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(54) **MONOCLONAL ANTIBODIES AGAINST TISSUE FACTOR PATHWAY INHIBITOR**

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(57) **ABSTRACT**

Isolated monoclonal antibodies that bind human tissue factor pathway inhibitor (TFPI) and the isolated nucleic acid molecules encoding them are provided. Pharmaceutical compositions comprising the anti-TFPI monoclonal antibodies and methods of treating deficiencies or defects in coagulation by administration of the antibodies are also provided. Methods of producing the antibodies are also provided.

Figure 1

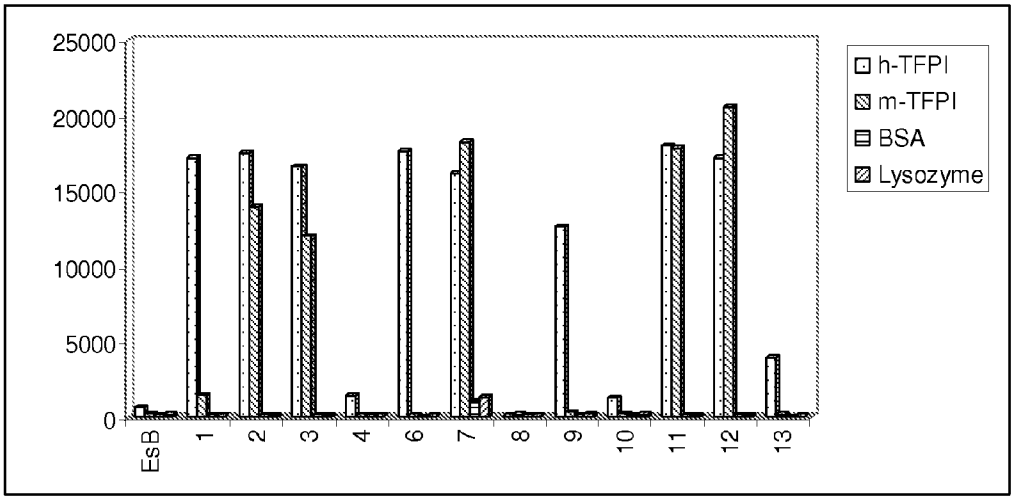

25000
20000
15000
10000
5000
0
EsB
1
2
3
4
6
7
8
9
10
11
12
13
h-TFPI
m-TFPI
BSA
Lysozyme

Figure 2

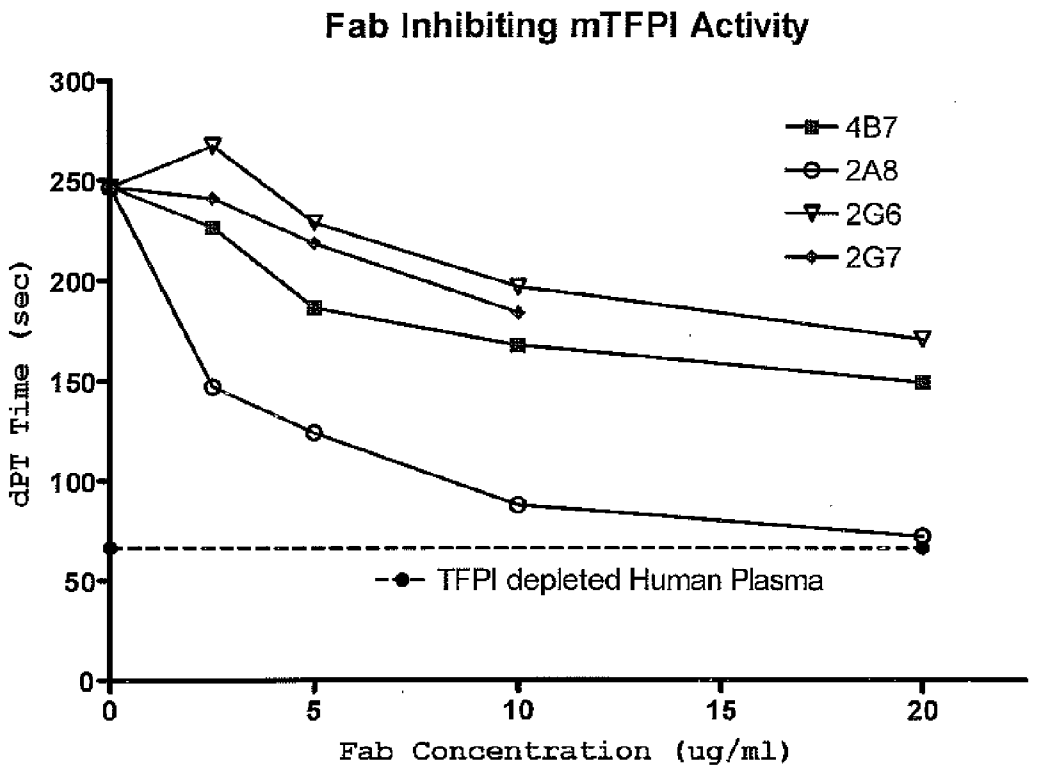

Fab Inhibiting mTFPI Activity
dPT Time (sec)
300
250
200
150
100
50
0
0
5
10
15
20
Fab Concentration (ug/ml)
4B7
2A8
2G6
2G7
TFPI depleted Human Plasma

Figure 3

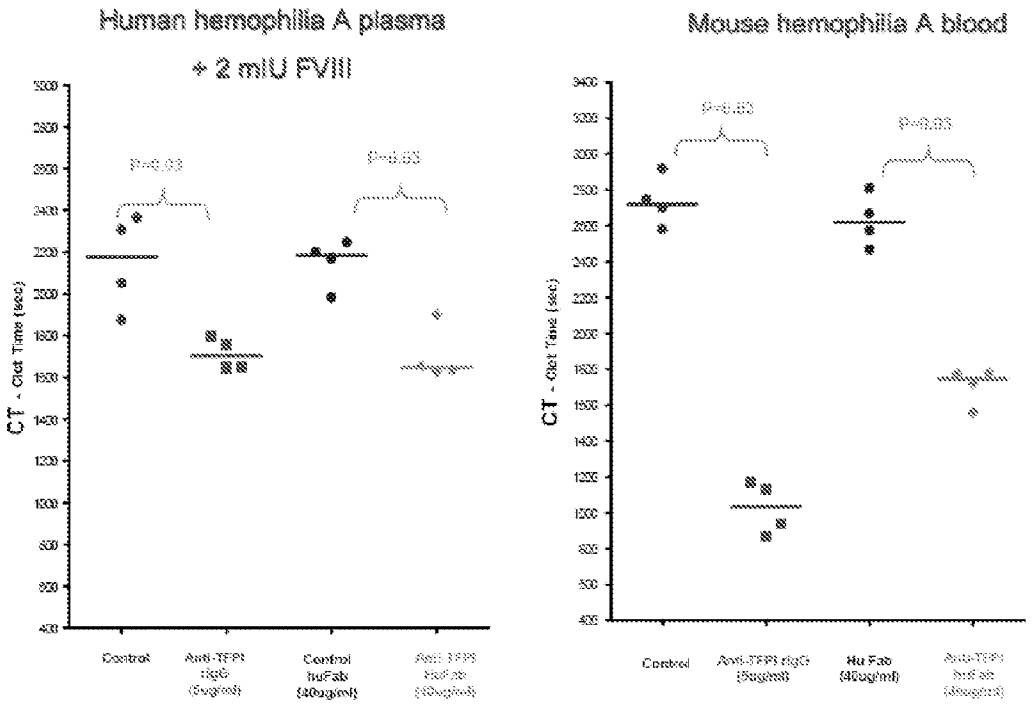

Human hemophilia A plasma
+ 2 mIU FVIII
CT - Clot Time (sec)
Control
Anti-TFPI IgG (5ug/ml)
Control huFab (40ug/ml)
Anti-TFPI huFab (40ug/ml)
Mouse hemophilia A blood
CT - Clot Time (sec)
Control
Anti-TFPI IgG (5ug/ml)
Hu Fab (40ug/ml)
Anti-TFPI huFab (40ug/ml)

Figure 4

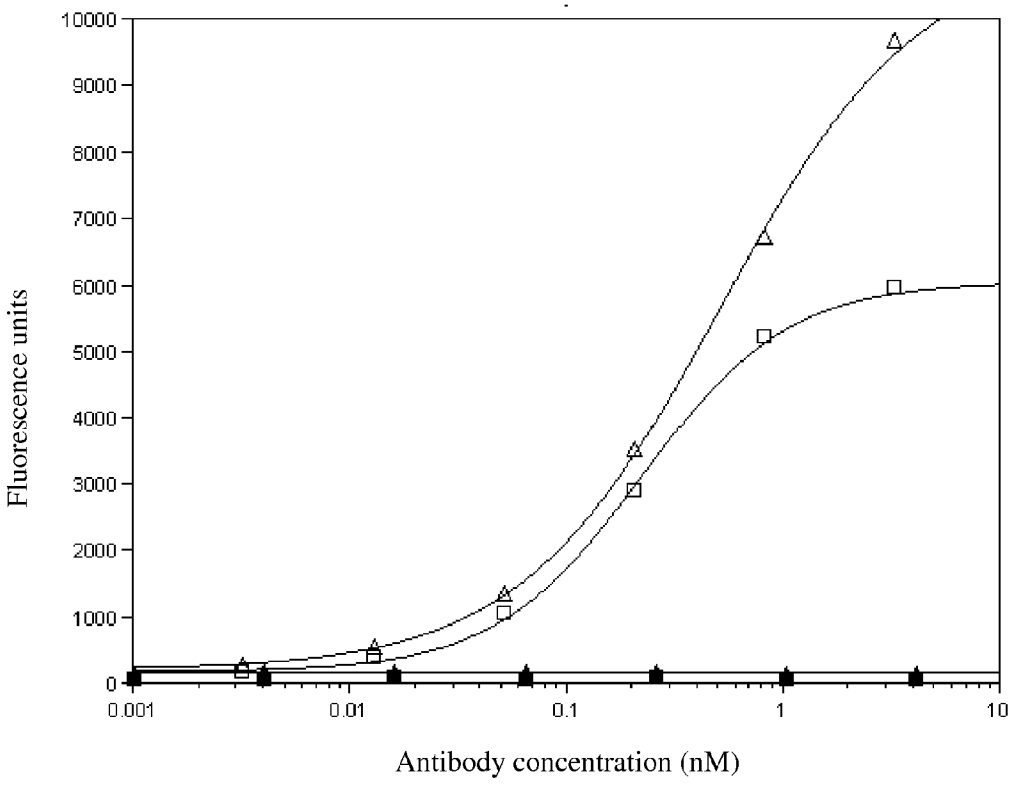

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Fluorescence units
0.001
0.01
0.1
1
10
Antibody concentration (nM)

Figure 5

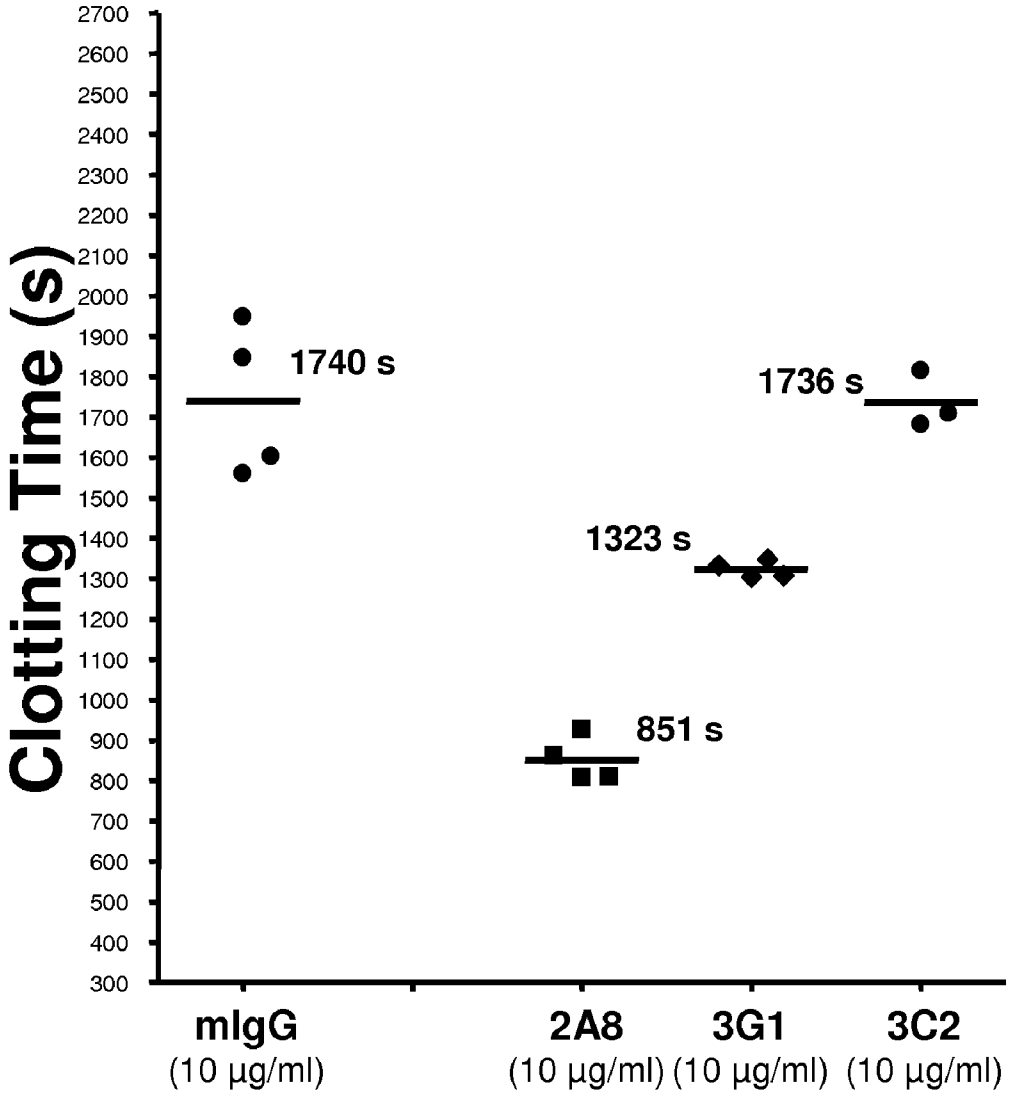

Clotting Time (s)
2700
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
1740 s
1736 s
1323 s
851 s
mIgG
(10 µg/ml)
2A8
(10 µg/ml)
3G1
(10 µg/ml)
3C2
(10 µg/ml)

Figure 6

Figure 7

Figure 8

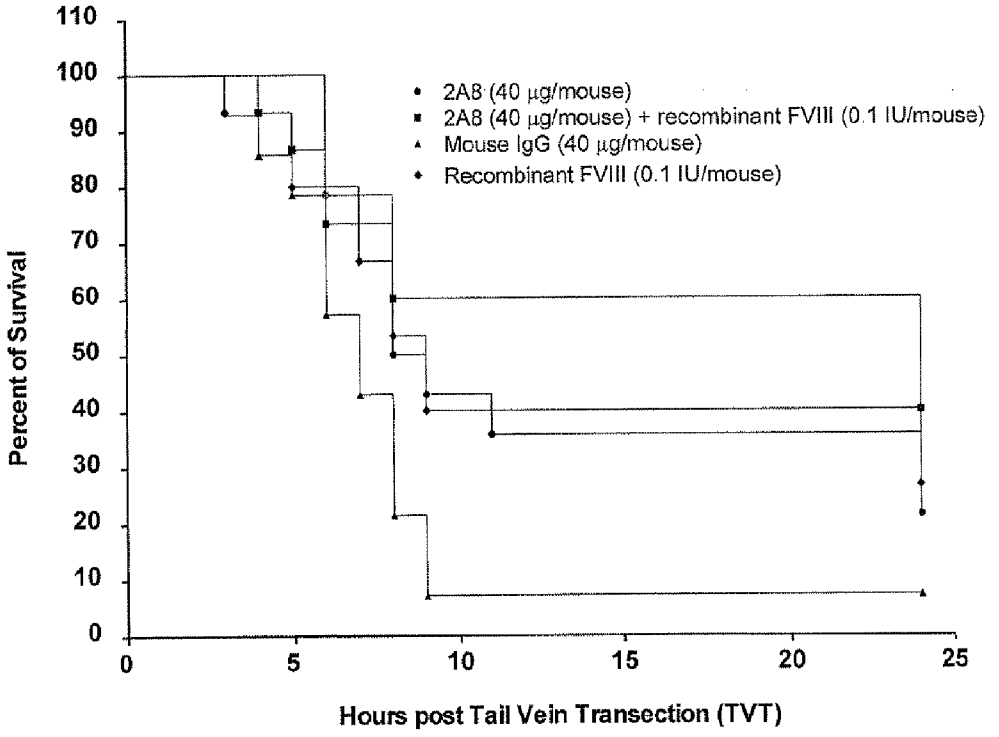
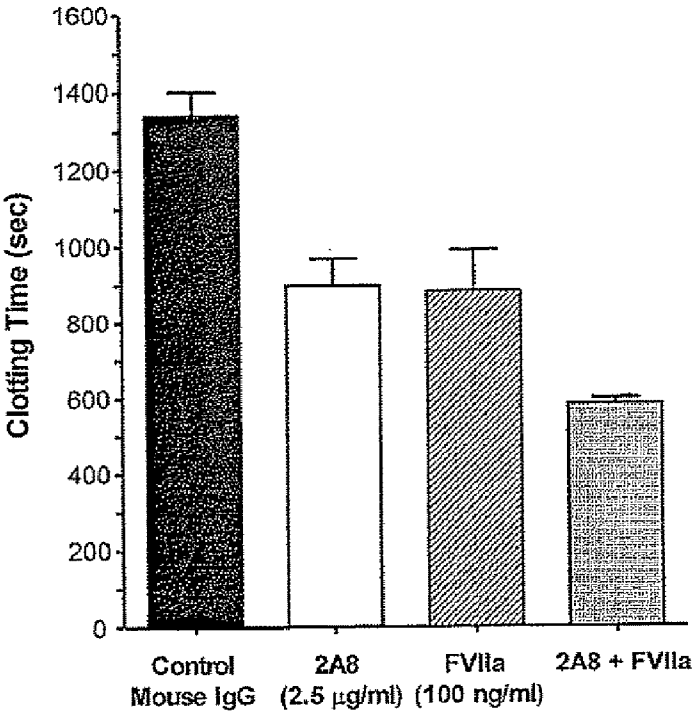

110
100
90
80
70
60
50
40
30
20
10
0
Percent of Survival
0
5
10
15
20
25
Hours post Tail Vein Transection (TVT)
2A8 (40 µg/mouse)
2A8 (40 µg/mouse) + recombinant FVIII (0.1 IU/mouse)
Mouse IgG (40 µg/mouse)
Recombinant FVIII (0.1 IU/mouse)

Figure 9


Clotting Time (sec)
1600
1400
1200
1000
800
600
400
200
0
Control Mouse IgG
2A8 (2.5 µg/ml)
FVIIa (100 ng/ml)
2A8 + FVIIa

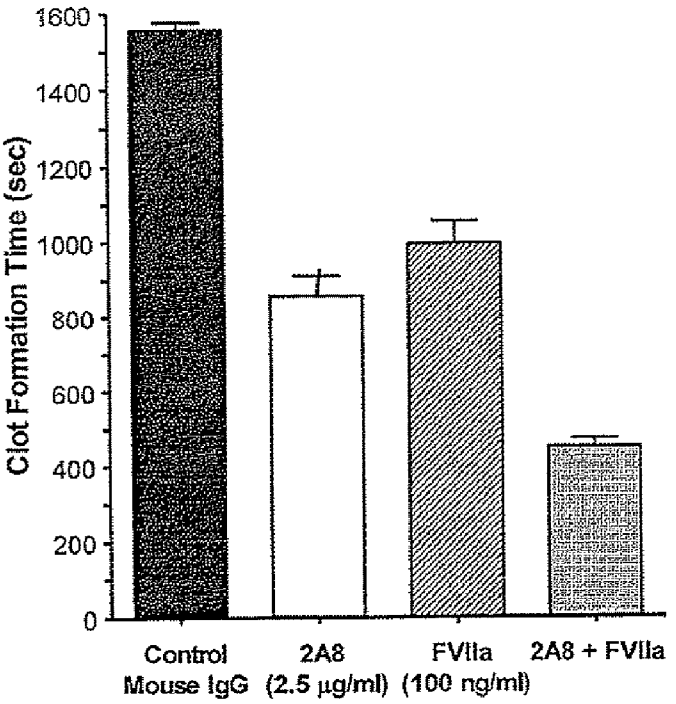
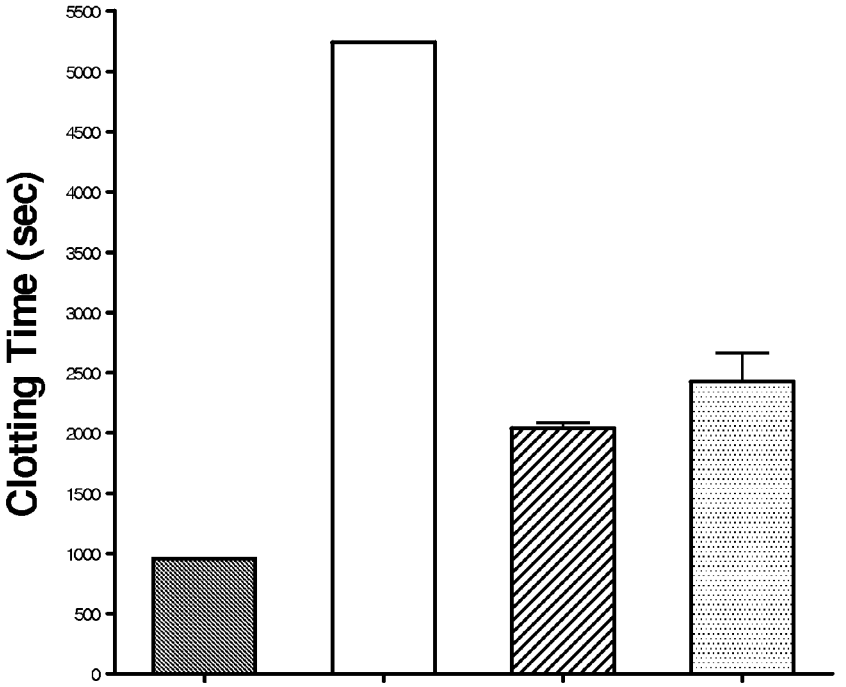

Clot Formation Time (sec)
1600
1400
1200
1000
800
600
400
200
0
Control Mouse IgG
2A8 (2.5 µg/ml)
FVIIa (100 ng/ml)
2A8 + FVIIa

Figure 10



FVIII inhibitor	—	+	+	+
Anti-TFPI antibody	—	—	2A8	4B7

MONOCLONAL ANTIBODIES AGAINST TISSUE FACTOR PATHWAY INHIBITOR

SEQUENCE LISTING SUBMISSION

[0001] The Sequence Listing associated with this application is filed in electronic format via EFS-Web and hereby incorporated by reference into the specification in its entirety. The name of the text file containing the Sequence Listing is MSB7329PCT_Sequence_Listing_ST25.

FIELD OF THE EMBODIMENTS

[0002] Provided are isolated monoclonal antibodies and fragments thereof that bind human tissue factor pathway inhibitor (TFPI) and related inventions.

BACKGROUND

[0003] Blood coagulation is a process by which blood forms stable clots to stop bleeding. The process involves a number of proenzymes and procofactors (or "coagulation factors") that are circulating in the blood. Those proenzymes and procofactors interact through several pathways through which they are converted, either sequentially or simultaneously, to the activated form. Ultimately, the process results in the activation of prothrombin to thrombin by activated Factor X (FXa) in the presence of Factor Va, ionic calcium, and platelets. The activated thrombin in turn induces platelet aggregation and converts fibrinogen into fibrin, which is then cross linked by activated Factor XIII (FXIIIa) to form a clot.

[0004] The process leading to the activation of Factor X can be carried out by two distinct pathways: the contact activation pathway (formerly known as the intrinsic pathway) and the tissue factor pathway (formerly known as the extrinsic pathway). It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the tissue factor pathway.

[0005] Factor X can be activated by tissue factor (TF) in combination with activated Factor VII (FVIIa). The complex of Factor VIIa and its essential cofactor, TF, is a potent initiator of the clotting cascade.

[0006] The tissue factor pathway of coagulation is negatively controlled by tissue factor pathway inhibitor ("TFPI"). TFPI is a natural, FXa-dependent feedback inhibitor of the FVIIa/TF complex. It is a member of the multivalent Kunitz-type serine protease inhibitors. Physiologically, TFPI binds to activated Factor X (FXa) to form a heterodimeric complex, which subsequently interacts with the FVIIa/TF complex to inhibit its activity, thus shutting down the tissue factor pathway of coagulation. In principle, blocking TFPI activity can restore FXa and FVIIa/TF activity, thus prolonging the duration of action of the tissue factor pathway and amplifying the generation of FXa, which is the common defect in hemophilia A and B.

[0007] Indeed, some preliminary experimental evidence has indicated that blocking the TFPI activity by antibodies against TFPI normalizes the prolonged coagulation time or shortens the bleeding time. For instance, Nordfang et al. showed that the prolonged dilute prothrombin time of hemophilia plasma was normalized after treating the plasma with antibodies to TFPI (Thromb. Haemost., 1991, 66 (4): 464-467). Similarly, Erhardtsen et al. showed that the bleeding time in hemophilia A rabbit model was significantly shortened by anti-TFPI antibodies (Blood Coagulation and Fibrinolysis, 1995, 6: 388-394). These studies suggest that inhibition of TFPI by anti-TFPI antibodies may be useful for the treatment of hemophilia A or B. Only polyclonal anti-TFPI antibody was used in these studies.

[0008] Using hybridoma techniques, monoclonal antibodies against recombinant human TFPI (rhTFPI) were prepared and identified. See Yang et al., Chin. Med. J., 1998, 111 (8): 718-721. The effect of the monoclonal antibody on dilute prothrombin time (PT) and activated partial thromboplastin time (APTT) was tested. Experiments showed that anti-TFPI monoclonal antibody shortened dilute thromboplastin coagulation time of Factor IX deficient plasma. It is suggested that the tissue factor pathway plays an important role not only in physiological coagulation but also in hemorrhage of hemophilia (Yang et al., Hunan Yi Ke Da Xue Xue Bao, 1997, 22 (4): 297-300).

[0009] U.S. Pat. No. 7,015,194 to Kjalke et al. discloses compositions comprising FVIIa and a TFPI inhibitor, including polyclonal or monoclonal antibodies, or a fragment thereof, for treatment or prophylaxis of bleeding episodes or coagulative treatment. The use of such composition to reduce clotting time in normal mammalian plasma is also disclosed. It is further suggested that a Factor VIII or a variant thereof may be included in the disclosed composition of FVIIa and TFPI inhibitor. A combination of FVIII or Factor IX with TFPI monoclonal antibody is not suggested.

[0010] In addition to the treatment for hemophilia, it has also been suggested that TFPI inhibitors, including polyclonal or monoclonal antibodies, can be used for cancer treatment (see U.S. Pat. No. 5,902,582 to Hung).

[0011] Accordingly, antibodies specific for TFPI are needed for treating hematological diseases and cancer.

[0012] Generally, therapeutic antibodies for human diseases have been generated using genetic engineering to create murine, chimeric, humanized or fully human antibodies. Murine monoclonal antibodies were shown to have limited use as therapeutic agents because of a short serum half-life, an inability to trigger human effector functions, and the production of human antimouse-antibodies. Brekke and Sandlie, "Therapeutic Antibodies for Human Diseases at the Dawn of the Twenty-first Century," *Nature* 2, 53, 52-62 (January 2003). Chimeric antibodies have been shown to give rise to human anti-chimeric antibody responses. Humanized antibodies further minimize the mouse component of antibodies. However, a fully human antibody avoids the immunogenicity associated with murine elements completely. Thus, there is a need to develop fully human antibodies to avoid the immunogenicity associated with other forms of genetically engineered monoclonal antibodies. In particular, chronic prophylactic treatment such as would be required for hemophilia treatment with an anti-TFPI monoclonal antibody has a high risk of development of an immune response to the therapy if an antibody with a murine component or murine origin is used due to the frequent dosing required and the long duration of therapy. For example, antibody therapy for hemophilia A may require weekly dosing for the lifetime of a patient. This would be a continual challenge to the immune system. Thus, the need exists for a fully human antibody for antibody therapy for hemophilia and related genetic and acquired deficiencies or defects in coagulation.

[0013] Therapeutic antibodies have been made through hybridoma technology described by Koehler and Milstein in "Continuous Cultures of Fused Cells Secreting Antibody of

Predefined Specificity," *Nature* 256, 495-497 (1975). Fully human antibodies may also be made recombinantly in prokaryotes and eukaryotes. Recombinant production of an antibody in a host cell rather than hybridoma production is preferred for a therapeutic antibody. Recombinant production has the advantages of greater product consistency, likely higher production level, and a controlled manufacture that minimizes or eliminates the presence of animal-derived proteins. For these reasons, it is desirable to have a recombinantly produced monoclonal anti-TFPI antibody.

SUMMARY

[0014] Monoclonal antibodies to human tissue factor pathway inhibitor (TFPI) are provided. Further provided are the isolated nucleic acid molecules encoding the same. Pharmaceutical compositions comprising the anti-TFPI monoclonal antibodies and methods of treatment of genetic and acquired deficiencies or defects in coagulation such as hemophilia A and B are also provided. Also provided are methods for shortening the bleeding time by administering an anti-TFPI monoclonal antibody to a patient in need thereof. Methods for producing a monoclonal antibody that binds human TFPI according to the present invention are also provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. **1**: The binding activity of representative examples of Fabs, selected from the panning and screening, to human TFPI ("h-TFPI") and mouse TFPI ("m-TFPI"). A control Fab against Estradiol-BSA ("EsB") and 12 Fabs (1-4 and 6-13) selected from panning TFPI were tested. Y-axis denotes fluorescence units of ELISA results.

[0016] FIG. **2**: The dose-dependent in vitro functional activity of four representative anti-TFPI antibodies (4B7: TP-4B7, 2A8: TP-2A8, 2G6: TP-2G6, 2G7: TP-2G7) obtained from the panning and screening of a human antibody library as shown by their shortening dPT. The experiment involved 0.5 ug/mL of mTFPI spiked into TFPI depleted plasma.

[0017] FIG. **3**: The in vitro functional activity of anti-TFPI Fab, Fab-2A8 (from TP-2A8), as tested in ROTEM assay.

[0018] FIG. **4**: The binding activity to human TFPI and mouse TFPI of clones TP-2G6 ("2G6") after the conversion to IgG. A: IgG-2G6 binding to mouse TFPI; □: IgG-2G6 binding to human TFPI; ▲: control IgG binding to mouse TFPI; ■: control IgG binding to human IgG.

[0019] FIG. **5**: The anti-TFPI antibodies TP-2A8 ("2A8"), TP-3G1 ("3G1"), and TP-3C2 ("3C2") shortened the whole blood clotting time in hemophilia A mice as tested in ROTEM assay. Each dot represents one individual hemophilia A mouse.

[0020] FIG. **6**: The amino acid sequence alignment between the variable light chains of anti-TFPI monoclonal antibodies TP-2A10 (SEQ ID NO: 18), TP-2B1 (SEQ ID NO: 22), TP-2A2 (SEQ ID NO: 2), TP-2G2 (SEQ ID NO: 66), TP-2A5.1 (SEQ ID NO: 6), TP-3A3 (SEQ ID NO: 98), TP-2A8 (SEQ ID NO: 14), TP-2B8 (SEQ ID NO: 34), TP-2G7 (SEQ ID NO: 82), TP-4H8 (SEQ ID NO: 170), TP-2G4 (SEQ ID NO: 70), TP-3F2 (SEQ ID NO: 134), TP-2A6 (SEQ ID NO: 10), TP-3A2 (SEQ ID NO: 94), TP-2C1 (SEQ ID NO: 42), TP-3E1 (SEQ ID NO: 126), TP-3F1 (SEQ ID NO: 130), TP-3D3 (SEQ ID NO: 122), TP-4A7 (SEQ ID NO: 150), TP-4G8 (SEQ ID NO: 166), TP-2B3 (SEQ ID NO: 26), TP-2F9 (SEQ ID NO: 62), TP-2G5 (SEQ ID NO: 74), TP-2G6 (SEQ ID NO: 78), TP-2H10 (SEQ ID NO: 90), TP-2B9 (SEQ ID NO: 38), TP-2C7 (SEQ ID NO: 46), TP-3G3 (SEQ ID NO: 142), TP-3C2 (SEQ ID NO: 114), TP-3B4 (SEQ ID NO: 110), TP-2E5 (SEQ ID NO: 58), TP-3C3 (SEQ ID NO: 118), TP-3G1 (SEQ ID NO: 138), TP-2D7 (SEQ ID NO: 50), TP-4B7 (SEQ ID NO: 158), TP-2E3 (SEQ ID NO: 54), TP-2G9 (SEQ ID NO: 86), TP-3C1 (SEQ ID NO: 86), TP-3A4 (SEQ ID NO: 102), TP-2B4 (SEQ ID NO: 30), TP-3H2 (SEQ ID NO: 146), TP-4A9 (SEQ ID NO: 154), TP-4E8 (SEQ ID NO: 162), and TP-3B3 (SEQ ID NO: 106).

[0021] FIG. **7**: The amino acid sequence alignment between the variable heavy chains of anti-TFPI monoclonal antibodies TP-2A10 (SEQ ID NO: 20), TP-3B3 (SEQ ID NO: 108), TP-2G4 (SEQ ID NO: 72), TP-2A5.1 (SEQ ID NO: 8), TP-4A9 (SEQ ID NO: 156), TP-2A8 (SEQ ID NO: 16), TP-2B3 (SEQ ID NO: 28), TP-2B9 (SEQ ID NO: 40), TP-2H10 (SEQ ID NO: 92), TP-3B4 (SEQ ID NO: 112), TP-2C7 (SEQ ID NO: 48), TP-2E3 (SEQ ID NO: 56), TP-3C3 (SEQ ID NO: 120), TP-2G5 (SEQ ID NO: 76), TP-4B7 (SEQ ID NO: 160), TP-2G6 (SEQ ID NO: 80), TP-3C2 (SEQ ID NO: 116), TP-2D7 (SEQ ID NO: 52), TP-3G1 (SEQ ID NO: 140), TP-2E5 (SEQ ID NO: 60), TP-2B8 (SEQ ID NO: 36), TP-3F1 (SEQ ID NO: 132), TP-3A3 (SEQ ID NO: 100), TP-4E8 (SEQ ID NO: 164), TP-4A7 (SEQ ID NO: 152), TP-4H8 (SEQ ID NO: 172), TP-2A6 (SEQ ID NO: 12), TP-2C1 (SEQ ID NO: 44), TP-3G3 (SEQ ID NO: 144), TP-2B1 (SEQ ID NO: 24), TP-2G7 (SEQ ID NO: 84), TP-3H2 (SEQ ID NO: 148), TP-2A2 (SEQ ID NO: 4), TP-3E1 (SEQ ID NO: 128), TP-2G2 (SEQ ID NO: 68), TP-3D3 (SEQ ID NO: 124), TP-2G9 (SEQ ID NO: 88), TP-2B4 (SEQ ID NO: 32), TP-3A2 (SEQ ID NO: 96), TP-2F9 (SEQ ID NO: 64), TP-3A4 (SEQ ID NO: 104), TP-3C1 (SEQ ID NO: 136), TP-3F2 (SEQ ID NO: 136), and TP-4G8 (SEQ ID NO: 168).

[0022] FIG. **8**: Graph showing the survival rate over 24 hours post-tail vein transection for mice treated with (1) the anti-TFPI antibody TP-2A8 ("2A8"), (2) 2A8 and recombinant factor VIII, (3) mouse IgG, and (4) recombinant factor VIII.

[0023] FIG. **9**: Graphs showing clotting time and clot formation time assays for mice treated with the anti-TFPI antibody TP-2A8 ("2A8"), factor VIIa, and the combination of 2A8 and factor VIIa.

[0024] FIG. **10**: Graph showing clotting time for normal human blood treated with a FVIII inhibitor with the anti-TFPI antibody TP-2A8 ("2A8")and anti-TFPI antibody TP-4B7 ("4B7") as compared to FVIII inhibitor alone.

DETAILED DESCRIPTION

Definitions

[0025] The term "tissue factor pathway inhibitor" or "TFPI" as used herein refers to any variant, isoform and species homolog of human TFPI that is naturally expressed by cells. In a preferred embodiment of the invention, the binding of an antibody of the invention to TFPI reduces the blood clotting time.

[0026] As used herein, an "antibody" refers to a whole antibody and any antigen binding fragment (i.e., "antigen-binding portion") or single chain thereof. The term includes a full-length immunoglobulin molecule (e.g., an IgG antibody) that is naturally occurring or formed by normal immunoglobulin gene fragment recombinatorial processes, or an immu-

nologically active portion of an immunoglobulin molecule, such as an antibody fragment, that retains the specific binding activity. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the full-length antibody. For example, an anti-TFPI monoclonal antibody fragment binds to an epitope of TFPI. The antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0027] As used herein, the terms "inhibits binding" and "blocks binding" (e.g., referring to inhibition/blocking of binding of TFPI ligand to TFPI) are used interchangeably and encompass both partial and complete inhibition or blocking. Inhibition and blocking are also intended to include any measurable decrease in the binding affinity of TFPI to a physiological substrate when in contact with an anti-TFPI antibody as compared to TFPI not in contact with an anti-TFPI antibody, e.g., the blocking of the interaction of TFPI with factor Xa or blocking the interaction of a TFPI-factor Xa complex with tissue factor, factor VIIa or the complex of tissue factor/factor VIIa by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%.

[0028] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo).

[0029] An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that binds to TFPI is substantially free of antibodies that bind antigens other than TFPI). An isolated antibody that binds to an epitope, isoform or variant of human TFPI may, however, have cross-reactivity to other related antigens, e.g., from other species (e.g., TFPI species homologs). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0030] As used herein, "specific binding" refers to antibody binding to a predetermined antigen. Typically, the antibody binds with an affinity of at least about 10^5 M^{-1} and binds to the predetermined antigen with an affinity that is higher, for example at least two-fold greater, than its affinity for binding to an irrelevant antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[0031] As used herein, the term "high affinity" for an IgG antibody refers to a binding affinity of at least about 10^7M^{-1}, in some embodiments at least about 10^8M^{-1}, in some embodiments at least about 10^9M^{-1}, $10^{10}M^{-1}$, $10^{11}M^{-1}$ or greater, e.g., up to $10^{13}M^{-1}$ or greater.

[0032] However, "high affinity" binding can vary for other antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to a binding affinity of at least about $1.0\times10^7M^{-1}$. As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by heavy chain constant region genes.

[0033] "Complementarity-determining region" or "CDR" refers to one of three hypervariable regions within the variable region of the heavy chain or the variable region of the light chain of an antibody molecule that form the N-terminal antigen-binding surface that is complementary to the three-dimensional structure of the bound antigen. Proceeding from the N-terminus of a heavy or light chain, these complementarity-determining regions are denoted as "CDR1," "CDR2," and "CDR3," respectively. CDRs are involved in antigen-antibody binding, and the CDR3 comprises a unique region specific for antigen-antibody binding. An antigen-binding site, therefore, may include six CDRs, comprising the CDR regions from each of a heavy and a light chain V region.

[0034] As used herein, "conservative substitutions" refers to modifications of a polypeptide that involve the substitution of one or more amino acids for amino acids having similar biochemical properties that do not result in loss of a biological or biochemical function of the polypeptide. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine), and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). It is envisioned that the antibodies of the present invention may have conservative amino acid substitutions and still retain activity.

[0035] For nucleic acids and polypeptides, the term "substantial homology" indicates that two nucleic acids or two polypeptides, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide or amino acid insertions or deletions, in at least about 80% of the nucleotides or amino acids, usually at least

about 85%, preferably about 90%, 91%, 92%, 93%, 94%, or 95%, more preferably at least about 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, or 99.5% of the nucleotides or amino acids. Alternatively, substantial homology for nucleic acids exists when the segments will hybridize under selective hybridization conditions to the complement of the strand. The invention includes nucleic acid sequences and polypeptide sequences having substantial homology to the specific nucleic acid sequences and amino acid sequences recited herein.

[0036] The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions×100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, such as without limitation the AlignX™ module of VectorNTI™ (Invitrogen Corp., Carlsbad, Calif.). For AlignX™, the default parameters of multiple alignment are: gap opening penalty: 10; gap extension penalty: 0.05; gap separation penalty range: 8; % identity for alignment delay: 40. (further details found at http://www.invitrogen.com/site/us/en/home/LINNEA-Online-Guides/LINNEA-Communities/Vector-NTI-Community/Sequence-analysis-and-data-management-software-for-PCs/AlignX-Module-for-Vector-NTI-Advance.reg.us.html).

[0037] Another method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the CLUSTALW computer program (Thompson et al., Nucleic Acids Research, 1994, 2 (22): 4673-4680), which is based on the algorithm of Higgins et al., (Computer Applications in the Biosciences (CABIOS), 1992, 8 (2): 189-191). In a sequence alignment the query and subject sequences are both DNA sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a CLUSTALW alignment of DNA sequences to calculate percent identity via pairwise alignments are: Matrix=IUB, k-tuple=1, Number of Top Diagonals=5, Gap Penalty=3, Gap Open Penalty=10, Gap Extension Penalty=0.1. For multiple alignments, the following CLUSTALW parameters are preferred: Gap Opening Penalty=10, Gap Extension Parameter=0.05; Gap Separation Penalty Range=8; % Identity for Alignment Delay=40.

[0038] The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components with which it is normally associated in the natural environment. To isolate a nucleic acid, standard techniques such as the following may be used: alkaline/SDS treatment, CsC1 banding, column chromatography, agarose gel electrophoresis and others well known in the art.

Monoclonal Antibodies

[0039] Forty-four TFPI-binding antibodies were identified from panning and screening of human antibody libraries against human TFPI. The heavy chain variable region and light chain variable region of each monoclonal antibody were sequenced and their CDR regions were identified. The sequence identifier numbers ("SEQ ID NO") correspond to these regions of each monoclonal antibody are summarized in Table 1.

TABLE 1

Summary of the sequence identifier numbers ("SEQ ID NO") of the heavy chain variable region ("VH") and light chain variable region ("VL") of each TFPI-binding monoclonal antibodies. The sequence identifier numbers for the CDR regions ("CDR1," "CDR2," and "CDR3") of each heavy and light chain are also provided.

	VL		VH		VL			VH		
Clone	N.A.	A.A.	N.A.	A.A.	CDR1	CDR2	CDR3	CDR1	CDR2	CDR3
TP-2A2	1	2	3	4	173	216	259	302	345	388
TP-2A5.1	5	6	7	8	174	217	260	303	346	389
TP-2A6	9	10	11	12	175	218	261	304	347	390
TP-2A8	13	14	15	16	176	219	262	305	348	391
TP-2A10	17	18	19	20	177	220	263	306	349	392
TP-2B1	21	22	23	24	178	221	264	307	350	393
TP-2B3	25	26	27	28	179	222	265	308	351	394
TP-2B4	29	30	31	32	180	223	266	309	352	395
TP-2B8	33	34	35	36	181	224	267	310	353	396
TP-2B9	37	38	39	40	182	225	268	311	354	397
TP-2C1	41	42	43	44	183	226	269	312	355	398
TP-2C7	45	46	47	48	184	227	270	313	356	399
TP-2D7	49	50	51	52	185	228	271	314	357	400
TP-2E3	53	54	55	56	186	229	272	315	358	401
TP-2E5	57	58	59	60	187	230	273	316	359	402
TP-2F9	61	62	63	64	188	231	274	317	360	403
TP-2G2	65	66	67	68	189	232	275	318	361	404
TP-2G4	69	70	71	72	190	233	276	319	362	405
TP-2G5	73	74	75	76	191	234	277	320	363	406
TP-2G6	77	78	79	80	192	235	278	321	364	407
TP-2G7	81	82	83	84	193	236	279	322	365	408
TP-2G9	85	86	87	88	194	237	280	323	366	409
TP-2H10	89	90	91	92	195	238	281	324	367	410
TP-3A2	93	94	95	96	196	239	282	325	368	411

TABLE 1-continued

Summary of the sequence identifier numbers ("SEQ ID NO") of the heavy chain variable region ("VH") and light chain variable region ("VL") of each TFPI-binding monoclonal antibodies. The sequence identifier numbers for the CDR regions ("CDR1," "CDR2," and "CDR3") of each heavy and light chain are also provided.

	VL		VH		VL			VH		
Clone	N.A.	A.A.	N.A.	A.A.	CDR1	CDR2	CDR3	CDR1	CDR2	CDR3
TP-3A3	97	98	99	100	197	240	283	326	369	412
TP-3A4	101	102	103	104	198	241	284	327	370	413
TP-3B3	105	106	107	108	199	242	285	328	371	414
TP-3B4	109	110	111	112	200	243	286	329	372	415
TP-3C2	113	114	115	116	201	244	287	330	373	416
TP-3C3	117	118	119	120	202	245	288	331	374	417
TP-3D3	121	122	123	124	203	246	289	332	375	418
TP-3E1	125	126	127	128	204	247	290	333	376	419
TP-3F1	129	130	131	132	205	248	291	334	377	420
TP-3F2	133	134	135	136	206	249	292	335	378	421
TP-3G1	137	138	139	140	207	250	293	336	379	422
TP-3G3	141	142	143	144	208	251	294	337	380	423
TP-3H2	145	146	147	148	209	252	295	338	381	424
TP-4A7	149	150	151	152	210	253	296	339	382	425
TP-4A9	153	154	155	156	211	254	297	340	383	426
TP-4B7	157	158	159	160	212	255	298	341	384	427
TP-4E8	161	162	163	164	213	256	299	342	385	428
TP-4G8	165	166	167	168	214	257	300	343	386	429
TP-4H8	169	170	171	172	215	258	301	344	387	430
TP-3C1	85	86	135	136	194	237	280	335	378	421

N.A.: nucleic acid sequence; A.A.: amino acid sequence.

[0040] In one embodiment, provided is an isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 388-430. These CDR3s are identified from the heavy chains of the antibodies identified during panning and screening. In a further embodiment, this antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387.

[0041] In another embodiment, provided are antibodies that share a CDR3 from one of the light chains of the antibodies identified during panning and screening. Thus, the present invention is directed to an isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 259-301. In further embodiments, the antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258.

[0042] In another embodiment, the antibody comprises a CDR3 from a heavy chain and a CDR3 from a light chain of the antibodies identified from screening and panning. Thus, provided is an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 388-430 and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 259-301. In a further embodiment, the antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387, (c) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and/or (d) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258.

[0043] In other specific embodiments, the antibody comprises heavy and light chain variable regions comprising:

[0044] (a) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 173, 216 and 259 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 302, 345 and 388;

[0045] (b) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 174, 217 and 260 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 303, 346 and 389;

[0046] (c) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 175, 218 and 261 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 304, 347 and 390;

[0047] (d) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 176, 219

and 262 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 305, 348 and 391;

[0048] (e) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 177, 220 and 263 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 306, 349 and 392;

[0049] (f) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 178, 221 and 264 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 307, 350 and 393;

[0050] (g) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 179, 222 and 265 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 308, 351 and 394;

[0051] (h) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 180, 223 and 266 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 309, 352 and 395;

[0052] (i) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 181, 224 and 267 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 310, 353 and 396;

[0053] (j) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 182, 225 and 268 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 311, 354 and 397;

[0054] (k) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 183, 226 and 269 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 312, 355 and 398;

[0055] (l) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 184, 227 and 270 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 313, 356 and 399;

[0056] (m) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 185, 228 and 271 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 314, 357 and 400;

[0057] (n) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 186, 229 and 272 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 315, 358 and 401;

[0058] (o) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 187, 230 and 273 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 316, 359 and 402;

[0059] (p) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 188, 231 and 274 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 317, 360 and 403;

[0060] (q) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 189, 232 and 275 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 318, 361 and 404;

[0061] (r) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 190, 233 and 276 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 319, 362 and 405;

[0062] (s) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 191, 234 and 277 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 320, 363 and 406;

[0063] (t) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 192, 235 and 278 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 321, 364 and 407;

[0064] (u) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 193, 236 and 279 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 322, 365 and 408;

[0065] (v) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 194, 237 and 280 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 323, 366 and 409;

[0066] (w) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 195, 238 and 281 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 324, 367 and 410;

[0067] (x) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 196, 239 and 282 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 325, 368 and 411;

[0068] (y) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 197, 240 and 283 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 326, 369 and 412;

[0069] (z) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 198, 241 and 284 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 327, 370 and 413;

[0070] (aa) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 199, 242 and 285 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 328, 371 and 414;

[0071] (bb) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 200, 243 and 286 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 329, 372 and 415;

[0072] (cc) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 201, 244 and 287 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 330, 373 and;

[0073] (dd) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 202, 245 and 288 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 331, 374 and 417;

[0074] (ee) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 203, 246 and 289 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 332, 375 and 418;

[0075] (ff) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 204, 247 and 290 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 333, 376 and 419;

[0076] (gg) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 205, 248 and 291 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 334, 377 and 420;

[0077] (hh) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 206, 249 and 292 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 335, 378 and 421;

[0078] (ii) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 207, 250 and 293 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 336, 379 and 422;

[0079] (jj) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 208, 251 and 294 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 337, 380 and 423;

[0080] (kk) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 209, 252 and 295 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 338, 381 and 424;

[0081] (ll) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 210, 253 and 296 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 339, 382 and 425;

[0082] (mm) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 211, 254 and 297 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 340, 383 and 426;

[0083] (nn) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 212, 255 and 298 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 341, 384 and 427;

[0084] (oo) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 213, 256 and 299 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 342, 385 and 428;

[0085] (pp) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 214, 257 and 300 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 343, 386 and 429;

[0086] (qq) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 215, 258 and 301 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 344, 387 and 430; or

[0087] (rr) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 194, 237 and 280 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 335, 378 and 421.

[0088] In another embodiment, the invention is directed to antibodies comprising:

[0089] (a) a light chain variable region having the polypeptide sequence of SEQ ID NO: 2 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 4;

[0090] (b) a light chain variable region having the polypeptide sequence of SEQ ID NO: 6 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 8;

[0091] (c) a light chain variable region having the polypeptide sequence of SEQ ID NO: 10 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12;

[0092] (d) a light chain variable region having the polypeptide sequence of SEQ ID NO: 14 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 16;

[0093] (e) a light chain variable region having the polypeptide sequence of SEQ ID NO: 18 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 20;

[0094] (f) a light chain variable region having the polypeptide sequence of SEQ ID NO: 22 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 24;

[0095] (g) a light chain variable region having the polypeptide sequence of SEQ ID NO: 26 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 28;

[0096] (h) a light chain variable region having the polypeptide sequence of SEQ ID NO: 30 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 32;

[0097] (i) a light chain variable region having the polypeptide sequence of SEQ ID NO: 34 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 36;

[0098] (j) a light chain variable region having the polypeptide sequence of SEQ ID NO: 38 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 40;

[0099] (k) a light chain variable region having the polypeptide sequence of SEQ ID NO: 42 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 44;

[0100] (l) a light chain variable region having the polypeptide sequence of SEQ ID NO: 46 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 48;

[0101] (m) a light chain variable region having the polypeptide sequence of SEQ ID NO: 50 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 52;

[0102] (n) a light chain variable region having the polypeptide sequence of SEQ ID NO: 54 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 56;

[0103] (o) a light chain variable region having the polypeptide sequence of SEQ ID NO: 58 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 60;

[0104] (p) a light chain variable region having the polypeptide sequence of SEQ ID NO: 62 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 64;

[0105] (q) a light chain variable region having the polypeptide sequence of SEQ ID NO: 66 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 68;

[0106] (r) a light chain variable region having the polypeptide sequence of SEQ ID NO: 70 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 72;

[0107] (s) a light chain variable region having the polypeptide sequence of SEQ ID NO: 74 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 76;

[0108] (t) a light chain variable region having the polypeptide sequence of SEQ ID NO: 78 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 80;

[0109] (u) a light chain variable region having the polypeptide sequence of SEQ ID NO: 82 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 84;

[0110] (v) a light chain variable region having the polypeptide sequence of SEQ ID NO: 86 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 88;

[0111] (w) a light chain variable region having the polypeptide sequence of SEQ ID NO: 90 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 92;

[0112] (x) a light chain variable region having the polypeptide sequence of SEQ ID NO: 94 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 96;

[0113] (y) a light chain variable region having the polypeptide sequence of SEQ ID NO: 98 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100;

[0114] (z) a light chain variable region having the polypeptide sequence of SEQ ID NO: 102 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 104;

[0115] (aa) a light chain variable region having the polypeptide sequence of SEQ ID NO: 106 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 108;

[0116] (bb) a light chain variable region having the polypeptide sequence of SEQ ID NO: 110 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 112;

[0117] (cc) a light chain variable region having the polypeptide sequence of SEQ ID NO: 114 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 116;

[0118] (dd) a light chain variable region having the polypeptide sequence of SEQ ID NO: 118 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 120;

[0119] (ee) a light chain variable region having the polypeptide sequence of SEQ ID NO: 122 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 124;

[0120] (ff) a light chain variable region having the polypeptide sequence of SEQ ID NO: 126 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 128;

[0121] (gg) a light chain variable region having the polypeptide sequence of SEQ ID NO: 130 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 132;

[0122] (hh) a light chain variable region having the polypeptide sequence of SEQ ID NO: 134 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 136;

[0123] (ii) a light chain variable region having the polypeptide sequence of SEQ ID NO: 138 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 140;

[0124] (jj) a light chain variable region having the polypeptide sequence of SEQ ID NO: 142 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144;

[0125] (kk) a light chain variable region having the polypeptide sequence of SEQ ID NO: 146 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148;

[0126] (ll) a light chain variable region having the polypeptide sequence of SEQ ID NO: 150 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 152;

[0127] (mm) a light chain variable region having the polypeptide sequence of SEQ ID NO: 154 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 156;

[0128] (nn) a light chain variable region having the polypeptide sequence of SEQ ID NO: 158 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160;

[0129] (oo) a light chain variable region having the polypeptide sequence of SEQ ID NO: 162 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 164;

[0130] (pp) a light chain variable region having the polypeptide sequence of SEQ ID NO: 166 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 168;

[0131] (qq) a light chain variable region having the polypeptide sequence of SEQ ID NO: 170 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 172; or

[0132] (rr) a light chain variable region having the polypeptide sequence of SEQ ID NO: 86 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 136.

[0133] Also provided is an isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a human heavy chain variable region comprising an amino acid sequence having at least 89%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% identity to an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:116, SEQ ID NO:120, SEQ ID NO:124, SEQ ID NO:128, SEQ ID NO:132, SEQ ID NO:136, SEQ ID NO:140, SEQ ID NO:144, SEQ ID NO:148, SEQ ID NO:152, SEQ ID NO:156, SEQ ID NO:160, SEQ ID NO:164, SEQ ID NO:168, and SEQ ID NO:172.

[0134] Also provided is an isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a human light chain variable region comprising an amino acid sequence having at least 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% identity to an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:54, SEQ ID NO:58, SEQ ID NO:62, SEQ ID NO:66, SEQ ID NO:70, SEQ ID NO:74, SEQ ID NO:78, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:90, SEQ ID NO:94, SEQ ID NO:98, SEQ ID NO:102, SEQ ID NO:106, SEQ ID NO:110, SEQ ID NO:114, SEQ ID NO:118, SEQ ID NO:122, SEQ ID NO:126, SEQ ID NO:130, SEQ ID NO:134, SEQ ID NO:138, SEQ ID NO:142, SEQ ID NO:146, SEQ ID NO:150, SEQ ID NO:154, SEQ ID NO:158, SEQ ID NO:162, SEQ ID NO:166, and SEQ ID NO:170.

[0135] In addition to relying on the antibody descriptions using the sequence identifiers discussed above, some embodiments may also be described by reference to the Fab clones isolated in the experiments described herein. In some embodiments, the recombinant antibodies comprise the heavy and/or light chain CDR3s of the following clones: TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8. In some embodiments, the antibodies further can comprise the CDR2s of these antibodies and still further comprise the CDR1s of these antibodies. In other embodiments, the antibodies can further comprise any combinations of the CDRs.

[0136] Accordingly, in another embodiment, provided are anti-TFPI antibodies comprising: (1) human heavy chain framework regions, a human heavy chain CDR1 region, a human heavy chain CDR2 region, and a human heavy chain CDR3 region, wherein the human heavy chain CDR3 region is the heavy chain CDR3 of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8; and (2) human light chain framework regions, a human light chain CDR1 region, a human light chain CDR2 region, and a human light chain CDR3 region, wherein the human light chain CDR3 region is the light chain CDR3 of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8, wherein the antibody binds TFPI. The antibody may further comprise the heavy chain CDR2 and/or the light chain CDR2 of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8. The antibody may further comprise the heavy chain CDR1 and/or the light chain CDR1 of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8.

[0137] The CDR1, 2, and/or 3 regions of the engineered antibodies described above can comprise the exact amino acid sequence(s) as those of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8 disclosed herein.

[0138] However, the ordinarily skilled artisan will appreciate that some deviation from the exact CDR sequences of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3, TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8 may be possible while still retaining the ability of the antibody to bind TFPI effectively. Accordingly, in another embodiment, the engineered antibody may be composed of one or more CDRs that are, for example, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% identical to one or more CDRs of TP-2A2, TP-2A5.1, TP-2A6, TP-2A8, TP-2A10, TP-2B1, TP-2B3, TP-2B4, TP-2B8, TP-2B9, TP-2C1, TP-2C7, TP-2D7, TP-2E3, TP-2E5, TP-2F9, TP-2G2, TP-2G4, TP-2G5, TP-2G6, TP-2G7, TP-2G9, TP-2H10, TP-3A2, TP-3A3, TP-3A4, TP-3B3, TP-3B4, TP-3C1, TP-3C2, TP-3C3, TP-3D3,

TP-3E1, TP-3F1, TP-3F2, TP-3G1, TP-3G3, TP-3H2, TP-4A7, TP-4A9, TP-4B7, TP-4E8, TP-4G8, or TP-4H8.

[0139] The antibody may be of any of the various classes of antibodies, such as without limitation an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

[0140] In one embodiment, provided is an isolated fully human monoclonal antibody to human tissue factor pathway inhibitor.

[0141] In another embodiment, provided is an isolated fully human monoclonal antibody to Kunitz domain 2 of human tissue factor pathway inhibitor.

Nucleic Acids

[0142] Also provided are isolated nucleic acid molecules encoding any of the monoclonal antibodies described above.

Methods of Preparing Antibodies To TFPI

[0143] The monoclonal antibody may be produced recombinantly by expressing a nucleotide sequence encoding the variable regions of the monoclonal antibody according to the embodiments of the invention in a host cell. With the aid of an expression vector, a nucleic acid containing the nucleotide sequence may be transfected and expressed in a host cell suitable for the production. Accordingly, also provided is a method for producing a monoclonal antibody that binds with human TFPI comprising:

[0144] (a) transfecting a nucleic acid molecule encoding a monoclonal antibody of the invention into a host cell,

[0145] (b) culturing the host cell so to express the monoclonal antibody in the host cell, and optionally

[0146] (c) isolating and purifying the produced monoclonal antibody,

wherein the nucleic acid molecule comprises a nucleotide sequence encoding a monoclonal antibody of the present invention.

[0147] In one example, to express the antibodies, or antibody fragments thereof, DNAs encoding partial or full-length light and heavy chains obtained by standard molecular biology techniques are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vectors or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). The light and heavy chain variable regions of the antibodies described herein can be used to create full-length antibody genes of any antibody isotype by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions of the desired isotype such that the V_H segment is operatively linked to the C_H segment(s) within the vector and the V_L segment is operatively linked to the C_L segment within the vector. Additionally or alternatively, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

[0148] In addition to the antibody chain encoding genes, the recombinant expression vectors of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals) that control the transcription or translation of the antibody chain genes. Such regulatory sequences are described, for example, in Goeddel; Gene Expression Technology. Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990). It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Examples of regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV), Simian Virus 40 (SV40), adenovirus, (e.g., the adenovirus major late promoter (AdMLP)) and polyoma. Alternatively, nonviral regulatory sequences may be used, such as the ubiquitin promoter or β-globin promoter.

[0149] In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see, e.g., U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017, all by Axel et al.). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Examples of selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr-host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

[0150] For expression of the light and heavy chains, the expression vector(s) encoding the heavy and light chains is transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, e.g., electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is theoretically possible to express the antibodies of the invention in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells, and most preferably mammalian host cells, is the most preferred because such eukaryotic cells, and in particular mammalian cells, are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody.

[0151] Examples of mammalian host cells for expressing the recombinant antibodies include Chinese Hamster Ovary (CHO cells) (including dhfr-CHO cells, described in Urlaub

and Chasin, (1980) Proc. Natl. Acad. Sci. USA 77:4216-4220, used with a DHFR selectable marker, e.g., as described in R. J. Kaufman and P. A. Sharp (1982) Mol. Biol. 159:601-621), NSO myeloma cells, COS cells, HKB11 cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods, such as ultrafiltration, size exclusion chromatography, ion exchange chromatography and centrifugation.

Use of Partial Antibody Sequences To Express Intact Antibodies

[0152] Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain CDRs. For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. See, e.g., FIGS. **6** and **7**, in which the CDR regions in the light and heavy variable chains, respectively, of the monoclonal antibody according to the present invention are identified. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, e.g., Riechmann, L. et al., 1998, Nature 332:323-327; Jones, P. et al., 1986, Nature 321:522-525; and Queen, C. et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:10029-10033). Such framework sequences can be obtained from public DNA databases that include germline antibody gene sequences. These germline sequences will differ from mature antibody gene sequences because they will not include completely assembled variable genes, which are formed by V(D)J joining during B cell maturation. It is not necessary to obtain the entire DNA sequence of a particular antibody in order to recreate an intact recombinant antibody having binding properties similar to those of the original antibody (see WO 99/45962). Partial heavy and light chain sequence spanning the CDR regions is typically sufficient for this purpose. The partial sequence is used to determine which germline variable and joining gene segments contributed to the recombined antibody variable genes. The germline sequence is then used to fill in missing portions of the variable regions. Heavy and light chain leader sequences are cleaved during protein maturation and do not contribute to the properties of the final antibody. For this reason, it is necessary to use the corresponding germline leader sequence for expression constructs. To add missing sequences, cloned cDNA sequences can be combined with synthetic oligonucleotides by ligation or PCR amplification. Alternatively, the entire variable region can be synthesized as a set of short, overlapping, oligonucleotides and combined by PCR amplification to create an entirely synthetic variable region clone. This process has certain advantages such as elimination or inclusion or particular restriction sites, or optimization of particular codons.

[0153] The nucleotide sequences of heavy and light chain transcripts are used to design an overlapping set of synthetic oligonucleotides to create synthetic V sequences with identical amino acid coding capacities as the natural sequences. The synthetic heavy and kappa chain sequences can differ from the natural sequences in three ways: strings of repeated nucleotide bases are interrupted to facilitate oligonucleotide synthesis and PCR amplification; optimal translation initiation sites are incorporated according to Kozak's rules (Kozak, 1991, J. Biol. Chem. 266:19867-19870); and HindIII sites are engineered upstream of the translation initiation sites.

[0154] For both the heavy and light chain variable regions, the optimized coding, and corresponding non-coding, strand sequences are broken down into 30-50 nucleotide sections at approximately the midpoint of the corresponding non-coding oligonucleotide. Thus, for each chain, the oligonucleotides can be assembled into overlapping double stranded sets that span segments of 150-400 nucleotides. The pools are then used as templates to produce PCR amplification products of 150-400 nucleotides. Typically, a single variable region oligonucleotide set will be broken down into two pools which are separately amplified to generate two overlapping PCR products. These overlapping products are then combined by PCR amplification to form the complete variable region. It may also be desirable to include an overlapping fragment of the heavy or light chain constant region in the PCR amplification to generate fragments that can easily be cloned into the expression vector constructs.

[0155] The reconstructed heavy and light chain variable regions are then combined with cloned promoter, translation initiation, constant region, 3' untranslated, polyadenylation, and transcription termination sequences to form expression vector constructs. The heavy and light chain expression constructs can be combined into a single vector, co-transfected, serially transfected, or separately transfected into host cells which are then fused to form a host cell expressing both chains.

[0156] Thus, in another aspect, the structural features of a human anti-TFPI antibody, e.g., TP2A8, TP2G6, TP2G7, TP4B7, etc., are used to create structurally related human anti-TFPI antibodies that retain the function of binding to TFPI. More specifically, one or more CDRs of the specifically identified heavy and light chain regions of the monoclonal antibodies of the invention can be combined recombinantly with known human framework regions and CDRs to create additional, recombinantly-engineered, human anti-TFPI antibodies of the invention.

[0157] Accordingly, in another embodiment, provided is a method for preparing an anti-TFPI antibody comprising: preparing an antibody comprising (1) human heavy chain framework regions and human heavy chain CDRs, wherein the human heavy chain CDR3 comprises an amino acid sequence selected from the amino acid sequences of SEQ ID NOs: 388-430 and/or (2) human light chain framework regions and human light chain CDRs, wherein the light chain CDR3 comprises an amino acid sequence selected from the amino acid sequences of SEQ ID NOs: 259-301; wherein the antibody retains the ability to bind to TFPI. In other embodiments, the method is practiced using other CDRs of the invention.

Pharmaceutical Compositions

[0158] Also provided are pharmaceutical compositions comprising therapeutically effective amounts of anti-TFPI monoclonal antibody and a pharmaceutically acceptable carrier. "Pharmaceutically acceptable carrier" is a substance that

may be added to the active ingredient to help formulate or stabilize the preparation and causes no significant adverse toxicological effects to the patient. Examples of such carriers are well known to those skilled in the art and include water, sugars such as maltose or sucrose, albumin, salts such as sodium chloride, etc. Other carriers are described for example in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will contain a therapeutically effective amount of at least one anti-TFPI monoclonal antibody.

[0159] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. The composition is preferably formulated for parenteral injection. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In some cases, it will include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition.

[0160] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, some methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Uses

[0161] The monoclonal antibody can be used for therapeutic purposes for treating genetic and acquired deficiencies or defects in coagulation. For example, the monoclonal antibodies in the embodiments described above may be used to block the interaction of TFPI with FXa, or to prevent TFPI-dependent inhibition of the TF/FVIIa activity. Additionally, the monoclonal antibody may also be used to restore the TF/FVIIa-driven generation of FXa to bypass the insufficiency of FVIII- or FIX-dependent amplification of FXa.

[0162] The monoclonal antibodies have therapeutic use in the treatment of disorders of hemostasis such as thrombocytopenia, platelet disorders and bleeding disorders (e.g., hemophilia A and hemophilia B). Such disorders may be treated by administering a therapeutically effective amount of the anti-TFPI monoclonal antibody to a patient in need thereof. The monoclonal antibodies also have therapeutic use in the treatment of uncontrolled bleeds in indications such as trauma and hemorrhagic stroke. Thus, also provided is a method for shortening the bleeding time comprising administering a therapeutically effective amount of an anti-TFPI monoclonal antibody of the invention to a patient in need thereof.

[0163] The antibodies can be used as monotherapy or in combination with other therapies to address a hemostatic disorder. For example, co-administration of one or more antibodies of the invention with a clotting factor such as factor VIIa, factor VIII or factor IX is believed useful for treating hemophilia. In one embodiment, provided is a method for treating genetic and acquired deficiencies or defects in coagulation comprising administering (a) a first amount of a monoclonal antibody that binds to human tissue factor pathway inhibitor and (b) a second amount of factor VIII or factor IX, wherein said first and second amounts together are effective for treating said deficiencies or defects. In another embodiment, provided is a method for treating genetic and acquired deficiencies or defects in coagulation comprising administering (a) a first amount of a monoclonal antibody that binds to human tissue factor pathway inhibitor and (b) a second amount of factor VIII or factor IX, wherein said first and second amounts together are effective for treating said deficiencies or defects, and further wherein factor VII is not coadministered. The invention also includes a pharmaceutical composition comprising a therapeutically effective amount of the combination of a monoclonal antibody of the invention and factor VIII or factor IX, wherein the composition does not contain factor VII. "Factor VII" includes factor VII and factor VIIa. These combination therapies are likely to reduce the necessary infusion frequency of the clotting factor. By co-administration or combination therapy is meant administration of the two therapeutic drugs each formulated separately or formulated together in one composition, and, when formulated separately, administered either at approximately the same time or at different times, but over the same therapeutic period.

[0164] The pharmaceutical compositions may be parenterally administered to subjects suffering from hemophilia A or B at a dosage and frequency that may vary with the severity of the bleeding episode or, in the case of prophylactic therapy, may vary with the severity of the patient's clotting deficiency.

[0165] The compositions may be administered to patients in need as a bolus or by continuous infusion. For example, a bolus administration of an inventive antibody present as a Fab fragment may be in an amount of from 0.0025 to 100 mg/kg body weight, 0.025 to 0.25 mg/kg, 0.010 to 0.10 mg/kg or 0.10-0.50 mg/kg. For continuous infusion, an inventive antibody present as an Fab fragment may be administered at 0.001 to 100 mg/kg body weight/minute, 0.0125 to 1.25 mg/kg/min., 0.010 to 0.75 mg/kg/min., 0.010 to 1.0 mg/kg/min. or 0.10-0.50 mg/kg/min. for a period of 1-24 hours, 1-12 hours, 2-12 hours, 6-12 hours, 2-8 hours, or 1-2 hours. For administration of an inventive antibody present as a full-length antibody (with full constant regions), dosage amounts may be about 1-10 mg/kg body weight, 2-8 mg/kg, or 5-6 mg/kg. Such full-length antibodies would typically be administered by infusion extending for a period of thirty minutes to three hours. The frequency of the administration would depend upon the severity of the condition. Frequency could range from three times per week to once every two or three weeks.

[0166] Additionally, the compositions may be administered to patients via subcutaneous injection. For example, a dose of 10 to 100 mg anti-TFPI antibody can be administered to patients via subcutaneous injection weekly, biweekly or monthly.

[0167] As used herein, "therapeutically effective amount" means an amount of an anti-TFPI monoclonal antibody or of a combination of such antibody and factor VIII or factor IX that is needed to effectively increase the clotting time in vivo or otherwise cause a measurable benefit in vivo to a patient in need. The precise amount will depend upon numerous fac-

tors, including, but not limited to the components and physical characteristics of the therapeutic composition, intended patient population, individual patient considerations, and the like, and can readily be determined by one skilled in the art.

EXAMPLES

General Materials And Methods

Example 1

Panning And Screening of Human Antibody Library Against Human TFPI

Panning Human Antibody Library Against TFPI

[0168] Anti-TFPI antibodies were selected by panning phage displayed combinatorial human antibody library HuCal Gold (Rothe et al., J. Mol. Biol., 2008, 376: 1182-1200) against human TFPI (American Diagnostica). Briefly, 200 μl of TFPI (5 μg/ml) was coated on 96-well Maxisorp plates for overnight at 4° C. and the plates were then blocked with a PBS buffer containing 5% milk. After the plates were washed with PBS containing 0.01% Tween-20 (PBST), an aliquot of combinatorial human antibody library was added to the TFPI-coated wells and incubated for 2 hours. Unbound phage was washed away with PBST, and the antigen-bound phage was eluted with dithiothreitol, infected and amplified in *E. coli* strain TG1. The phage was rescued by helper phage for next round of panning. A total of three rounds of panning were conducted and the clones from last two rounds were screened against human TFPI in an ELISA assay.

Screening Antibody Clones By Antigen-Binding In An ELISA

[0169] To select antibody clones that bind to human TFPI, Fab genes of the phage clones from the second and third round of panning were subcloned into a bacterial expression vector and expressed in *E. coli* strain TG1. The bacterial lysate was added to the wells of the human TFPI-coated Maxisorp plates. After washing, HRP-conjugated goat anti-human Fab was used as a detection antibody and the plates were developed by adding AmplexRed (Invitrogen) with hydrogen peroxide. A signal of at least five-fold higher than the background was considered as positive. The cross reactivity of the anti-human TFPI antibodies to mouse TFPI was determined by a similar mouse TFPI-binding ELISA. The plates were coated with mouse TFPI (R&D System), BSA and lysozyme. The later two antigens were used as negative controls. A representative set of data is shown in FIG. **1**.

Sequences of Anti-TFPI Human Antibodies

[0170] After the panning and screening of the HuCal Gold human antibody library against TFPI, DNA sequencing was performed on the positive antibody clones, resulting in 44 unique antibody sequences (Table 2). Among these antibody sequences, 29 were lambda light chains and 15 were kappa light chains. Our analysis of variable region of heavy chains reveals 28 of VH3, 14 of VH6, 1 of VH1 and 1 of VH5.

TABLE 2

Peptide sequence of variable region of 44 anti-TFPI antibodies

Clone	VL	VH
TP-2A2	DIELTQPPSVSVAPGQTARISCSGDNIRTYYVHWYQQKPGQ APVVVIYGDSKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSEADSEVFGGGTKLTVLGQ (SEQ ID NO: 2)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNNAMNWVRQAP GKGLEWVSTISYDGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARQAGGWTYSYTDVWGQGTLVTVSS (SEQ ID NO: 4)
TP-2A5.1	DIELTQPPSVSVAPGQTARISCSGDNIPEKYVHWYQQKPGQ APVLVIHGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSFDAGSYFVFGGGTKLTVLGQ (SEQ ID NO: 6)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGSWVRQAPG KGLEWVSVISGSGSSTYYADSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCARVNISTHFDVWGQGTLVTVSS (SEQ ID NO: 8)
TP-2A6	DIELTQPPSVSVAPGQTARISCSGDKIGSKYVYWYQQKPGQ APVLVIYDSNRPSGIPERFSGSNSGNTATLTISGTQAEDEA DYYCASYDSIYSYWVFGGGTKLTVLGQ (SEQ ID NO: 10)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYAMSWVRQAP GKGLEWVSSIISSSSETYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARLMGYGHYYPFDYWGQGTLVTVSS (SEQ ID NO: 12)
TP-2A8	DIELTQPPSVSVAPGQTARISCSGDNLRNYYAHWYQQKPGQ APVVVIYYDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDDGVPVFGGGTKLTVLGQ (SEQ ID NO: 14)	QVQLVESGGGLVQPGGSLRLSCAASGFTFRSYGMSWVRQAP GKGLEWVSSIRGSSSSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARKYRYWFDYWGQGTLVTVSS (SEQ ID NO: 16)
TP-2A10	DIELTQPPSVSVAPGQTARISCSGDKLGKKYVHWYQQKPGQ APVLVIYGDDKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAWGSISRFVFGGGTKLTVLGQ (SEQ ID NO: 18)	QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYSMNWVRQAP GKGLEWVSAISYTGSNTHYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARAFLGYKESYFDIWGQGTLVTVSS (SEQ ID NO: 20)
TP-2B1	DIELTQPPSVSVAPGQTARISCSGDNLGNKYAHWYQQKPGQ APVLVIYYDNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWTPGSNTMVFGGGTRLTVLGQ (SEQ ID NO: 22)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMSWVRQAS GKGLEWVSSIKGSGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARNGGLIDVWGQGTLVTVSS (SEQ ID NO: 24)
TP-2B3	DIVLTQSPATLSLSPGERATLSCRASQNIGSNYLAWYQQKP GQAPRLLIYGASTRATGVPARFNGSGSGTDFTLTISSLEPE DFAVYYCQQLNSIPVTFGQGTKVEIKRT (SEQ ID NO: 26)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGMIYYRSKWYNSYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARTMSKYGGPGMDVWGQGTLVTVS S (SEQ ID NO: 28)

TABLE 2-continued

Peptide sequence of variable region of 44 anti-TFPI antibodies

Clone	VL	VH
TP-2B4	DIELTQPPSVSVAPGQTARISCSGDALGTYYAYWYQQKPGQ APVLVIYGDMNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDAGVKPAVFGGGTKLTVLGQ (SEQ ID NO: 30)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYSMTWVRQAP GKGLEWVSGISYNGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARIYYMNLLAGWGQGTLVTVSS (SEQ ID NO: 32)
TP-2B8	DIELTQPPSVSVAPGQTARISCSGDNLRGYYASWYQQKPGQ APVLVIYEDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDSPYVHVFGGGTKLTVLGQ (SEQ ID NO: 34)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGNSMHWVRQAP GQGLEWMGTIFPYDGTTKYAQKFQGRVTMTRDTSISTAYME LSSLRSEDTAVYYCARGVHSYFDYWGQGTLVTVSS (SEQ ID NO: 36)
TP-2B9	DIQMTQSPSSLSASVGDRVTITCRASQSIRSYLAWYQQKPG KAPKLLIYKASNLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCHQYSDSPVTFGQGTKVEIKRT (SEQ ID NO: 38)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGMIYHRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARYSSIGHMDYWGQGTLVTVSS (SEQ ID NO: 40)
TP-2C1	DIELTQPPSVSVAPGQTARISCSGDSIGSYYAHWYQQKPGQ APVLVIYYDSKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAYTGQSISRVFGGGTKLTVLGQ (SEQ ID NO: 42)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSPYVMSWVRQAP GKGLEWVSSISSSSSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGDSYMYDVWGQGTLVTVSS (SEQ ID NO: 44)
TP-2C7	DIQMTQSPSSLSASVGDRVTITCRASQDIRNNLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCQQRNGFPLTFGQGTKVEIKRT (SEQ ID NO: 46)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGIIYYRSKWYNHYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARSNWSGYFDYWGQGTLVTVSS (SEQ ID NO: 48)
TP-2D7	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYTYLSWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCQQYDNAPITEGQGTKVEIKRT (SEQ ID NO: 50)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGLIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARFGDTNRNGTDVWGQGTLVTVSS (SEQ ID NO: 52)
TP-2E3	DIALTQPASVSGSPGQSITISCTGTSSDIGGYNYVSWYQQH PGKAPKLMIYGVNYRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCSSADKFTMSIVFGGGTKLTVLGQ (SEQ ID NO: 54)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGMIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARVNQYTSSDYWGQGTLVTVSS (SEQ ID NO: 56)
TP-2E5	DIQMTQSPSSLSASVGDRVTITCRASQPIYNSLSWYQQKPG KAPKLLIYGVSNLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCLQVDNLPITFGQGTKVEIKRT (SEQ ID NO: 58)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWSWIRQ SPGRGLEWLGMIFYRSKWNNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARVNANGYYAYVDLWGQGTLVTVS S (SEQ ID NO: 60)
TP-2F9	DIVLTQSPATLSLSPGERATLSCRASQSVSSQYLAWYQQKP GQAPRLLIYAASSRATGVPARFSGSGSGTDFTLTISSLEPE DFAVYYCQQDSNLPATFGQGTKVEIKRT (SEQ ID NO: 62)	QVQLVESGGGLVQPGGSLRLSCAASGFTFYKYAMHWVRQAP GKGLEWVSGIQYDGSYTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARYYCKCVDLWGQGTLVTVSS (SEQ ID NO: 64)
TP-2G2	DIELTQPPSVSVAPGQTARISCSGDNIRKFYVHWYQQKPGQ APVLVIYGTNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSKFNTVFGGGTKLTVLGQ (SEQ ID NO: 66)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAP GKGLEWVSAILSDGSSTSMADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARYPDWGWYTDVWGQGTLVTVSS (SEQ ID NO: 68)
TP-2G4	DIELTQPPSVSVAPGQTARISCSGDALRKHYVYWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDKPYPILVFGGGTKLTVLGQ (SEQ ID NO: 70)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAP GKGLEWVSNISYSGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARVGYYYGFDYWGQGTLVTVSS (SEQ ID NO: 72)
TP-2G5	DIVLTQSPATLSLSPGERATLSCRASQNVSSNYLAWYQQKP GQAPRLLIYDASNRATGVPARFSGSGSGTDFTLTISSLEPE DFAVYYCQQFYDSPQTFGQGTKVEIKRT (SEQ ID NO: 74)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWSWIRQ SPGRGLEWLGFIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARHNPDLGFDYWGQGTLVTVSS (SEQ ID NO: 76)
TP-2G6	DIVLTQSPATLSLSPGERATLSCRASQYVTSSYLAWYQQKP GQAPRLLIYGSSRATGVPARFSGSGSGTDFTLTISSLEPED FATYYCQQYSSSPITFGQGTKVEIKRT (SEQ ID NO: 78)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSSSAAWSWIRQ SPGRGLEWLGIIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARHSMVGFDVWGQGTLVTVSS (SEQ ID NO: 80)
TP-2G7	DIELTQPPSVSVAPGQTARISCSGDNLGTYYVHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQTYDSNNESIVFGGGTKLTVLGQ (SEQ ID NO: 82)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAP GKGLEWVSNISSNSSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARKGGGEHGFFPSDIWGQGTLVTVSS (SEQ ID NO: 84)

TABLE 2-continued

Peptide sequence of variable region of 44 anti-TFPI antibodies

Clone	VL	VH
TP-2G9	DIALTQPASVSGSPGQSITISCTGTSSDLGGFNTVSWYQQH PGKAPKLMIYSVSSRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCQSYDLNNLVFGGGTKLTVLGQ (SEQ ID NO: 86)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMTWVRQAP GKGLEWVSAIKSDGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARNDSGWFDVWGQGTLVTVSS (SEQ ID NO: 88)
TP-2H10	DIVLTQSPATLSLSPGERATLSCRASQSVSSFYLAWYQQKP GQAPRLLIYGSSSRATGVPARFSGSGSGTDFTLTISSLEPE DFATYYCQQYDSTPSTFGQGTKVEIKRT (SEQ ID NO: 90)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNGAAWGWIRQ SPGRGLEWLGFIYRRSKWYNSYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARQDGMGGMDSWGQGTLVTVSS (SEQ ID NO: 92)
TP-3A2	DIELTQPPSVSVAPGQTARISCSGDNIGSRYAYWYQQKPGQ APVVVIYDDSDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCAAYTFYARTVFGGGTKLTVLGQ (SEQ ID NO: 94)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYYLSWVRQAP GKGLEWVSGISYNGSSTNYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARMWRYSLGADSWGQGTLVTVSS (SEQ ID NO: 96)
TP-3A3	DIELTQPPSVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQ APVVVIYEDSDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDKSEGYVFGGGTKLTVLGQ (SEQ ID NO: 98)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNNNAISWVRQAP GKGLEWVSAINSSSSSTSMADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGHHRGHSWASFIDYWGQGTLVTVSS (SEQ ID NO: 100)
TP-3A4	DIELTQPPSVSVAPGQTARISCSGDNLRDKYASWYQQKPGQ APVLVIYSKSERPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSSYTLNPNLNYVFGGGTKLTVLGQ (SEQ ID NO: 102)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAP GKGLEWVSSISYDSSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARYGGMDYWGQGTLVTVSS (SEQ ID NO: 104)
TP-3B3	DIELTQPASVSVAPGQTARISCSGDNLRSKYAHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSAYAMGSSPVFGGGTKLTVLGQ (SEQ ID NO: 106)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVSNISYMGSNTNYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGLFPGYFDYWGQGTLVTVSS (SEQ ID NO: 108)
TP-3B4	DIQMTQSPSSLSASVGDRVTITCRASQNISNYLNWYQQKPG KAPKLLIYGESSLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCQQYGNNPTTFGQGTKVEIKRT (SEQ ID NO: 110)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNGAAWGWIRQ SPGRGLEWLGHIYYRSKWYNSYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARWGGIHDGDIYFDYWGQGTLVTV SS (SEQ ID NO: 112)
TP-3C1	DIALTQPASVSGSPGQSITISCTGTSSDLGGFNTVSWYQQH PGKAPKLMIYSVSSRPSGVSNRFSGSKSGNTASLTISGLQA EDEADYYCQSYDLNNLVFGGGTKLTVLGQ (SEQ ID NO: 86)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMHWVRQAP GKGLEWVSGISYSSSFTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARALGGGVDYWGQGTLVTVSS (SEQ ID NO: 136)
TP-3C2	DIQMTQSPSSLSASVGDRVTITCRASQSITNYLNWYQQKPG KAPKLLIYDVSNLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCQQYSGYPLTFGQGTKVEIKRT (SEQ ID NO: 114)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSSSAAWSWIRQ SPGRGLEWLGMIYYRSKWYNHYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARGGSGVMDVWGQGTLVTVSS (SEQ ID NO: 116)
TP-3C3	DIQMTQSPSSLSASVGDRVTITCRASQSINPYLNWYQQKPG KAPKLLIYAASNLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCQQLDNRSITFGQGTKVEIKRT (SEQ ID NO: 118)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWGWIRQ SPGRGLEWLGVIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARARAKKSGGFDYWGQGTLVTVSS (SEQ ID NO: 120)
TP-3D3	DIELTQPPSVSVAPGQTARISCSGDSLGSKFAHWYQQKPGQ APVLVIYDDSNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSTYTSRSHSYVFGGGTKLTVLGQ (SEQ ID NO: 122)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYASWVRQAPG KGLEWVSGISGDGSNTHYADSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCARYDNFYFDVWGQGTLVTVSS (SEQ ID NO: 124)
TP-3E1	DIELTQPPSVSVAPGQTARISCSGDNIGSYYAYWYQQKPGQ APVLVIYDDSNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSTGLLVFGGGTKLTVLGQ (SEQ ID NO: 126)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMTWVRQAP GKGLEWVSVISSVGSNTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARPTKAGRTWWWGPYMDVWGQGTLVTV SS (SEQ ID NO: 128)
TP-3F1	DIELTQPPSVSVAPGQTARISCSGDNIGSYFASWYQQKPGQ APVLVIYDDSNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCEGSNVFGGGTKLTVLGQ (SEQ ID NO: 130)	QVQLVQSGAEVKKPGESLKISCKGSGYSFTDYWIGWVRQMP GKGLEWMGIIQPSDSDTNYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARFNWWGKYDSGEDVWGQGTLVIVSS (SEQ ID NO: 132)
TP-3F2	DIELTQPPSVSVAPGQTARISCSGDNLPSKSVYWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWTSRPMVVFGGGTKLTVLGQ (SEQ ID NO: 134)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMHWVRQAP GKGLEWVSGISYSSSFTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARALGGGVDYWGQGTLVTVSS (SEQ ID NO: 136)

TABLE 2-continued

Peptide sequence of variable region of 44 anti-TFPI antibodies

Clone	VL	VH
TP-3G1	DIQMTQSPSSLSASVGDRVTITCRASQGISSYLHWYQQKPG KAPKLLIYGASTLQSGVPSRFSGSGSGTDFILTISSLQPED FATYYCQQQNGYPFTFGQGTKVEIKRT (SEQ ID NO: 138)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSGGWGWIRQ SPGRGLEWLGLIYYRSKWYNAYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARYLGSNFYVYSDVWGQGTLVTVS S (SEQ ID NO: 140)
TP-3G3	DIQMTQSPSSLSASVGDRVTITCRASQNIHSHLNWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFILTISSLQPED FAVYYCQQYYDYPLTFGQGTKVEIKRT (SEQ ID NO: 142)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMSWVRQAP GKGLEWVSSISSSSSNTYYGDSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARMHYKGMDIWGQGTLVTVSS (SEQ ID NO: 144)
TP-3H2	DIELTQPPSVSVAPGQTARISCSGDKLGKYYAYWYQQKPGQ APVLVIYGDSKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSSAAFGSTVFGGGTKLTVLGQ (SEQ ID NO: 146)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYYMSWVRQAP GKGLEWVSNISSSGSNTNYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARVHYGFDFWGQGTLVTVSS (SEQ ID NO: 148)
TP-4A7	DIELTQPPSVSVAPGQTARISCSGDALGSKFAHWYQQKPGQ APVLVIYDDSERPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAYDSGLLYVFGGGTKLTVLGQ (SEQ ID NO: 150)	QVQLVESGGGLVQPGGSLRLSCAASGFTFRNYAMNWVRQAP GKGLEWVSVISGSSSYTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARADLPYMVFDYWGQGTLVTVSS (SEQ ID NO: 152)
TP-4A9	DIELTQPPSVSVAPGQTARISCSGDALGKYYASWYQQKPGQ APVLVIYGDNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYTTRSLVFGGGTKLTVLGQ (SEQ ID NO: 154)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAP GKGLEWVSLISGVSSSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARSYLGYFDVWGQGTLVTVSS (SEQ ID NO: 156)
TP-4B7	DIVMTQSPLSLPVTPGEPASISCRSSQSLVFSDGNTYLNWY LQKPGQSPQLLIYKGSNRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCQQYDSYPLITGQGTKVEIKRT (SEQ ID NO: 158)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWSWIRQ SPGRGLEWLGIIYKRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARWHSDKHWGFDYWGQGTLVTVSS (SEQ ID NO: 160)
TP-4E8	DIELTQPPSVSVAPGQTARISCSGDALGSKYVSWYQQKPGQ APVLVIYGDNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYTYSLNQVFGGGTKLTVLGQ (SEQ ID NO: 162)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNDYAMSWVRQAP GKGLEWVSLIESVSSSTYYADSVKGRFTISRDNSKEELYLQ MNSLRAEDTAVYYCARTIGVLWDDVWGQGTLVTVSS (SEQ ID NO: 164)
TP-4G8	DIELTQPPSVSVAPGQTARISCSGDKLGSKSVHWYQQKPGQ APVLVIYRDTDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQTYDYILNVFGGGTKLTVLGQ (SEQ ID NO: 166)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMHWVRQAP GKGLEWVSTISGYGSPTYYADSVKGRFTISRDNSKEELYLQ MNSLRAEDTAVYYCARNGRKYGQMDNWGQGTLVTVSS (SEQ ID NO: 168)
TP-4H8	DIELTQPPSVSVAPGQTARISCSGDSIGKKYVHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSTADSVITYKNVFGGGTKLTVLGQ (SEQ ID NO: 170)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSDHAMHWVRQAP GKGLEWVSVIEYSGSKTNYADSVKGRFTISRDNSKEELYLQ MNSLRAEDTAVYYCARGDYYPYLVFAIWGQGTLVTVSS (SEQ ID NO: 172)

Cross-Reactivity To Mouse TFPI

[0171] The above 44 human TFPI-binding clones were also tested for binding to mouse TFPI in ELISA. Nineteen antibodies were found cross-reactive to mouse TFPI. To facilitate the study using mouse hemophilia model, we further characterized these 19 antibodies as well as five antibodies that were specific to human TFPI. A representative set of data is shown in FIG. **1**. None of these antibodies bound to BSA or lysozyme in ELISA.

Example 2

Expression And Purification of Anti-TFPI Antibodies

[0172] Anti-TFPI antibodies (as Fab fragments) were expressed and purified from the bacterial strain TG1. Briefly, a single colony of bacterial strain TG1 containing the antibody expression plasmid was picked and grown overnight in 8 ml of 2xYT medium in the presence of 34 μg/mlchloramphenicol and 1% glucose. A volume of 7 ml culture was transferred to 250 ml fresh 2xYT medium containing 34 μg/ml chloramphenicol and 0.1% glucose. After 3 hours of incubation, 0.5 mM IPTG was added to induce Fab expression. The culture was continued overnight at 25° C. The culture was centrifuged to pellet the bacterial cells. The pellet was then resuspended in a Bug Buster lysis buffer (Novagen). After centrifugation, the supernatant of bacterial lysis was filtered. The Fab fragments were affinity-purified through a Ni-NTA column (Qiagen) according to the manufacturer's instruction.

Example 3

Determination of EC_{50} And Binding Affinity of Anti-TFPI Antibodies

[0173] Purified Fab antibodies were used to determine EC_{50} of anti-TFPI antibodies to human or mouse TFPI. EC_{50} was assessed in an ELISA, similarly as described above. The results were analyzed using SoftMax. The binding affinity of

anti-TFPI antibodies was determined in a Biacore assay. Briefly, the antigen, either human or mouse TFPI, was immobilized on the CM5-chips using the amine coupling kit (GE HealthCare) according to the instructions of the manufacturer. The amount of immobilized TFPI was adjusted to the mass of the antigen to give approximate 300 RU. The antibody Fabs were analyzed in mobile phase and at least five different concentrations (0.1, 0.4, 1.6, 6.4 and 25 nM) of the purified antibodies were used in the Biacore assay. The kinetics and binding affinity were calculated using Biacore T100 Evaluation software.

[0174] As shown in Table 3, the 24 anti-TFPI Fabs showed various EC_{50} to human TFPI (0.09 to 792 nM) and mouse TFPI (0.06 to 1035 nM), and the affinity determined by Biacore was accordingly various to human TFPI (1.25 to 1140 nM). In the Biacore study of the Fabs to mouse TFPI, the variation of affinity was smaller (3.08 to 51.8 nM).

TABLE 3

The binding activity of 24 antibodies against human or mouse TFPI as determined by ELISA and Biacore (hTFPI: human TFPI; mTFPI: mouse TFPI; Neg: signal was less than two fold of background; ND, not done).

	Binding EC_{50} (nM)		Affinity (nM)	
Antibody clones	hTFPI	mTFPI	hTFPI	mTFPI
TP-2A2	0.62	1035.88	6.57	29.8
TP-2A5	28.64	14.54	35.4	19.6
TP-2A8	0.09	0.06	1.25	3.08
TP-2B11	11.52	0.52	21.5	16.3
TP-2B3	0.84	20.18	7.40	27.0
TP-2C1	0.40	Neg	2.64	Neg
TP-2C7	0.60	0.60	2.01	9.33
TP-2E5	791.60	202.28	115	25.2
TP-2G5	342.52	871.34	42.1	16.1
TP-2G6	0.48	5.18	5.06	46.1
TP-2G7	23.48	Neg	26.9	Neg
TP-2G9	10.80	194.42	48.5	35.7
TP-2H10	2.18	32.40	10.2	11.5
TP-3A4	42.84	326.58	21.6	23.7
TP-3B4	35.76	34.62	14.1	20.4
TP-3C1	32.80	108.40	21.6	33.6
TP-3C2	59.00	956.68	17.1	28.5
TP-3G1	74.40	8.68	1140	49.1
TP-3G3	33.60	47.06	16.0	25.7
TP-4A9	0.17	117.68	7.60	Neg
TP-4B7	0.74	2.64	15.8	51.8
TP-4E8	36.94	Neg	35.9	ND
TP-4G8	846.92	Neg	25.2	ND
TP-4H8	72.50	Neg	32.2	ND

Example 4

Conversion of Anti-TFPI Fab To IgG

[0175] All of the identified anti-TFPI antibodies are fully human Fabs that can be feasibly converted to human IgG as therapeutic agent. In this example, however, the selected Fabs were converted to a chimeric antibody containing a mouse IgG constant region, so they are more suitable for testing in mouse model. The variable region of the selected antibodies was grafted into a mammalian expression vector containing mouse constant regions. The fully assembled IgG molecule was then transfected and expressed in HKB11 cells (Mei et al., Mol. Biotechnol., 2006, 34: 165-178). The culture supernatant was collected and concentrated. The anti-TFPI IgG molecules were affinity purified through a Hitrap Protein G column (GE Healthcare) following the manufacturer's instruction.

Example 5

Selection of Anti-TFPI Neutralizing Antibodies

[0176] Anti-TFPI neutralizing antibodies were selected based on their inhibition of the TFPI activity under three experimental conditions. The activity of TFPI was measured using ACTICHROME® TFPI activity assay (American Diagnostica Inc., Stamford, Conn.), a three stage chromogenic assay to measures the ability of TFPI to inhibit the catalytic activity of the TF/FVIIa complex to activate factor X to factor Xa. The neutralizing activity of the anti-TFPI antibody is proportional to the amount of the restored FXa generation. In the first setting, purified anti-TFPI antibodies were incubated with human or mouse recombinant TFPI (R&D System) at the indicated concentrations. After incubation, the samples were mixed with TF/FVIIa and FX, and the residual activity of the TF/FVIIa complex was then measured using SPECTROZYME® FXa, a highly specific fXa chromogenic substrate. This substrate was cleaved only by FXa generated in the assay, releasing a p-nitroaniline (pNA) chromophore, which was measured at 405 nm. The TFPI activity present in the sample was interpolated from a standard curve constructed using known TFPI activity levels. The assay was performed in an end-point mode. In two other settings, anti-TFPI antibodies were spiked into normal human plasma or hemophilic A plasma, and the restored FXa generation was measured.

Example 6

Anti-TFPI Antibodies Shorten Clotting Time In A Diluted Prothrombin Time (dPT) Assay

[0177] The dPT assay was carried out essentially as described in Welsch et al., Thrombosis Res., 1991, 64 (2): 213-222. Briefly, human normal plasma (FACT, George King Biomedical), human TFPI depleted plasma (American Diagnostica) or hemophilic A plasma (George King Biomedical) were prepared by mixing plasma with 0.1 volumes of control buffer or anti-TFPI antibodies. After incubation for 30 min at 25° C., plasma samples (100 μl) were combined with 200 μl of appropriately diluted (1:500 dilution) Simplastin (Biometieux) as a source of thromboplastin and the clotting time was determined using a fibrometer STA4 (Stago). Thromboplastin was diluted with PBS or 0.05 M Tris based buffer (pH 7.5) containing 0.1 M sodium chloride, 0.1% bovine serum albumin and 20 μM calcium chloride.

Example 7

Anti-TFPI Antibodies, Alone Or In Combination With Recombinant Factor VIII Or Factor IX, Shorten Blood Clotting Time In A ROTEM Assay

[0178] The ROTEM system (Pentapharm GmbH) included a four-channel instrument, a computer, plasma standards, activators and disposable cups and pins. Thrombelastographic parameters of ROTEM hemostasis systems included: Clotting Time (CT), which reflects the reaction time (the time required to obtain 2 mm amplitude following the initiation of data collection) to initiate blood clotting; Clot Formation Time (CFT) and the alpha angle to reflect clotting propaga-

tion, and the maximum amplitude and the maximum elastic modulus to reflect clot firmness. In the ROTEM assay, 300 μl of fresh citrated whole blood or plasma was assessed. All constituents were reconstituted and mixed according to the manufacturer's instructions, with data collection for the time period required for each system. Briefly, samples were mixed by withdrawing/dispensing 300 μl of blood or plasma with an automated pipette into ROTEM cups with 20 μl of $CaCl_2$ (200 mmol) added, followed immediately by mixing of the sample and initiation of data collection. Data were collected for 2 hr using a computer-controlled (software version 2.96) ROTEM system.

[0179] An exemplary result of ROTEM assay in detecting the effect of anti-TFPI antibodies in shortening blood clotting time is shown in FIGS. **3** and **5**. FIG. **3** shows that TP-2A8-Fab shortened clotting time in human hemophiliac A plasma or mouse hemophiliac A whole blood, alone or in combination with recombinant FVIII, when ROTEM system was initiated with NATEM. FIG. **5** shows that anti-TFPI antibodies in IgG format (TP-2A8, TP-3G1, and TP-3C2) shortened clotting times as compared to a negative control mouse IgG antibody. Based on these results and the understanding in the field, the skilled person would expect that these anti-TFPI antibodies also shorten clotting time in combination with recombinant FIX as compared to these antibodies alone.

Example 8

In Vitro Functional Activity of Anti-TFPI Antibodies

[0180] To investigate the TFPI antibodies in blocking the function of TFPI, both chromogenic assay ACTICHROME and diluted prothrombin time (dPT) were used to test the functional activity of the antibodies obtained from the panning and screening. In both assays, a monoclonal rat anti-TFPI antibody (R&D System) was used as positive control and human polyclonal Fab was used as negative control. In the chromogenic assay, eight of the antibodies inhibited more than 50% of TFPI activity compared with the rat monoclonal antibody (Table 4). In dPT assay, all of these eight anti-TFPI Fabs showed a highly inhibitory effect, shortening the clotting time below 80 seconds, and four of the eight Fabs shortened dPT below 70 seconds. Dose-dependence of four of representative clones in shortening the dPT is shown in FIG. **2**. However, other human anti-TFPI Fabs with low or no TFPI inhibitory activity also shortened clotting time in dPT. For example, TP-3B4 and TP-2C7, although showing less than 25% inhibitory activity, could shorten the dPT to less than 70 seconds. A simple linear regression analysis of inhibitory activity and dPT suggests significant correlation (p=0.0095) but large variance (R square=0.258).

TABLE 4

The in vitro functional activity of the anti-TFPI antibodies as determined by their inhibition activity in human TFPI assay and dPT assay.

clone	% inhibition of hTFPI activity	dPT in hemoA plasma (sec)
anti-TFPI	100%	63.5
TP-2B3	100%	74.0
TP-4B7	100%	53.9
TP-3G1	93%	75.1
TP-3C2	92%	68.9
TP-2G6	86%	62.8
TP-2A8	100%	57.9

TABLE 4-continued

The in vitro functional activity of the anti-TFPI antibodies as determined by their inhibition activity in human TFPI assay and dPT assay.

clone	% inhibition of hTFPI activity	dPT in hemoA plasma (sec)
TP-2H10	63%	79.5
TP-2G7	55%	72.2
TP-4G8	39%	73.9
TP-2G5	36%	73.2
TP-2A5	30%	70.8
TP-4E8	29%	71.9
TP-4H8	28%	76.5
TP-3B4	25%	69.1
TP-2A2	23%	70.9
TP-2C1	21%	70.9
TP-3G3	15%	70.7
TP-2E5	0%	79.0
TP-3A4	0%	72.3
TP-3C1	0%	72.3
TP-2B11	0%	82.6
TP-2C7	0%	62.5
TP-2G9	0%	82.7
Untreated	0%	92.9

[0181] One of the anti-TFPI Fab, Fab-2A8, was also tested in ROTEM assay in which either human hemophilia A plasma with a low level of factor VIII or mouse hemophilia A whole blood was used. As shown in FIG. **3**, comparing a polyclonal rabbit anti-TFPI antibody, Fab-2A8 showed similar activity in human hemophilia A plasma, decreasing clotting time (CT) from 2200 seconds to approximate 1700 seconds. When mouse hemophilia A whole blood was used, the control antibody, rabbit anti-TFPI shortened CT from 2700 seconds to 1000 seconds, whereas Fab-2A8 shorten CT from 2650 seconds to 1700 seconds. These results indicate that Fab-2A8 can significantly shorten clotting time in both human plasma and mouse blood (p=0.03).

Example 9

Function of Anti-TFPI Antibodies Following Conversion To Chimeric IgG

[0182] In-vitro assays of factor Xa generation and diluted prothrombin time indicate that at least six of the 24 anti-TFPI Fabs, TP-2A8, TP-2B3, TP-2G6, TP-3C2, TP-3G1 and TP-4B7, could block TFPI function. To facilitate in vivo study using hemophilia A mice, we converted these six anti-TFPI human Fabs into chimeric IgG, using the murine IgG1 isotype. The IgG expression vector was transfected into HKB11 cells, and the expressed antibody was collected in the culture supernatant and purified on Protein G column. When a representative clone 2G6-Fab was converted to IgG, the 2G6-IgG showed two fold increase of EC_{50} binding to human TFPI (from 0.48 nM to 0.22 nM) and 10-fold increase to mouse TFPI (from 5.18 nM to 0.51 nM). The results of IgG-2G6 binding to human and mouse TFPI are shown in FIG. **4**.

Example 10

Effect On Survival Rate In Hemophilia A (HemA) Mouse Tail Vein Transection Model

[0183] A mouse tail vein transection model has been established for pharmacologic evaluation. This model simulates the wide range of bleeding phenotypes observed between

normal individuals and severe hemophiliacs. For these studies, male hemophilia A mice (8 weeks old and 20 to 26 grams) were used. Mice were dosed via tail vein infusion with anti-TFPI monoclonal antibody (40 μg/mouse), alone or together with a clotting factor such as FVIII (0.1 IU/mouse) prior to the injury. At 24 hours post-dosing, the left vein of the tail at 2.7 mm from the tip (in diameter) was transected. Survival was observed over 24 hours post transection. Survival rate was demonstrated to be dose-dependent when given with recombinant FVIII (data not shown). Data shown in FIG. **8** were from two separate studies (n=15 and n=10, respectively). The results showed that TP-2A8-IgG significantly prolonged the survival of hemophilia A mice as compared to control mouse IgG; and, in combination with recombinant FVIII, displayed a better survival rate than either agent alone.

Example 11

Combination of Anti-TFPI Antibody With Recombinant Factor VIIa Further Shortened Clotting Time And Clot Formation Time

[0184] The combined effect of anti-TFPI antibody and recombinant FVIIa (Novo Nordisk) was assessed in a ROTEM system using EXTEM (1:1000 dilution) and mouse hemophilia A whole blood. The indicated amounts of anti-TFPI antibody, TP-2A8-IgG ("2A8"), and recombinant FVIIa ("FVIIa"), were added into 300 μl of citrated mouse hemophilia A whole blood, and blood clotting was initiated using EXTEM system. FIG. **9** shows that addition of TP-2A8-IgG or recombinant FVIIa into mouse hemophilia A whole blood shortened clotting time and clot formation time, respectively. Combination of TP-2A8-IgG and recombinant FVIIa ("2A8+FVIIa") further shortened clotting time and clot formation time, indicating that combination of anti-TFPI antibody with recombinant FVIIa is useful in the treatment of hemophilia patients with or without inhibitors.

Example 12

Anti-TFPI Antibodies Shortened Clotting Time In FVIII Inhibitor-Induced Human Hemophiliac Blood

[0185] Selected anti-TFPI antibodies, 2A8 and 4B7 were also tested in a ROTEM assay using neutralizing FVIII antibodies to induce hemophilia in whole blood drawn from non-hemophilic patienst. FIG. **10** shows that normal human blood has a clotting time of approximately 1000 seconds. In the presence of FVIII neutralizing antibodies (PAH, 100 microgram/mL), the clotting time was prolonged to approximately 5200 seconds. The prolonged clotting time was significantly shortened by addition of an anti-TFPI antibody, 2A8 or 4B7, indicating that anti-TFPI antibody is useful in the treatment of hemophilia patients with inhibitors.

Example 13

Inhibitory Anti-TFPI Antibodies Bind To Kunitz Domain 2 of Human TFPI

[0186] Western blots and ELISA were used to determine which domain(s) of TFPI of the inhibitory antibodies bind. Recombinant full length human TFPI or TFPI domains were used for these studies. ELISA was similar to Example 3. In the Western Blot, human TFPI or domains were run on 4-12% Bis-Tris SDS PAGE running buffer MES (Invitrogen, Carlsbad, Calif.) and then transferred to cellulose membrane. After incubation with inhibitory antibodies for 10 min, the membrane was washed three times using SNAPid system (Millipore, Billerica, Mass.). A HRP conjugated donkey anti-mouse antibody (Pierce, Rockford, Ill.) at 1 to 10,000 dilution was incubated with the membrane for 10 min. After a similar wash step, the membrane was developed using SuperSignal substrate (Pierce, Rockford, Ill.). Whereas the control anti-Kunitz domain 1 antibody binds to full length TFPI, truncated TFPI and domains, inhibitory anti-TFPI antibodies only bind to TFPI containing Kunitz domain 2. This indicates that binding to Kunitz domain 2 is necessary for antibody's inhibitory function.

TABLE 5

The domains bound by antibodies as determined by Western blots and ELISA

	Anti-K1	mIgG	TP-2A8	TP-2B3	TP-2G6	TP-3C2	TP-3G1	TP-4B7
Full length	+	−	+	+	+	+	+	+
K1 + K2 + K3	+	−	+	+	+	+	+	+
K1 + K2	+	−	+	+	+	+	+	+
K1	+	−	−	−	−	−	−	−

[0187] While the present invention has been described with reference to the specific embodiments and examples, it should be understood that various modifications and changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. The specification and examples are, accordingly, to be regarded in an illustrative rather then a restrictive sense. Furthermore, all articles, books, patent applications and patents referred to herein are incorporated herein by reference in their entireties.

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35 40 45

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50 55 60

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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

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His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile His
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Gly Asp Asn Asn 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

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Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
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<400> SEQUENCE: 16

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 Arg Ser Tyr
20 25 30

-continued

```
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Arg Gly Ser Ser Ser 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 Lys Tyr Arg Tyr Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 17
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc     60

tcgtgtagcg gcgataagct tggtaagaag tatgttcatt ggtaccagca gaaacccggg    120

caggcgccag ttcttgtgat ttatggtgat gataagcgtc cctcaggcat cccggaacgc    180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa    240

gacgaagcgg attattattg ccaggcttgg ggttctattt ctcgttttgt gtttggcggc    300

ggcacgaagt taaccgttct tggccag                                        327


<210> SEQ ID NO 18
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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 Lys Leu Gly Lys Lys Tyr Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Gly Asp Asp Lys 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 Ala Trp Gly Ser Ile Ser Arg Phe
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 19
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60
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agctgcgcgg cctccggatt tacctttact tcttattcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atctcttata ctggtagcaa tacccattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgctttt 300

cttggttata aggagtctta ttttgatatt tggggccaag gcaccctggt gacggttagc 360

tcagc 365

<210> SEQ ID NO 20
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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 Thr Ser Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Tyr Thr Gly Ser Asn Thr His 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 Ala Phe Leu Gly Tyr Lys Glu Ser Tyr Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 21
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggtaataag tatgctcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattatgat aataagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg actcctggtt ctaatactat ggtgtttggc 300

ggcggcacga ggttaaccgt tcttggccag 330

<210> SEQ ID NO 22
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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

-continued

```
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Asn Lys Tyr Ala
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Asn Lys 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 Thr Pro Gly Ser Asn Thr
                85                  90                  95

Met Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 23
<211> LENGTH: 350
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60

agctgcgcgg cctccggatt tacctttttct tcttattcta tgtcttgggt gcgccaagcc    120

tctgggaagg gtctcgagtg ggtgagctct atcaagggtt ctggtagcaa tacctattat    180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaatggt    300

ggtcttattg atgtttgggg ccaaggcacc ctggtgacgg ttagctcagc               350


<210> SEQ ID NO 24
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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

Ser Met Ser Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Lys Gly Ser Gly Ser Asn 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 Asn Gly Gly Leu Ile Asp Val Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser
        115


<210> SEQ ID NO 25
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 25

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gaatattggt tctaattatc tggcttggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat ggtgcttcta ctcgtgcaac tggggtcccg 180

gcgcgtttta acggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240

cctgaagact ttgcggttta ttattgccag cagcttaatt ctattcctgt tacctttggc 300

cagggtacga aagttgaaat taaacgtacg 330

<210> SEQ ID NO 26
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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 Asn Ile Gly Ser Asn
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 Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Asn
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 Leu Asn Ser Ile Pro
85 90 95

Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> SEQ ID NO 27
<211> LENGTH: 374
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcatgatct attatcgtag caagtggtat 180

aactcttatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtactatgt ctaagtatgg tggtcctggt atggatgttt ggggccaagg caccctggtg 360

acggttagct cagc 374

<210> SEQ ID NO 28
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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

-continued

```
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Met Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ser 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 Thr Met Ser Lys Tyr Gly Gly Pro Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 29
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc     60

tcgtgtagcg gcgatgctct tggtacttat tatgcttatt ggtaccagca gaaacccggg    120

caggcgccag ttcttgtgat ttatggtgat atgaatcgtc cctcaggcat cccggaacgc    180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa    240

gacgaagcgg attattattg ccagtcttat gatgctggtg ttaagcctgc tgtgtttggc    300

ggcggcacga agttaaccgt tcttggccag                                     330


<210> SEQ ID NO 30
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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 Thr Tyr Tyr Ala
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Gly Asp Met Asn 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 Ala Gly Val Lys Pro
                85                  90                  95

Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 31
<211> LENGTH: 355
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 31

caggtgcaat tggtggaaag cggcggcggc ctggtgcacc gggcggcagc ctgcgtctga 60

gctgcgcggc ctccggattt acctttttcta attattctat gacttgggtg cgccaagccc 120

ctgggaaggg tctcgagtgg gtgagcggta tctcttataa tggtagcaat acctattatg 180

cggatagcgt gaaaggccgt tttaccattt cacgtgataa ttcgaaaaac accctgtatc 240

tgcaaatgaa cagcctgcgt gcggaagata cggccgtgta ttattgcgcg cgtatttatt 300

atatgaatct tcttgctggt tggggccaag gcaccctggt gacggttagc tcagc 355

<210> SEQ ID NO 32
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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 Asn Tyr
20 25 30

Ser Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asn Gly Ser Asn 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 Ile Tyr Tyr Met Asn Leu Leu Ala Gly Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 33
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tcgtggttat tatgcttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg gattctcctt atgttcatgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 34
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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

-continued

```
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Arg Gly Tyr Tyr Ala
            20                  25                  30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Glu Asp Asn Asn 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 Ser Pro Tyr Val His
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 35
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg     60

agctgcaaag cctccggata tacctttact ggtaattcta tgcattgggt ccgccaagcc    120

cctgggcagg gtctcgagtg gatgggcact atctttccgt atgatggcac tacgaagtac    180

gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat    240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtgtt    300

cattcttatt ttgattattg gggccaaggc accctggtga cggttagctc agc           353


<210> SEQ ID NO 36
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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 Gly Asn
            20                  25                  30

Ser Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Thr Ile Phe Pro Tyr Asp Gly Thr Thr Lys 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 Gly Val His Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 37
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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-continued

<400> SEQUENCE: 37

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctattcgt tcttatctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttataag gcttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccatcag tattctgatt ctcctgttac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 38
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Ser Asp Ser Pro Val
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 39
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcatgatct atcatcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttattctt ctattggtca tatggattat tggggccaag gcaccctggt gacggttagc 360

tcagc 365

<210> SEQ ID NO 40
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

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

-continued

```
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Met Ile Tyr His 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 Tyr Ser Ser Ile Gly His Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 41
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc     60

tcgtgtagcg gcgattctat tggttcttat tatgctcatt ggtaccagca gaaacccggg    120

caggcgccag ttcttgtgat ttattatgat tctaagcgtc cctcaggcat cccggaacgc    180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa    240

gacgaagcgg attattattg ccaggcttat actggtcagt ctatttctcg tgtgtttggc    300

ggcggcacga agttaaccgt tcttggccag                                     330


<210> SEQ ID NO 42
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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 Ser Ile Gly Ser Tyr Tyr Ala
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Ser Lys 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 Ala Tyr Thr Gly Gln Ser Ile Ser
                85                  90                  95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 43
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 43

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct ccttatgtta tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctct atctcttctt cttctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtgat 300

tcttatatgt atgatgtttg gggccaaggc accctggtga cggttagctc agc 353

<210> SEQ ID NO 44
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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 Pro Tyr
20 25 30

Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Ser Ser Ser Ser Asn 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 Asp Ser Tyr Met Tyr Asp Val Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 45
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca ggatattcgt aataatctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatgct gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag cgtaatggtt ttcctcttac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 46
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

-continued

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Gly Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 47
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcattatct attatcgtag caagtggtat 180

aaccattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttctaatt ggtctggtta ttttgattat tggggccaag gcaccctggt gacggttagc 360

tcagc 365

<210> SEQ ID NO 48
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

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 Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Ile Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn His 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 Ser Asn Trp Ser Gly Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 49

-continued

<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

gatatcgtga tgacccagag cccactgagc ctgccagtga ctccgggcga gcctgcgagc 60

attagctgca gaagcagcca aagcctgctt cattctaatg gctatactta tctgtcttgg 120

taccttcaaa aaccaggtca aagcccgcag ctattaattt atcttggttc taatcgtgcc 180

agtggggtcc cggatcgttt tagcggctct ggatccggca ccgattttac cctgaaaatt 240

agccgtgtgg aagctgaaga cgtgggcgtg tattattgcc agcagtatga taatgctcct 300

attacctttg gccagggtac gaaagttgaa attaaacgta cg 342

<210> SEQ ID NO 50
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Thr Tyr Leu Ser Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
85 90 95

Asp Asn Ala Pro Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr

<210> SEQ ID NO 51
<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggccttatct attatcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttttggtg atactaatcg taatggtact gatgtttggg gccaaggcac cctggtgacg 360

gttagctcag c 371

<210> SEQ ID NO 52
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 52

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 Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Leu Ile 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 Phe Gly Asp Thr Asn Arg Asn Gly Thr Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 53
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatggtgtta attatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttctgctg ataagtttac tatgtctatt 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> SEQ ID NO 54
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

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 Ile 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 Gly Val Asn Tyr 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 Ser Ser Ala Asp Lys Phe
85 90 95

Thr Met Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

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Gln

<210> SEQ ID NO 55
<211> LENGTH: 306
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

gacctgtgcg atttccggag atagcgtgag ctctaattct gctgcttggg gttggattcg 60

ccagtctcct gggcgtggcc tcgagtggct gggcatgatc tattatcgta gcaagtggta 120

taacgattat gcggtgagcg tgaaaagccg gattaccatc aacccggata cttcgaaaaa 180

ccagtttagc ctgcaactga acagcgtgac cccggaagat acggccgtgt attattgcgc 240

gcgtgttaat cagtatactt cttctgatta ttggggccaa ggcaccctgg tgacggttag 300

ctcagc 306

<210> SEQ ID NO 56
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

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 Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Met Ile 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 Val Asn Gln Tyr Thr Ser Ser Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 57
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gcctatttat aattctctgt cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt gtttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccttcag gttgataatc ttcctattac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 58

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<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Pro Ile Tyr Asn Ser
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Val Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Val Asp Asn Leu Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 59
<211> LENGTH: 374
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttggtc ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcatgatct tttatcgtag caagtggaat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtgttaatg ctaatggtta ttatgcttat gttgatcttt ggggccaagg caccctggtg 360

acggttagct cagc 374

<210> SEQ ID NO 60
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

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 Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Met Ile Phe Tyr Arg Ser Lys Trp Asn 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 Val Asn Ala Asn Gly Tyr Tyr Ala Tyr Val Asp

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            100                 105                 110

Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 61
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc     60

ctgagctgca gagcgagcca gtctgtttct tctcagtatc tggcttggta ccagcagaaa    120

ccaggtcaag caccgcgtct attaatttat gctgcttctt ctcgtgcaac tggggtcccg    180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa    240

cctgaagact ttgcggttta ttattgccag caggattcta atcttcctgc tacctttggc    300

cagggtacga aagttgaaat taaacgtacg                                     330


<210> SEQ ID NO 62
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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 Gln
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Ala 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 Asp Ser Asn Leu Pro
                85                  90                  95

Ala Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210> SEQ ID NO 63
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60

agctgcgcgg cctccggatt tacctttttat aagtatgcta tgcattgggt gcgccaagcc    120

cctgggaagg gtctcgagtg ggtgagcggt atccagtatg atggtagcta tacctattat    180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttattat    300

tgtaagtgtg ttgatctttg gggccaaggc accctggtga cggttagctc a              351


<210> SEQ ID NO 64
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-continued

<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

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 Tyr Lys Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Gln Tyr Asp Gly Ser Tyr 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 Cys Lys Cys Val Asp Leu Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 65
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tcgtaagttt tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtact aataagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat gattctaagt ttaatactgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 66
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

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 Asn Ile Arg Lys Phe Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Thr Asn Lys 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 Ser Lys Phe Asn Thr
85 90 95

-continued

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 67
<211> LENGTH: 359
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatgcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atcctttctg atggtagctc tacctcttat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttatcct 300

gattggggtt ggtatactga tgtttggggc caaggcaccc tggtgacggt tagctcagc 359

<210> SEQ ID NO 68
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

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 Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Leu Ser Asp Gly Ser Ser Thr Ser 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 Pro Asp Trp Gly Trp Tyr Thr Asp Val Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 69
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgatgctct tcgtaagcat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat gataagcctt atcctattct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

-continued

<210> SEQ ID NO 70
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

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 Arg Lys His Tyr Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Asn 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 Lys Pro Tyr Pro Ile
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 71
<211> LENGTH: 356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatgcta tgacttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atctcttatt ctggtagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgttggt 300

tattattatg gttttgatta ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> SEQ ID NO 72
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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 Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Tyr Ser Gly Ser Asn 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 Val Gly Tyr Tyr Tyr Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

-continued

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 73
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gaatgtttct tctaattatc tggcttggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat gatgcttcta atcgtgcaac tggggtcccg 180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240

cctgaagact ttgcggttta ttattgccag cagttttatg attctcctca gacctttggc 300

cagggtacga aagttgaaat taaacgtacg 330

<210> SEQ ID NO 74
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

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 Asn Val Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Asn 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 Tyr Asp Ser Pro
85 90 95

Gln Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> SEQ ID NO 75
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttggtc ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggctttatct attatcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtcataatc ctgatcttgg ttttgattat tggggccaag gcaccctggt gacggttagc 360

tcagc 365

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<210> SEQ ID NO 76
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

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 Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Phe Ile 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 His Asn Pro Asp Leu Gly Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 77
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gtatgttact tcttcttatc tggcttggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat ggttcttctc gtgcaactgg ggtcccggcg 180

cgttttagcg gctctggatc cggcacggat tttaccctga ccattagcag cctggaacct 240

gaagactttg cgacttatta ttgccagcag tattcttctt ctcctattac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 78
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

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 Tyr Val Thr 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 Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Ser Pro Ile
85 90 95

-continued

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 79
<211> LENGTH: 362
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tcttcttctg ctgcttggtc ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcattatct attatcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtcattcta tggttggttt tgatgtttgg ggccaaggca ccctggtgac ggttagctca 360

gc 362

<210> SEQ ID NO 80
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

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 Ser
20 25 30

Ser Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Ile Ile 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 His Ser Met Val Gly Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 81
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggtacttat tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gattctaata atgagtctat tgtgtttggc 300

-continued

ggcggcacga agttaaccgt tcttggccag 330

<210> SEQ ID NO 82
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

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 Asn Leu Gly Thr Tyr Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Asn 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 Thr Tyr Asp Ser Asn Asn Glu Ser
85 90 95

Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 83
<211> LENGTH: 368
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttaat tcttatgcta tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atctcttcta attctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaagggt 300

ggtggtgagc atggtttttt tccttctgat atttggggcc aaggcaccct ggtgacggtt 360

agctcagc 368

<210> SEQ ID NO 84
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

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 Asn 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 Asn Ile Ser Ser Asn Ser Ser Asn 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

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Lys Gly Gly Gly Glu His Gly Phe Phe Pro Ser Asp Ile Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 85
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc     60

tcgtgtacgg gtactagcag cgatcttggt ggttttaata ctgtgtcttg gtaccagcag    120

catcccggga aggcgccgaa acttatgatt tattctgttt cttctcgtcc ctcaggcgtg    180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg    240

caagcggaag acgaagcgga ttattattgc cagtcttatg atcttaataa tcttgtgttt    300

ggcggcggca cgaagttaac cgttcttggc cag                                 333


<210> SEQ ID NO 86
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

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 Leu Gly Gly Phe
            20                  25                  30

Asn Thr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Ser Val Ser Ser 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 Asn
                85                  90                  95

Asn Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 87
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60

agctgcgcgg cctccggatt tacctttaat tcttatgcta tgacttgggt gcgccaagcc    120

cctgggaagg gtctcgagtg ggtgagcgct atcaagtctg atggtagcaa tacctattat    180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaatgat    300
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tctggttggt ttgatgtttg gggccaaggc accctggtga cggttagctc agc          353


<210> SEQ ID NO 88
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

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 Asn Ser Tyr
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Lys Ser Asp Gly Ser Asn 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 Asn Asp Ser Gly Trp Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 89
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc     60

ctgagctgca gagcgagcca gtctgtttct tctttttatc tggcttggta ccagcagaaa    120

ccaggtcaag caccgcgtct attaatttat ggttcttctt ctcgtgcaac tggggtcccg    180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa    240

cctgaagact ttgcgactta ttattgccag cagtatgatt ctactccttc tacctttggc    300

cagggtacga aagttgaaat taaacgtacg                                     330


<210> SEQ ID NO 90
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

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 Phe
            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 Ser 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
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Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Ser Thr Pro
85 90 95

Ser Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> SEQ ID NO 91
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaatggtg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggctttatct atcgtcgtag caagtggtat 180

aactcttatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtcaggatg gtatgggtgg tatggattct tggggccaag gcaccctggt gacggttagc 360

tcagc 365

<210> SEQ ID NO 92
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

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

Gly Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Phe Ile Tyr Arg Arg Ser Lys Trp Tyr Asn Ser 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 Gln Asp Gly Met Gly Gly Met Asp Ser Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 93
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggttctcgt tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttgttgtgat ttatgatgat tctgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

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gacgaagcgg attattattg cgctgcttat acttttttatg ctcgtactgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 94
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

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 Asn Ile Gly Ser Arg Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val 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 Ala Ala Tyr Thr Phe Tyr Ala Arg Thr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 95
<211> LENGTH: 359
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct aattattatc tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggt atctcttata atggtagctc taccaattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtatgtgg 300

cgttattctc ttggtgctga ttcttggggc caaggcaccc tggtgacggt tagctcagc 359

<210> SEQ ID NO 96
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

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 Asn Tyr
20 25 30

Tyr Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asn Gly Ser Ser Thr Asn 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

-continued

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Met Trp Arg Tyr Ser Leu Gly Ala Asp Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 97
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggttctaag tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttgttgtgat ttatgaggat tctgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg gataagtctg agggttatgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 98
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

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 Asn Ile Gly Ser Lys Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr
35 40 45

Glu 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 Lys Ser Glu Gly Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 99
<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttaat aataatgcta tttcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atcaattctt cttctagctc tacctcttat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtcat 300

-continued

catcgtggtc attcttgggc ttcttttatt gattattggg gccaaggcac cctggtgacg 360

gttagctcag c 371

<210> SEQ ID NO 100
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

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 Asn Asn Asn
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Asn Ser Ser Ser Ser Ser Thr Ser 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 His Arg Gly His Ser Trp Ala Ser Phe Ile Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 101
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tcgtgataag tatgcttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattctaag tctgagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctcttcttat actcttaatc ctaatcttaa ttatgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cag 333

<210> SEQ ID NO 102
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

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 Asn Leu Arg 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

Ser Lys Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

-continued

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 Ser Ser Tyr Thr Leu Asn Pro Asn Leu
85 90 95

Asn Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 103
<211> LENGTH: 347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattgga tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctct atctcttatg attctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttatggt 300

ggtatggatt attggggcca aggcaccctg gtgacggtta gctcagc 347

<210> SEQ ID NO 104
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Tyr Asp Ser Ser Asn 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 Gly Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 105
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

gatatcgaac tgacccagcc ggcttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tcgttctaag tatgctcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

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tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctgcttat gctatgggtt cttctcctgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 106
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Arg Ser Lys Tyr Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Asn 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 Ser Ala Tyr Ala Met Gly Ser Ser Pro
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 107
<211> LENGTH: 356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atctcttata tgggtagcaa taccaattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtctt 300

tttcctggtt attttgatta ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> SEQ ID NO 108
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

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

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Tyr Met Gly Ser Asn Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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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 Leu Phe Pro Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 109
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gaatatttct aattatctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt acttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tatggtaata atcctactac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 110
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Asn Asn Pro Thr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 111
<211> LENGTH: 377
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaatggtg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggccatatct attatcgtag caagtggtat 180

aactcttatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

-continued

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttggggtg gtattcatga tggtgatatt tattttgatt attggggcca aggcaccctg 360

gtgacggtta gctcagc 377

<210> SEQ ID NO 112
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

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

Gly Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly His Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ser 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 Gly Gly Ile His Asp Gly Asp Ile Tyr Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 113
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctattact aattatctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatgat gtttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattctggtt atcctcttac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 114
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Val Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

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```
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Gly Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105
```

<210> SEQ ID NO 115
<211> LENGTH: 362
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

```
caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg     60

acctgtgcga tttccggaga tagcgtgagc tcttcttctg ctgcttggtc ttggattcgc    120

cagtctcctg ggcgtggcct cgagtggctg ggcatgatct attatcgtag caagtggtat    180

aaccattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac    240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg    300

cgtggtggtt ctggtgttat ggatgtttgg ggccaaggca ccctggtgac ggttagctca    360

gc                                                                     362
```

<210> SEQ ID NO 116
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

```
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 Ser
            20                  25                  30

Ser Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Met Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn His 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 Gly Ser Gly Val Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> SEQ ID NO 117
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

```
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc     60

attacctgca gagcgagcca gtctattaat ccttatctga attggtacca gcagaaacca    120
```

-continued

ggtaaagcac cgaaactatt aatttatgct gcttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag cttgataatc gttctattac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

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

<400> SEQUENCE: 118

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Pro Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Asp Asn Arg Ser Ile
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 119
<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcgttatct attatcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgtgctcgtg ctaagaagtc tggtggtttt gattattggg gccaaggcac cctggtgacg 360

gttagctcag c 371

<210> SEQ ID NO 120
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

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 Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

-continued

Trp Leu Gly Val Ile 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 Ala Arg Ala Lys Lys Ser Gly Gly Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 121
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggttctaag tttgctcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttat acttctcgtt ctcattctta tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

<210> SEQ ID NO 122
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

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 Ser Leu Gly Ser Lys Phe Ala
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Ser Asn 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 Ser Thr Tyr Thr Ser Arg Ser His Ser
85 90 95

Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 123
<211> LENGTH: 350
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt taccttttct tcttatgctt cttgggtgcg ccaagcccct 120

-continued

gggaagggtc tcgagtgggt gagcggtatc tctggtgatg gtagcaatac ccattatgcg 180

gatagcgtga aaggccgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg ttatgataat 300

ttttattttg atgtttgggg ccaaggcacc ctggtgacgg ttagctcagc 350

<210> SEQ ID NO 124
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

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 Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
35 40 45

Gly Ile Ser Gly Asp Gly Ser Asn Thr His Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Tyr Asp Asn Phe Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 125
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggttcttat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat gattctactg gtcttcttgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 126
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 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 Asn Ile Gly Ser Tyr Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

-continued

```
        35                  40                  45

Asp Asp Ser Asn 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 Ser Thr Gly Leu Leu
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 127
<211> LENGTH: 377
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60

agctgcgcgg cctccggatt tacctttttct aattatgcta tgacttgggt gcgccaagcc    120

cctgggaagg gtctcgagtg ggtgagcgtt atctcttctg ttggtagcaa tacctattat    180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcctact    300

aaggctggtc gtacttggtg gtggggtcct tatatggatg tttggggcca aggcaccctg    360

gtgacggtta gctcagc                                                   377


<210> SEQ ID NO 128
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

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 Asn Tyr
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Val Ile Ser Ser Val Gly Ser Asn 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 Pro Thr Lys Ala Gly Arg Thr Trp Trp Trp Gly Pro Tyr Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 129
<211> LENGTH: 312
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129
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-continued

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggttcttat tttgcttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgagggttct aatgtgtttg gcggcggcac gaagttaacc 300

gttcttggcc ag 312

<210> SEQ ID NO 130
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

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 Asn Ile Gly Ser Tyr Phe 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 Asn 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 Glu Gly Ser Asn Val Phe Gly Gly Gly
85 90 95

Thr Lys Leu Thr Val Leu Gly Gln
100

<210> SEQ ID NO 131
<211> LENGTH: 368
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact gattattgga ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atccagccgt ctgatagcga taccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttttatg 300

tggtggggta agtatgattc tggttttgat gtttggggcc aaggcaccct ggtgacggtt 360

agctcagc 368

<210> SEQ ID NO 132
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

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 Asp Tyr
20 25 30

-continued

```
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Gln Pro Ser Asp Ser Asp Thr Asn 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 Met Trp Trp Gly Lys Tyr Asp Ser Gly Phe Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 133
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc     60

tcgtgtagcg gcgataatct tccttctaag tctgtttatt ggtaccagca gaaacccggg    120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc    180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa    240

gacgaagcgg attattattg ccagtcttgg acttctcgtc ctatggttgt gtttggcggc    300

ggcacgaagt taaccgttct tggccag                                        327


<210> SEQ ID NO 134
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 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 Asn Leu Pro Ser Lys Ser Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Gly Asp Asn Asn 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 Thr Ser Arg Pro Met Val
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 135
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (156)..(156)
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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 135

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggt atctcntatt cttctagctt tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgctctt 300

ggtggtggtg ttgattattg gggccaaggc accctggtga cggttagctc agc 353

<210> SEQ ID NO 136
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

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

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Ser Ser Ser Phe 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 Ala Leu Gly Gly Gly Val Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 137
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gggtatttct tcttatctgc attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt gcttctactt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag cagaatggtt atcctttac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 138
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

-continued

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30

Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gln Asn Gly Tyr Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105
```

<210> SEQ ID NO 139
<211> LENGTH: 374
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

```
caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg     60

acctgtgcga tttccggaga tagcgtgagc tctaattctg gtggttgggg ttggattcgc    120

cagtctcctg ggcgtggcct cgagtggctg ggccttatct attatcgtag caagtggtat    180

aacgcttatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac    240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg    300

cgttatcttg gttctaattt ttatgtttat tctgatgttt ggggccaagg caccctggtg    360

acggttagct cagc                                                      374
```

<210> SEQ ID NO 140
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

```
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 Gly Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Leu Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ala 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 Tyr Leu Gly Ser Asn Phe Tyr Val Tyr Ser Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

-continued

<210> SEQ ID NO 141
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gaatattcat tctcatctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatgat gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattatgatt atcctcttac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 142
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile His Ser His
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asp Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 143
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattcta tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctct atctcttctt cttctagcaa tacctattat 180

ggggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtatgcat 300

tataagggta tggatatttg gggccaaggc accctggtga cggttagctc agc 353

<210> SEQ ID NO 144
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

-continued

```
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

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Ser Ser Ser Ser Asn Thr Tyr Tyr Gly 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 Met His Tyr Lys Gly Met Asp Ile Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 145
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc     60

tcgtgtagcg gcgataagct tggtaagtat tatgcttatt ggtaccagca gaaacccggg    120

caggcgccag ttcttgtgat ttatggtgat tctaagcgtc cctcaggcat cccggaacgc    180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa    240

gacgaagcgg attattattg ctcttctgct gcttttggtt ctactgtgtt tggcggcggc    300

acgaagttaa ccgttcttgg ccag                                           324


<210> SEQ ID NO 146
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

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 Lys Leu Gly Lys Tyr Tyr Ala
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Gly Asp Ser Lys 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 Ser Ser Ala Ala Phe Gly Ser Thr Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 147
<211> LENGTH: 350
```

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttaat tcttattata tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atctcttctt ctggtagcaa taccaattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgttcat 300

tatggttttg atttttgggg ccaaggcacc ctggtgacgg ttagctcagc 350

<210> SEQ ID NO 148
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 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 Asn Ser Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Ser Ser Gly Ser Asn Thr Asn 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 Val His Tyr Gly Phe Asp Phe Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 149
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgatgctct tggttctaag tttgctcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctgagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttat gattctggtc ttctttatgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 150
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

-continued

```
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 Ser Lys Phe Ala
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Asp Asp Ser Glu 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 Ala Tyr Asp Ser Gly Leu Leu Tyr
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 151
<211> LENGTH: 359
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg     60

agctgcgcgg cctccggatt tacctttcgt aattatgcta tgaattgggt gcgccaagcc    120

cctgggaagg gtctcgagtg ggtgagcgtt atctctggtt cttctagcta tacctattat    180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat    240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgctgat    300

cttccttata tggtttttga ttattggggc caaggcaccc tggtgacggt tagctcagc     359


<210> SEQ ID NO 152
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 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 Arg Asn Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Val Ile Ser Gly Ser Ser Ser Tyr 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 Ala Asp Leu Pro Tyr Met Val Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 153
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-continued

<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgatgctct tggtaagtat tatgcttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat actactcgtt ctcttgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 154
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

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 Lys Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Lys 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 Thr Thr Arg Ser Leu Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 155
<211> LENGTH: 353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatggta tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcctt atctctggtg tttctagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttcttat 300

cttggttatt ttgatgtttg gggccaaggc accctggtga cggttagctc agc 353

<210> SEQ ID NO 156
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

-continued

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Val Ser Ser 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 Ser Tyr Leu Gly Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 157
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

gatatcgtga tgacccagag cccactgagc ctgccagtga ctccgggcga gcctgcgagc 60

attagctgca gaagcagcca aagcctggtt ttttctgatg gcaatactta tctgaattgg 120

taccttcaaa aaccaggtca aagcccgcag ctattaattt ataagggttc taatcgtgcc 180

agtggggtcc cggatcgttt tagcggctct ggatccggca ccgattttac cctgaaaatt 240

agccgtgtgg aagctgaaga cgtgggcgtg tattattgcc agcagtatga ttcttatcct 300

cttacctttg gccagggtac gaaagttgaa attaaacgta cg 342

<210> SEQ ID NO 158
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Phe Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
85 90 95

Asp Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr

<210> SEQ ID NO 159

-continued

<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

caggtgcaat tgcaacagtc tggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60

acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttggtc ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggcattatct ataagcgtag caagtggtat 180

aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttggcatt ctgataagca ttggggtttt gattattggg gccaaggcac cctggtgacg 360

gttagctcag c 371

<210> SEQ ID NO 160
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

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 Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Ile Ile Tyr Lys 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 His Ser Asp Lys His Trp Gly Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 161
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgatgctct tggttctaag tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat acttattctc ttaatcaggt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 162
<211> LENGTH: 109
<212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

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 Ser Lys Tyr Val
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Lys 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 Thr Tyr Ser Leu Asn Gln
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 163
<211> LENGTH: 356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttaat gattatgcta tgtcttgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcctt atcgagtctg tttctagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtactatt 300

ggtgttcttt gggatgatgt ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> SEQ ID NO 164
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

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 Asn Asp Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Glu Ser Val Ser Ser 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 Ile Gly Val Leu Trp Asp Asp Val Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

-continued

<210> SEQ ID NO 165
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataagct tggttctaag tctgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatcgtgat actgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gattatattc ttaatgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 166
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

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 Lys Leu Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Arg Asp Thr 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 Thr Tyr Asp Tyr Ile Leu Asn Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 167
<211> LENGTH: 359
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct acttatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcact atctctggtt atggtagctt tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaatggt 300

cgtaagtatg gtcagatgga taattggggc caaggcaccc tggtgacggt tagctcagc 359

<210> SEQ ID NO 168
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 168

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 Thr Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Tyr Gly Ser Phe 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 Asn Gly Arg Lys Tyr Gly Gln Met Asp Asn Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 169
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tggtaagaag tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctactgct gattctgtta ttacttataa gaatgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cag 333

<210> SEQ ID NO 170
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

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 Ser Ile Gly Lys Lys Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asp Asn Asn 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 Ser Thr Ala Asp Ser Val Ile Thr Tyr
85 90 95

Lys Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

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<210> SEQ ID NO 171
<211> LENGTH: 362
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct gatcatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt atcgagtatt ctggtagcaa gaccaattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggtgat 300

tattatcctt atcttgtttt tgctatttgg ggccaaggca ccctggtgac ggttagctca 360

gc 362

<210> SEQ ID NO 172
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

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 Asp His
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Glu Tyr Ser Gly Ser Lys Thr Asn 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 Asp Tyr Tyr Pro Tyr Leu Val Phe Ala Ile Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 173
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Ser Gly Asp Asn Ile Arg Thr Tyr Tyr Val His
1 5 10

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

<400> SEQUENCE: 174

Ser Gly Asp Asn Ile Pro Glu Lys Tyr Val His
1 5 10

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<210> SEQ ID NO 175
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Ser Gly Asp Lys Ile Gly Ser Lys Tyr Val Tyr
1 5 10

<210> SEQ ID NO 176
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Ser Gly Asp Asn Leu Arg Asn Tyr Tyr Ala His
1 5 10

<210> SEQ ID NO 177
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Ser Gly Asp Lys Leu Gly Lys Lys Tyr Val His
1 5 10

<210> SEQ ID NO 178
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Ser Gly Asp Asn Leu Gly Asn Lys Tyr Ala His
1 5 10

<210> SEQ ID NO 179
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

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

<210> SEQ ID NO 180
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

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

<210> SEQ ID NO 181
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

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

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<210> SEQ ID NO 182
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

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

<210> SEQ ID NO 183
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Ser Gly Asp Ser Ile Gly Ser Tyr Tyr Ala His
1 5 10

<210> SEQ ID NO 184
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

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

<210> SEQ ID NO 185
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Thr Tyr Leu Ser
1 5 10 15

<210> SEQ ID NO 186
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

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

<210> SEQ ID NO 187
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Arg Ala Ser Gln Pro Ile Tyr Asn Ser Leu Ser
1 5 10

<210> SEQ ID NO 188
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

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

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<210> SEQ ID NO 189
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Ser Gly Asp Asn Ile Arg Lys Phe Tyr Val His
1 5 10

<210> SEQ ID NO 190
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Ser Gly Asp Ala Leu Arg Lys His Tyr Val Tyr
1 5 10

<210> SEQ ID NO 191
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

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

<210> SEQ ID NO 192
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Arg Ala Ser Gln Tyr Val Thr Ser Ser Tyr Leu Ala
1 5 10

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

<400> SEQUENCE: 193

Ser Gly Asp Asn Leu Gly Thr Tyr Tyr Val His
1 5 10

<210> SEQ ID NO 194
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

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

<210> SEQ ID NO 195
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Arg Ala Ser Gln Ser Val Ser Ser Phe Tyr Leu Ala

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1 5 10

<210> SEQ ID NO 196
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

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

<210> SEQ ID NO 197
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Ser Gly Asp Asn Ile Gly Ser Lys Tyr Val His
1 5 10

<210> SEQ ID NO 198
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Ser Gly Asp Asn Leu Arg Asp Lys Tyr Ala Ser
1 5 10

<210> SEQ ID NO 199
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Ser Gly Asp Asn Leu Arg Ser Lys Tyr Ala His
1 5 10

<210> SEQ ID NO 200
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

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

<210> SEQ ID NO 201
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Arg Ala Ser Gln Ser Ile Thr Asn Tyr Leu Asn
1 5 10

<210> SEQ ID NO 202
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

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Arg Ala Ser Gln Ser Ile Asn Pro Tyr Leu Asn
1 5 10

<210> SEQ ID NO 203
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Ser Gly Asp Ser Leu Gly Ser Lys Phe Ala His
1 5 10

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

<400> SEQUENCE: 204

Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Ala Tyr
1 5 10

<210> SEQ ID NO 205
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

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

<210> SEQ ID NO 206
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Ser Gly Asp Asn Leu Pro Ser Lys Ser Val Tyr
1 5 10

<210> SEQ ID NO 207
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu His
1 5 10

<210> SEQ ID NO 208
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

Arg Ala Ser Gln Asn Ile His Ser His Leu Asn
1 5 10

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

<400> SEQUENCE: 209

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Ser Gly Asp Lys Leu Gly Lys Tyr Tyr Ala Tyr
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Ser Gly Asp Ala Leu Gly Ser Lys Phe Ala His
1 5 10

<210> SEQ ID NO 211
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Ser Gly Asp Ala Leu Gly Lys Tyr Tyr Ala Ser
1 5 10

<210> SEQ ID NO 212
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

Arg Ser Ser Gln Ser Leu Val Phe Ser Asp Gly Asn Thr Tyr Leu Asn
1 5 10 15

<210> SEQ ID NO 213
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

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

<210> SEQ ID NO 214
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Ser Gly Asp Lys Leu Gly Ser Lys Ser Val His
1 5 10

<210> SEQ ID NO 215
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

Ser Gly Asp Ser Ile Gly Lys Lys Tyr Val His
1 5 10

<210> SEQ ID NO 216
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 216

Gly Asp Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 217
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 218
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Asp Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 219
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Tyr Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 220
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Gly Asp Asp Lys Arg Pro Ser
1 5

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

<400> SEQUENCE: 221

Tyr Asp Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 222
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> SEQ ID NO 223
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 223

Gly Asp Met Asn Arg Pro Ser
1 5

<210> SEQ ID NO 224
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Glu Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 225
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

Lys Ala Ser Asn Leu Gln Ser
1 5

<210> SEQ ID NO 226
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

Tyr Asp Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 227
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 228
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Leu Gly Ser Asn Arg Ala Ser
1 5

<210> SEQ ID NO 229
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Gly Val Asn Tyr Arg Pro Ser
1 5

<210> SEQ ID NO 230
<211> LENGTH: 7
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

Gly Val Ser Asn Leu Gln Ser
1 5

<210> SEQ ID NO 231
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

Ala Ala Ser Ser Arg Ala Thr
1 5

<210> SEQ ID NO 232
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Gly Thr Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 233
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 234
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> SEQ ID NO 235
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Gly Ser Ser Arg Ala Thr
1 5

<210> SEQ ID NO 236
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 237
<211> LENGTH: 7

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Ser Val Ser Ser Arg Pro Ser
1 5

<210> SEQ ID NO 238
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Gly Ser Ser Ser Arg Ala Thr
1 5

<210> SEQ ID NO 239
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> SEQ ID NO 240
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

Glu Asp Ser Asp Arg Pro Ser
1 5

<210> SEQ ID NO 241
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

Ser Lys Ser Glu Arg Pro Ser
1 5

<210> SEQ ID NO 242
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 243
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

Gly Thr Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 244

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

Asp Val Ser Asn Leu Gln Ser
1 5

<210> SEQ ID NO 245
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

Ala Ala Ser Asn Leu Gln Ser
1 5

<210> SEQ ID NO 246
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

Asp Asp Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 247
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

Asp Asp Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 248
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Asp Asp Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 249
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 250
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

Gly Ala Ser Thr Leu Gln Ser
1 5

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<210> SEQ ID NO 251
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Asp Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 252
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

Gly Asp Ser Lys Arg Pro Ser
1 5

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

<400> SEQUENCE: 253

Asp Asp Ser Glu Arg Pro Ser
1 5

<210> SEQ ID NO 254
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

Gly Asp Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 255
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

Lys Gly Ser Asn Arg Ala Ser
1 5

<210> SEQ ID NO 256
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

Gly Asp Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 257
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

Arg Asp Thr Asp Arg Pro Ser
1 5

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<210> SEQ ID NO 258
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 259
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

Gln Ser Tyr Asp Ser Glu Ala Asp Ser Glu Val
1 5 10

<210> SEQ ID NO 260
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

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

<210> SEQ ID NO 261
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Ala Ser Tyr Asp Ser Ile Tyr Ser Tyr Trp Val
1 5 10

<210> SEQ ID NO 262
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

Gln Ser Trp Asp Asp Gly Val Pro Val
1 5

<210> SEQ ID NO 263
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Gln Ala Trp Gly Ser Ile Ser Arg Phe Val
1 5 10

<210> SEQ ID NO 264
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

Gln Ser Trp Thr Pro Gly Ser Asn Thr Met Val
1 5 10

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<210> SEQ ID NO 265
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

Gln Gln Leu Asn Ser Ile Pro Val Thr
1 5

<210> SEQ ID NO 266
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

Gln Ser Tyr Asp Ala Gly Val Lys Pro Ala Val
1 5 10

<210> SEQ ID NO 267
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

Gln Ser Trp Asp Ser Pro Tyr Val His Val
1 5 10

<210> SEQ ID NO 268
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

His Gln Tyr Ser Asp Ser Pro Val Thr
1 5

<210> SEQ ID NO 269
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

Gln Ala Tyr Thr Gly Gln Ser Ile Ser Arg
1 5 10

<210> SEQ ID NO 270
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

Gln Gln Arg Asn Gly Phe Pro Leu Thr
1 5

<210> SEQ ID NO 271
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

Gln Gln Tyr Asp Asn Ala Pro Ile Thr

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1 5

<210> SEQ ID NO 272
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

Ser Ser Ala Asp Lys Phe Thr Met Ser Ile Val
1 5 10

<210> SEQ ID NO 273
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

Leu Gln Val Asp Asn Leu Pro Ile Thr
1 5

<210> SEQ ID NO 274
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

Gln Gln Asp Ser Asn Leu Pro Ala Thr
1 5

<210> SEQ ID NO 275
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

Gln Ser Tyr Asp Ser Lys Phe Asn Thr Val
1 5 10

<210> SEQ ID NO 276
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

Gln Ser Tyr Asp Lys Pro Tyr Pro Ile Leu Val
1 5 10

<210> SEQ ID NO 277
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

Gln Gln Phe Tyr Asp Ser Pro Gln Thr
1 5

<210> SEQ ID NO 278
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

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Gln Gln Tyr Ser Ser Ser Pro Ile Thr
1 5

<210> SEQ ID NO 279
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

Gln Thr Tyr Asp Ser Asn Asn Glu Ser Ile Val
1 5 10

<210> SEQ ID NO 280
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

Gln Ser Tyr Asp Leu Asn Asn Leu Val
1 5

<210> SEQ ID NO 281
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

Gln Gln Tyr Asp Ser Thr Pro Ser Thr
1 5

<210> SEQ ID NO 282
<211> LENGTH: 10
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

Ala Ala Tyr Thr Phe Tyr Ala Arg Thr Val
1 5 10

<210> SEQ ID NO 283
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

Gln Ser Trp Asp Lys Ser Glu Gly Tyr Val
1 5 10

<210> SEQ ID NO 284
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

Ser Ser Tyr Thr Leu Asn Pro Asn Leu Asn Tyr Val
1 5 10

<210> SEQ ID NO 285
<211> LENGTH: 10
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

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Ser Ala Tyr Ala Met Gly Ser Ser Pro Val
1 5 10

<210> SEQ ID NO 286
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

Gln Gln Tyr Gly Asn Asn Pro Thr Thr
1 5

<210> SEQ ID NO 287
<211> LENGTH: 9
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<400> SEQUENCE: 287

Gln Gln Tyr Ser Gly Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 288
<211> LENGTH: 9
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<400> SEQUENCE: 288

Gln Gln Leu Asp Asn Arg Ser Ile Thr
1 5

<210> SEQ ID NO 289
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

Ser Thr Tyr Thr Ser Arg Ser His Ser Tyr Val
1 5 10

<210> SEQ ID NO 290
<211> LENGTH: 10
<212> TYPE: PRT
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<400> SEQUENCE: 290

Gln Ser Tyr Asp Ser Thr Gly Leu Leu Val
1 5 10

<210> SEQ ID NO 291
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

Glu Gly Ser Asn Val
1 5

<210> SEQ ID NO 292
<211> LENGTH: 10
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<400> SEQUENCE: 292

Gln Ser Trp Thr Ser Arg Pro Met Val Val
1 5 10

<210> SEQ ID NO 293
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

Gln Gln Gln Asn Gly Tyr Pro Phe Thr
1 5

<210> SEQ ID NO 294
<211> LENGTH: 9
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<400> SEQUENCE: 294

Gln Gln Tyr Tyr Asp Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 295
<211> LENGTH: 9
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<400> SEQUENCE: 295

Ser Ser Ala Ala Phe Gly Ser Thr Val
1 5

<210> SEQ ID NO 296
<211> LENGTH: 10
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

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

<210> SEQ ID NO 297
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

Gln Ser Tyr Thr Thr Arg Ser Leu Val
1 5

<210> SEQ ID NO 298
<211> LENGTH: 9
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<400> SEQUENCE: 298

Gln Gln Tyr Asp Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 299
<211> LENGTH: 10
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<400> SEQUENCE: 299

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

<210> SEQ ID NO 300
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

Gln Thr Tyr Asp Tyr Ile Leu Asn Val
1 5

<210> SEQ ID NO 301
<211> LENGTH: 12
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<400> SEQUENCE: 301

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

<210> SEQ ID NO 302
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

Asn Asn Ala Met Asn
1 5

<210> SEQ ID NO 303
<211> LENGTH: 4
<212> TYPE: PRT
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<400> SEQUENCE: 303

Ser Tyr Gly Ser
1

<210> SEQ ID NO 304
<211> LENGTH: 5
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<400> SEQUENCE: 304

Arg Tyr Ala Met Ser
1 5

<210> SEQ ID NO 305
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

Ser Tyr Gly Met Ser
1 5

<210> SEQ ID NO 306
<211> LENGTH: 5
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

Ser Tyr Ser Met Asn
1 5

<210> SEQ ID NO 307
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

Ser Tyr Ser Met Ser
1 5

<210> SEQ ID NO 308
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 309
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

Asn Tyr Ser Met Thr
1 5

<210> SEQ ID NO 310
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

Gly Asn Ser Met His
1 5

<210> SEQ ID NO 311
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 312
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

Pro Tyr Val Met Ser
1 5

<210> SEQ ID NO 313
<211> LENGTH: 7

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 314
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 315
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 316
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

Ser Asn Ser Ala Ala Trp Ser
1 5

<210> SEQ ID NO 317
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Lys Tyr Ala Met His
1 5

<210> SEQ ID NO 318
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Ser Tyr Ala Met Asn
1 5

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

<400> SEQUENCE: 319

Ser Tyr Ala Met Thr
1 5

<210> SEQ ID NO 320

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<211> LENGTH: 7
<212> TYPE: PRT
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<400> SEQUENCE: 320

Ser Asn Ser Ala Ala Trp Ser
1 5

<210> SEQ ID NO 321
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

Ser Ser Ser Ala Ala Trp Ser
1 5

<210> SEQ ID NO 322
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

Ser Tyr Ala Met Ser
1 5

<210> SEQ ID NO 323
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

Ser Tyr Ala Met Thr
1 5

<210> SEQ ID NO 324
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Ser Asn Gly Ala Ala Trp Gly
1 5

<210> SEQ ID NO 325
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

Asn Tyr Tyr Leu Ser
1 5

<210> SEQ ID NO 326
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

Asn Asn Ala Ile Ser
1 5

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<210> SEQ ID NO 327
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Ser Tyr Trp Met His
1 5

<210> SEQ ID NO 328
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 329
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

Ser Asn Gly Ala Ala Trp Gly
1 5

<210> SEQ ID NO 330
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

Ser Ser Ser Ala Ala Trp Ser
1 5

<210> SEQ ID NO 331
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

Ser Asn Ser Ala Ala Trp Gly
1 5

<210> SEQ ID NO 332
<211> LENGTH: 4
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

Ser Tyr Ala Ser
1

<210> SEQ ID NO 333
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

Asn Tyr Ala Met Thr
1 5

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<210> SEQ ID NO 334
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Asp Tyr Trp Ile Gly
1 5

<210> SEQ ID NO 335
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Ser Tyr Ser Met His
1 5

<210> SEQ ID NO 336
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

Ser Asn Ser Gly Gly Trp Gly
1 5

<210> SEQ ID NO 337
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Ser Tyr Ser Met Ser
1 5

<210> SEQ ID NO 338
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

Ser Tyr Tyr Met Ser
1 5

<210> SEQ ID NO 339
<211> LENGTH: 5
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

Asn Tyr Ala Met Asn
1 5

<210> SEQ ID NO 340
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

Ser Tyr Gly Met Ser
1 5

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<210> SEQ ID NO 341
<211> LENGTH: 7
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

Ser Asn Ser Ala Ala Trp Ser
1 5

<210> SEQ ID NO 342
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

Asp Tyr Ala Met Ser
1 5

<210> SEQ ID NO 343
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

Thr Tyr Ala Met His
1 5

<210> SEQ ID NO 344
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Asp His Ala Met His
1 5

<210> SEQ ID NO 345
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

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

Gly

<210> SEQ ID NO 346
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

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

Gly

<210> SEQ ID NO 347
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 347

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

Gly

<210> SEQ ID NO 348
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

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

Gly

<210> SEQ ID NO 349
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

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

Gly

<210> SEQ ID NO 350
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

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

Gly

<210> SEQ ID NO 351
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

Met Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ser Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 352
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

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

Gly

<210> SEQ ID NO 353
<211> LENGTH: 17

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

Thr Ile Phe Pro Tyr Asp Gly Thr Thr Lys Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 354
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

Met Ile Tyr His Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 355
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

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

Gly

<210> SEQ ID NO 356
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

Ile Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn His Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 357
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

Leu Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 358
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

Met Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

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<210> SEQ ID NO 359
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

Met Ile Phe Tyr Arg Ser Lys Trp Asn Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 360
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

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

Gly

<210> SEQ ID NO 361
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

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

Gly

<210> SEQ ID NO 362
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

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

Gly

<210> SEQ ID NO 363
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

Phe Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 364
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

Ile Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

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<210> SEQ ID NO 365
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

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

Gly

<210> SEQ ID NO 366
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

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

Gly

<210> SEQ ID NO 367
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

Phe Ile Tyr Arg Arg Ser Lys Trp Tyr Asn Ser Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 368
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

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

Gly

<210> SEQ ID NO 369
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369

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

Gly

<210> SEQ ID NO 370
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

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

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Gly

<210> SEQ ID NO 371
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

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

Gly

<210> SEQ ID NO 372
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

His Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ser Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 373
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

Met Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn His Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 374
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

Val Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 375
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

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

Gly

<210> SEQ ID NO 376
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

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

Gly

<210> SEQ ID NO 377
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Ile Ile Gln Pro Ser Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 378
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

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

Gly

<210> SEQ ID NO 379
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Leu Ile Tyr Tyr Arg Ser Lys Trp Tyr Asn Ala Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 380
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

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

Gly

<210> SEQ ID NO 381
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

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

Gly

<210> SEQ ID NO 382
<211> LENGTH: 17
<212> TYPE: PRT
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<400> SEQUENCE: 382

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

Gly

<210> SEQ ID NO 383
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

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

Gly

<210> SEQ ID NO 384
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

Ile Ile Tyr Lys Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 385
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

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

Gly

<210> SEQ ID NO 386
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

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

Gly

<210> SEQ ID NO 387
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

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

Gly

<210> SEQ ID NO 388
<211> LENGTH: 12
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Gln Ala Gly Gly Trp Thr Tyr Ser Tyr Thr Asp Val
1 5 10

<210> SEQ ID NO 389
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

Val Asn Ile Ser Thr His Phe Asp Val
1 5

<210> SEQ ID NO 390
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

Leu Met Gly Tyr Gly His Tyr Tyr Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 391
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

Lys Tyr Arg Tyr Trp Phe Asp Tyr
1 5

<210> SEQ ID NO 392
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

Ala Phe Leu Gly Tyr Lys Glu Ser Tyr Phe Asp Ile
1 5 10

<210> SEQ ID NO 393
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

Asn Gly Gly Leu Ile Asp Val
1 5

<210> SEQ ID NO 394
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

Thr Met Ser Lys Tyr Gly Gly Pro Gly Met Asp Val
1 5 10

<210> SEQ ID NO 395
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

Ile Tyr Tyr Met Asn Leu Leu Ala Gly
1 5

<210> SEQ ID NO 396
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Gly Val His Ser Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 397
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

Tyr Ser Ser Ile Gly His Met Asp Tyr
1 5

<210> SEQ ID NO 398
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Gly Asp Ser Tyr Met Tyr Asp Val
1 5

<210> SEQ ID NO 399
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

Ser Asn Trp Ser Gly Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 400
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

Phe Gly Asp Thr Asn Arg Asn Gly Thr Asp Val
1 5 10

<210> SEQ ID NO 401
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

Val Asn Gln Tyr Thr Ser Ser Asp Tyr
1 5

<210> SEQ ID NO 402

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<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

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

<210> SEQ ID NO 403
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

Tyr Tyr Cys Lys Cys Val Asp Leu
1 5

<210> SEQ ID NO 404
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

Tyr Pro Asp Trp Gly Trp Tyr Thr Asp Val
1 5 10

<210> SEQ ID NO 405
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

Val Gly Tyr Tyr Tyr Gly Phe Asp Tyr
1 5

<210> SEQ ID NO 406
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

His Asn Pro Asp Leu Gly Phe Asp Tyr
1 5

<210> SEQ ID NO 407
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

His Ser Met Val Gly Phe Asp Val
1 5

<210> SEQ ID NO 408
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

Lys Gly Gly Gly Glu His Gly Phe Phe Pro Ser Asp Ile
1 5 10

-continued

<210> SEQ ID NO 409
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

Asn Asp Ser Gly Trp Phe Asp Val
1 5

<210> SEQ ID NO 410
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

Gln Asp Gly Met Gly Gly Met Asp Ser
1 5

<210> SEQ ID NO 411
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

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

<210> SEQ ID NO 412
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

Gly His His Arg Gly His Ser Trp Ala Ser Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 413
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

Tyr Gly Gly Met Asp Tyr
1 5

<210> SEQ ID NO 414
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

Gly Leu Phe Pro Gly Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 415
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

Trp Gly Gly Ile His Asp Gly Asp Ile Tyr Phe Asp Tyr
1 5 10

-continued

<210> SEQ ID NO 416
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

Gly Gly Ser Gly Val Met Asp Val
1 5

<210> SEQ ID NO 417
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

Ala Arg Ala Lys Lys Ser Gly Gly Phe Asp Tyr
1 5 10

<210> SEQ ID NO 418
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 418

Tyr Asp Asn Phe Tyr Phe Asp Val
1 5

<210> SEQ ID NO 419
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

Pro Thr Lys Ala Gly Arg Thr Trp Trp Trp Gly Pro Tyr Met Asp Val
1 5 10 15

<210> SEQ ID NO 420
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

Phe Met Trp Trp Gly Lys Tyr Asp Ser Gly Phe Asp Val
1 5 10

<210> SEQ ID NO 421
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

Ala Leu Gly Gly Gly Val Asp Tyr
1 5

<210> SEQ ID NO 422
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

Tyr Leu Gly Ser Asn Phe Tyr Val Tyr Ser Asp Val
1 5 10

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<210> SEQ ID NO 423
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

Met His Tyr Lys Gly Met Asp Ile
1 5

<210> SEQ ID NO 424
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

Val His Tyr Gly Phe Asp Phe
1 5

<210> SEQ ID NO 425
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

Ala Asp Leu Pro Tyr Met Val Phe Asp Tyr
1 5 10

<210> SEQ ID NO 426
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 426

Ser Tyr Leu Gly Tyr Phe Asp Val
1 5

<210> SEQ ID NO 427
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 427

Trp His Ser Asp Lys His Trp Gly Phe Asp Tyr
1 5 10

<210> SEQ ID NO 428
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 428

Thr Ile Gly Val Leu Trp Asp Asp Val
1 5

<210> SEQ ID NO 429
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

Asn Gly Arg Lys Tyr Gly Gln Met Asp Asn

-continued

1 5 10

<210> SEQ ID NO 430
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

Gly Asp Tyr Tyr Pro Tyr Leu Val Phe Ala Ile
1 5 10

We claim:

1. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 388-430.

2. The isolated antibody of claim **1**, wherein the antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387.

3. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 259-301.

4. The isolated antibody of claim **3**, wherein the antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, or (c) both a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215 and a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258.

5. The antibody of claim **1**, wherein the antibody further comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 259-301.

6. The antibody of claim **5**, wherein the antibody further comprises (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 302-344, (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 345-387, (c) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and (d) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258.

7. The antibody of claim **1**, wherein the antibody comprises heavy and light chain variable regions comprising:

(a) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 173, 216 and 259 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 302, 345 and 388;

(b) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 174, 217 and 260 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 303, 346 and 389;

(c) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 175, 218 and 261 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 304, 347 and 390;

(d) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 176, 219 and 262 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 305, 348 and 391;

(e) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 177, 220 and 263 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 306, 349 and 392;

(f) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 178, 221 and 264 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 307, 350 and 393;

(g) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 179, 222 and 265 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 308, 351 and 394;

(h) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 180, 223 and 266 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 309, 352 and 395;

(i) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 181, 224 and 267 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 310, 353 and 396;

(j) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 182, 225 and 268 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 311, 354 and 397;

(k) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 183, 226 and 269 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 312, 355 and 398;

(l) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 184, 227 and 270 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 313, 356 and 399;

(m) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 185, 228 and 271 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 314, 357 and 400;

(n) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 186, 229 and 272 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 315, 358 and 401;

(o) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 187, 230 and 273 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 316, 359 and 402;

(p) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 188, 231 and 274 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 317, 360 and 403;

(q) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 189, 232 and 275 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 318, 361 and 404;

(r) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 190, 233 and 276 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 319, 362 and 405;

(s) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 191, 234 and 277 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 320, 363 and 406;

(t) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 192, 235 and 278 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 321, 364 and 407;

(u) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 193, 236 and 279 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 322, 365 and 408;

(v) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 194, 237 and 280 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 323, 366 and 409;

(w) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 195, 238 and 281 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 324, 367 and 410;

(x) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 196, 239 and 282 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 325, 368 and 411;

(y) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 197, 240 and 283 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 326, 369 and 412;

(z) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 198, 241 and 284 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 327, 370 and 413;

(aa) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 199, 242 and 285 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 328, 371 and 414;

(bb) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 200, 243 and 286 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 329, 372 and 415;

(cc) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 201, 244 and 287 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 330, 373 and;

(dd) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 202, 245 and 288 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 331, 374 and 417;

(ee) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 203, 246 and 289 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 332, 375 and 418;

(ff) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 204, 247 and 290 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 333, 376 and 419;

(gg) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 205, 248 and 291 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 334, 377 and 420;

(hh) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 206, 249 and 292 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 335, 378 and 421;

(ii) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 207, 250 and 293 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 336, 379 and 422;

(jj) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 208, 251 and 294 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 337, 380 and 423;

(kk) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 209, 252 and 295

and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 338, 381 and 424;

(ll) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 210, 253 and 296 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 339, 382 and 425;

(mm) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 211, 254 and 297 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 340, 383 and 426;

(nn) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 212, 255 and 298 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 341, 384 and 427;

(oo) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 213, 256 and 299 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 342, 385 and 428;

(pp) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 214, 257 and 300 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 343, 386 and 429;

(qq) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 215, 258 and 301 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 344, 387 and 430; or

(rr) a light chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 194, 237 and 280 and a heavy chain variable region comprising an amino acid sequence comprising SEQ ID NOs: 335, 378 and 421.

8. The monoclonal antibody of claim **1**, comprising:

(a) a light chain variable region having the polypeptide sequence of SEQ ID NO: 2 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 4;

(b) a light chain variable region having the polypeptide sequence of SEQ ID NO: 6 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 8;

(c) a light chain variable region having the polypeptide sequence of SEQ ID NO: 10 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12;

(d) a light chain variable region having the polypeptide sequence of SEQ ID NO: 14 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 16;

(e) a light chain variable region having the polypeptide sequence of SEQ ID NO: 18 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 20;

(f) a light chain variable region having the polypeptide sequence of SEQ ID NO: 22 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 24;

(g) a light chain variable region having the polypeptide sequence of SEQ ID NO: 26 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 28;

(h) a light chain variable region having the polypeptide sequence of SEQ ID NO: 30 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 32;

(i) a light chain variable region having the polypeptide sequence of SEQ ID NO: 34 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 36;

(j) a light chain variable region having the polypeptide sequence of SEQ ID NO: 38 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 40;

(k) a light chain variable region having the polypeptide sequence of SEQ ID NO: 42 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 44;

(l) a light chain variable region having the polypeptide sequence of SEQ ID NO: 46 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 48;

(m) a light chain variable region having the polypeptide sequence of SEQ ID NO: 50 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 52;

(n) a light chain variable region having the polypeptide sequence of SEQ ID NO: 54 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 56;

(o) a light chain variable region having the polypeptide sequence of SEQ ID NO: 58 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 60;

(p) a light chain variable region having the polypeptide sequence of SEQ ID NO: 62 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 64;

(q) a light chain variable region having the polypeptide sequence of SEQ ID NO: 66 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 68;

(r) a light chain variable region having the polypeptide sequence of SEQ ID NO: 70 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 72;

(s) a light chain variable region having the polypeptide sequence of SEQ ID NO: 74 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 76;

(t) a light chain variable region having the polypeptide sequence of SEQ ID NO: 78 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 80;

(u) a light chain variable region having the polypeptide sequence of SEQ ID NO: 82 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 84;

(v) a light chain variable region having the polypeptide sequence of SEQ ID NO: 86 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 88;

(w) a light chain variable region having the polypeptide sequence of SEQ ID NO: 90 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 92;

(x) a light chain variable region having the polypeptide sequence of SEQ ID NO: 94 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 96;

(y) a light chain variable region having the polypeptide sequence of SEQ ID NO: 98 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100;

(z) a light chain variable region having the polypeptide sequence of SEQ ID NO: 102 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(aa) a light chain variable region having the polypeptide sequence of SEQ ID NO: 106 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 108;

(bb) a light chain variable region having the polypeptide sequence of SEQ ID NO: 110 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 112;

(cc) a light chain variable region having the polypeptide sequence of SEQ ID NO: 114 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 116;

(dd) a light chain variable region having the polypeptide sequence of SEQ ID NO: 118 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 120;

(ee) a light chain variable region having the polypeptide sequence of SEQ ID NO: 122 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 124;

(ff) a light chain variable region having the polypeptide sequence of SEQ ID NO: 126 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 128;

(gg) a light chain variable region having the polypeptide sequence of SEQ ID NO: 130 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 132;

(hh) a light chain variable region having the polypeptide sequence of SEQ ID NO: 134 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 136;

(ii) a light chain variable region having the polypeptide sequence of SEQ ID NO: 138 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 140;

(jj) a light chain variable region having the polypeptide sequence of SEQ ID NO: 142 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144;

(kk) a light chain variable region having the polypeptide sequence of SEQ ID NO: 146 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148;

(ll) a light chain variable region having the polypeptide sequence of SEQ ID NO: 150 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(mm) a light chain variable region having the polypeptide sequence of SEQ ID NO: 154 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 156;

(nn) a light chain variable region having the polypeptide sequence of SEQ ID NO: 158 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160;

(oo) a light chain variable region having the polypeptide sequence of SEQ ID NO: 162 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(pp) a light chain variable region having the polypeptide sequence of SEQ ID NO: 166 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 168;

(qq) a light chain variable region having the polypeptide sequence of SEQ ID NO: 170 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: **172**; or

(rr) a light chain variable region having the polypeptide sequence of SEQ ID NO: 86 and a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 136.

9. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a human heavy chain variable region comprising an amino acid sequence having at least 96% identity to an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:116, SEQ ID NO:120, SEQ ID NO:124, SEQ ID NO:128, SEQ ID NO:132, SEQ ID NO:136, SEQ ID NO:140, SEQ ID NO:144, SEQ ID NO:148, SEQ ID NO:152, SEQ ID NO:156, SEQ ID NO:160, SEQ ID NO:164, SEQ ID NO:168, and SEQ ID NO:172.

10. An isolated monoclonal antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a human light chain variable region comprising an amino acid sequence having at least 97% identity to an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:54, SEQ ID NO:58, SEQ ID NO:62, SEQ ID NO:66, SEQ ID NO:70, SEQ ID NO:74, SEQ ID NO:78, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:90, SEQ ID NO:94, SEQ ID NO:98, SEQ ID NO:102, SEQ ID NO:106, SEQ ID NO:110, SEQ ID NO:114, SEQ ID NO:118, SEQ ID NO:122, SEQ ID NO:126, SEQ ID NO:130, SEQ ID NO:134, SEQ ID NO:138, SEQ ID NO:142, SEQ ID NO:146, SEQ ID NO:150, SEQ ID NO:154, SEQ ID NO:158, SEQ ID NO:162, SEQ ID NO:166, and SEQ ID NO:170.

11. The antibody of claim **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, or **10**, wherein the antibody is selected from the group consisting of

an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

12. The antibody of claim **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10** or **11**, wherein blood clotting time in the presence of the antibody is shortened as measured by diluted prothrombin time.

13. The antibody of claim **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10** or **11** that is an antibody fragment or a single chain antibody.

14. A pharmaceutical composition comprising a therapeutically effective amount of the monoclonal antibody of claim **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** or **13** and a pharmaceutically acceptable carrier.

15. A method for treating genetic and acquired deficiencies or defects in coagulation comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **14** to a patient.

16. The method of claim **15**, wherein the method treats hemophilia A or B.

17. A method for shortening bleeding time comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **14** to a patient.

18. A method for treating genetic and acquired deficiencies in coagulation comprising administering (a) a first amount of a monoclonal antibody that binds to human tissue factor pathway inhibitor and (b) a second amount of factor VIII or factor IX, wherein said first and second amounts together are effective for treating said deficiencies or defects, and further wherein factor VII is not coadministered.

19. A pharmaceutical composition comprising a therapeutically effective amount of the combination of (a) a monoclonal antibody of claim **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** or **13** and (b) factor VIII or factor IX; wherein the composition does not contain factor VII.

20. A method for treating genetic and acquired deficiencies or defects in coagulation comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **19** to a patient in need thereof.

21. A method for shortening bleeding time comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **19** to a patient.

22. An isolated fully human monoclonal antibody to human tissue factor pathway inhibitor.

23. A pharmaceutical composition comprising a therapeutically effective amount of the monoclonal antibody of claim **22** and a pharmaceutically acceptable carrier.

24. A method for treating genetic and acquired deficiencies or defects in coagulation comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **23** to a patient.

25. The method of claim **24**, further comprising administering with factor VIII or factor IX.

26. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 388-430.

27. An isolated nucleic acid molecule encoding an antibody that binds to human tissue factor pathway inhibitor, wherein the antibody comprises a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 259-301.

28. A method for producing a fully human monoclonal antibody that binds human tissue factor pathway inhibitor comprising:

(i) transfecting a nucleotide sequence encoding the fully human monoclonal antibody into a host cell, and

(ii) culturing the host cell so to express the monoclonal antibody.

29. The method of claim **28**, wherein the monoclonal antibody comprises a CDR3 comprising an amino acid sequence selected from the group of sequences consisting of SEQ ID NOs: 388-430.

30. A method for producing a monoclonal antibody that binds human tissue factor pathway inhibitor comprising:

(i) transfecting a nucleotide sequence encoding the monoclonal antibody into a host cell, and

(ii) culturing the host cell so to express the monoclonal antibody,

wherein the monoclonal antibody comprises a CDR3 comprising an amino acid sequence selected from the group of sequences consisting of SEQ ID NOs: 259-301.

31. The method of claim **29**, wherein the monoclonal antibody comprises a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 388-430 and a light chain CDR3 comprising an amino amino acid sequence selected from the group of sequences consisting of SEQ ID NOs: 259-301.

32. An isolated fully human monoclonal antibody to Kunitz domain 2 of human tissue factor pathway inhibitor.

33. A pharmaceutical composition comprising a therapeutically effective amount of the monoclonal antibody of claim **32** and a pharmaceutically acceptable carrier.

34. A method for treating genetic and acquired deficiencies or defects in coagulation comprising administering a therapeutically effective amount of the pharmaceutical composition of claim **33** to a patient.

35. The method of claim **34**, further comprising administering with factor VII, factor VIII or factor IX.

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