DNA
 <213> Homo sapiens

<400> 341

gatatcgaac	tgacccagcc	gccttcagtg	agcgttgca	caggtcagac	cgcgcgatc	60
tcgtgtacg	gcgatgcgt	gggcgataa	tacgcgagc	ggtaccagca	gaaacccgg	120
caggcgccag	ttctgggtg	ttatgatgat	tctgaccgt	cctcaggcat	cccggaacg	180
tttagcggt	ccaacagcg	caacaccgc	accctgacca	ttagcggcac	tcaggcgga	240
gacgaagcg	attattattg	ccagagctat	gaccttcgt	attctcatgt	gtttggcgg	300
ggcacgaagt	taaccgttct	tggccagccg	aaagccgcac	cgagtgtgac	gctgtttccg	360
ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	cacctccaa	acaaagcaac	aacaagtacg	cggccagcag	ctatctgagc	540
ctgacgcctg	agcagtggaa	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
agcaccgtgg	aaaaaaccgt	tgcgccgact	gaggcc			636

<210> 342

<211> 642

<212> DNA

<213> Homo sapiens

<400> 342

gatatcgac	tgacccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	accttcgtaa	tcgtgtgttt	300
ggcggcgga	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgccga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctgggtgtg	cctgattagc	420
gacttttatc	cgggagccgt	gacagtggcc	tggaaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggtcacgcgt	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 343

<211> 645

<212> DNA

<213> Homo sapiens

<400> 343

gatatcgac	tgacccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttactta	tggttctgtg	300
tttggcgggc	gcacgaagt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 344

<211> 645

<212> DNA
 <213> Homo sapiens

<400> 344
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 ccaggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tggggtccc 180
 gcgcgtttta gcggctctgg atccggcacg gatttttacc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag cagtttaaat attctcctta tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg 360
 ccgagcgatg aacaactgaa aagcggcacg gcgagcgtgg tgtgcctgct gaacaacttt 420
 tatccgcgtg aagcgaaagt tcagtggaaa gtagacaacg cgctgcaaaag cggcaacagc 480
 caggaaagcg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcaccctg 540
 accctgagca aagcggatta tgaaaaacat aaagtgtatg cgtgcgaagt gacccatcaa 600
 ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc 645

<210> 345
 <211> 649
 <212> DNA
 <213> Homo sapiens

<400> 345
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 catctcgtgt acgggtacta gcagcgatgt gggcggtctat aactatgtga gctggtacca 120
 gcagcatccc ggggaaggcgc cgaaactgat gatttatgat gtgagcaacc gtccctcagg 180
 cgtgagcaac cgttttagcg gatccaaaag cggcaacacc gcgagcctga ccattagcgg 240
 cctgcaagcg gaagacgaag cggattatta ttgccagagc tatgacattt ctggttatcc 300
 tgtgtttggc ggccggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt 360
 gacgctgttt ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tgggtgtgct 420
 gatttagcgac ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt 480
 caaggcggga gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag 540
 cagctatctg agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccagggt 600
 cacgcatgag gggagcaccg tggaaaaaac cgttgcgccg actgagggc 649

<210> 346
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 346
 gatatacgca tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctgaggcgtg 180
 agcaaccggt tttagcgatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagccgtg acctttatta tgtttattat 300
 gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
 acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgctg 420
 attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480
 aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540
 agctatctga gcctgacgcc tgagcagtg aagtccaca gaagctacag ctgccaggtc 600

acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc 648

<210> 347
 <211> 633
 <212> DNA
 <213> Homo sapiens

<400> 347
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 tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg 120
 caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
 tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
 gacgaagcgg attattattg ccagagctat gaccgttcta tgtgggtgtt tggcggcggc 300
 acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccc 360
 agcagcgaag aattgcaggc gaacaaagcg accctggtgt gctgattag cgacttttat 420
 ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480
 accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540
 acgcctgagc agtggaaagtc ccacagaagc tacagctgcc aggtcacgca tgagggggagc 600
 accgtgga aaaccgttgc gccgactgag gcc 633

<210> 348
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 348
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 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
 agcaaccggt tttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcggg ttattattgc cagagctggg acgttcagac tgataagggtg 300
 tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg 360
 ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt 420
 agcgaacttt atccgggagc cgtgacagtg gctggaagg cagatagcag ccccgtaag 480
 gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
 tatctgagcc tgacgcctga gcagtggag tcccacagaa gctacagctg ccaggtcacg 600
 catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 349
 <211> 636
 <212> DNA
 <213> Homo sapiens

<400> 349
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 tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg 120
 caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc 180
 tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
 gacgaagcgg attattattg ccagagctgg gacccttctc attattatgt gtttggcggc 300
 ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360

ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	caccctccaa	acaaagcaac	aacaagtacg	cggccagcag	ctatctgagc	540
ctgacgcctg	agcagtggaa	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
agcaccgtgg	aaaaaaccgt	tgcgccgact	gaggcc			636

<210> 350

<211> 645

<212> DNA

<213> Homo sapiens

<400> 350

gatatcgac	tgacccagcc	agcttcagtg	agcgggtcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acattatgcc	tgagcgtgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 351

<211> 645

<212> DNA

<213> Homo sapiens

<400> 351

gatatcgac	tgacccagcc	agcttcagtg	agcgggtcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagcatgg	actttcgtct	tatgcatgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 352

<211> 645

<212> DNA

<213> Homo sapiens

<400> 352

gatatcgac	tgacccagcc	agcttcagtg	agcgggtcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120

catccccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctttg	acatgattca	tccttatgtg	300
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tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 353
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 353						
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tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catccccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagcgact	ttcctgttat	ggtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtg	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccc	tggaaaaaac	cgttgcgccg	actgaggcc			639

<210> 354
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 354						
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tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catccccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagcgaca	atccttatct	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtg	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccc	tggaaaaaac	cgttgcgccg	actgaggcc			639

<210> 355
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 355

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ala	Met	Ser
1				5					10

<210> 356

<211> 10

<212> PRT

<213> Homo sapiens

<400> 356

Gly	Phe	Thr	Phe	Asn	Ser	Tyr	Ala	Met	Ser
1				5					10

<210> 357

<211> 17

<212> PRT

<213> Homo sapiens

<400> 357

Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 358

<211> 17

<212> PRT

<213> Homo sapiens

<400> 358

Val	Ile	Ser	Gly	Asn	Gly	Ser	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 359

<211> 17

<212> PRT

<213> Homo sapiens

<400> 359

Gly	Ile	Ser	Gly	Asn	Gly	Val	Leu	Ile	Phe	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 360

<211> 5

<212> PRT

<213> Homo sapiens

<400> 360
Gly Leu Met Asp Tyr
1 5

<210> 361
<211> 4
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<400> 361
Trp Phe Asp His
1

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<211> 4
<212> PRT
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<400> 362
Trp Phe Asp Val
1

<210> 363
<211> 14
<212> PRT
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<400> 363
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 364
<211> 7
<212> PRT
<213> Homo sapiens

<400> 364
Asp Val Ser Asn Arg Pro Ser
1 5

<210> 365
<211> 9
<212> PRT
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<400> 365
Gln Ser Tyr Asp Phe Ile Arg Phe Met
1 5

<210> 366
<211> 10
<212> PRT
<213> Homo sapiens

<400> 366
Gly Gly Thr Phe Ser Ser Tyr Ala Ile Ser
1 5 10

<210> 367
<211> 10
<212> PRT
<213> Homo sapiens

<400> 367
Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
1 5 10

<210> 368
<211> 17
<212> PRT
<213> Homo sapiens

<400> 368
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15
Gly

<210> 369
<211> 17
<212> PRT
<213> Homo sapiens

<400> 369
Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15
Gly

<210> 370
<211> 16
<212> PRT
<213> Homo sapiens

<400> 370
Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe Asp Val
1 5 10 15

<210> 371
<211> 13
<212> PRT
<213> Homo sapiens

<400> 371
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser
1 5 10

<210> 372
<211> 14
<212> PRT
<213> Homo sapiens

<400> 372
Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 373
<211> 11
<212> PRT
<213> Homo sapiens

<400> 373
Leu Met Ile Tyr Asp Asn Asn Gln Arg Pro Ser
1 5 10

<210> 374
<211> 11
<212> PRT
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