

Monoclonal Antibodies against Tissue Factor Pathway Inhibitor (TFPI)**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. Patent 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 (Jan. 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. Δ: 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 immunologically 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 10^7 M^{-1} , in some embodiments at least about 10^8 M^{-1} , in some embodiments at least about 10^9 M^{-1} , 10^{10} M^{-1} , 10^{11} M^{-1} or greater, e.g., up to 10^{13} M^{-1} or greater. 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 $1.0 \times 10^7 \text{ M}^{-1}$. As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by heavy chain constant region genes.

[0032] "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.

[0033] 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.

[0034] 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.

[0035] 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 x 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, CA). 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>).

[0036] 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.

[0037] 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, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art.

Monoclonal Antibodies

[0038] 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.

[0039] 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. N.A.: nucleic acid sequence; A.A.: amino acid sequence.

Clone	VL		VH		VL			VH		
	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
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

Clone	VL		VH		VL			VH		
	N.A.	A.A.	N.A.	A.A.	CDR1	CDR2	CDR3	CDR1	CDR2	CDR3
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

[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:

- (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.

[0044] In another embodiment, the invention is directed to antibodies 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] In one embodiment, provided is an isolated fully human monoclonal antibody to human tissue factor pathway inhibitor.

[0053] In another embodiment, provided is an isolated fully human monoclonal antibody to Kunitz domain 2 of human tissue factor pathway inhibitor.

Nucleic Acids

[0054] Also provided are isolated nucleic acid molecules encoding any of the monoclonal antibodies described above.

Methods of Preparing Antibodies to TFPI

[0055] 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:

- (a) transfecting a nucleic acid molecule encoding a monoclonal antibody of the invention into a host cell,
- (b) culturing the host cell so to express the monoclonal antibody in the host cell, and optionally
- (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.

[0056] 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).

[0057] 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.

[0058] 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).

[0059] 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.

[0060] 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

[0061] 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 of particular restriction sites, or optimization of particular codons.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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

[0067] 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.

[0068] 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.

[0069] 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

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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 factors, 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

[0077] 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

[0078] 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

[0079] 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.

[0080] Table 2. Peptide sequence of variable region of 44 anti-TFPI antibodies

Clone	VL	VH
TP-2A2	DIELTQPPSVSVAPGQTARISCSGDNIRYYVHWYQQKPGQ APVVVIYGD SKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSEADSEVFGGGTKLTVLGQ (SEQ ID NO: 2)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSNNAMNWRQAP GKGLEWVSTISYDGSNTYYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARQAGGWTSYTDVWGQGT LVTVSS (SEQ ID NO: 4)
TP-2A5.1	DIELTQPPSVSVAPGQTARISCSGDNIPKEYVHWYQQKPGQ APVLVIHGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSF DAGSYFVFGGGTKLTVLGQ (SEQ ID NO: 6)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSYGSWVRQAPG KGLEWVSVISGSGSSTYYADSVKGRFTISRDN SKNTLYLQ NSLRAEDTAVYYCARVNISTHFDVWGQGT LVTVSS (SEQ ID NO: 8)
TP-2A6	DIELTQPPSVSVAPGQTARISCSGDKIGSKYVYVYQQKPGQ APVLVIYDSNRPSGIPERFSGSNSGNTATLTISGTQAEDEA DYCASYDSIYSYVWFGGGTKLTVLGQ (SEQ ID NO: 10)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSRYAMSWVRQAP GKGLEWVSSIISSESSTYYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARLMGYGHYFPDYWGQGT LVTVSS (SEQ ID NO: 12)
TP-2A8	DIELTQPPSVSVAPGQTARISCSGDNLRNYAHWYQQKPGQ APVVVIYDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDDGVPVFGGGTKLTVLGQ (SEQ ID NO: 14)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSYGMWSVRQAP GKGLEWVSSIIRGSSSTYYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARKYRYWFDYWGQGT LVTVSS (SEQ ID NO: 16)
TP-2A10	DIELTQPPSVSVAPGQTARISCSGDKLGKYYVHWYQQKPGQ APVLVIYGD DKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAWGSISREVFVFGGGTKLTVLGQ (SEQ ID NO: 18)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSYSMNWRQAP GKGLEWVSAISYTGSNTHYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARAF LGYKESYFDI WGQGT LVTVSS (SEQ ID NO: 20)
TP-2B1	DIELTQPPSVSVAPGQTARISCSGDN LGNKYAHWYQQKPGQ APVLVIYDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWTPGSNTMVFGGGTRLTVLGQ (SEQ ID NO: 22)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSYSMSWVRQAS GKGLEWVSSIKSGSNTYYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARNGLIDVWGQGT LVTVSS (SEQ ID NO: 24)
TP-2B3	DIVLTQSPATLSLSPGERATLSCRASQNI GSNYLA WYQQKP GQAPRLLIYGASTRATGVPARFNGSGSGTDFLTIS SLEPE DFAVYYCQQLNSIPVTFGQGTKEIKRT (SEQ ID NO: 26)	QVQLQQSGPGLVKPSQTLTSLTCAISGDSVSSNSAAWGIRQ SPGRGLEWLGMIYYRSKWNSYAVSVKSRITINPDT SKNQF SLQLNSVTPEDTAVYYCARTMSKYGGPGMDVWGQGT LVTVS S (SEQ ID NO: 28)
TP-2B4	DIELTQPPSVSVAPGQTARISCSGDALGYAYWYQQKPGQ APVLVIYGD MNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDAGVKPAVFGGGTKLTVLGQ (SEQ ID NO: 30)	QVQLVESGGGLVQPGGSLRLS CAASGFTFSNYSMTWVRQAP GKGLEWVSGISYNGSNTYYADSVKGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARIYMNLLAGWGQGT LVTVSS (SEQ ID NO: 32)
TP-2B8	DIELTQPPSVSVAPGQTARISCSGDNLRGYYASWYQQKPGQ APVLVIYEDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDSPYVHVFGGGTKLTVLGQ (SEQ ID NO: 34)	QVQLVQSGAEVKKPGASVKVSKASGYTFTGNSMHWVRQAP GQGLEWMGTIFPYDGTTKYAKQKGRVTMTRDTSISTAYME LSSLRSED TAVYYCARGVHSYFDYWGQGT LVTVSS (SEQ ID NO: 36)

Clone	VL	VH
TP-2B9	DIQMTQSPSSLSASVGDRTITCRASQSIRSYLAWYQQKPG KAPKLLIYKASNLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCHQYSDSPVTFGGQGTKVEIKRT (SEQ ID NO: 38)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIQ SPGRGLEWLGMIYHRKSWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARYSSIGHMDYWGQGLTVTVSS (SEQ ID NO: 40)
TP-2C1	DIELTQPPSVSVAPGQTARISCSGDSIGSYAHWYQQKPGQ APVLVIYYDSKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAYTGQSSISRVFGGGKTLTVLGQ (SEQ ID NO: 42)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSPYVMSWVRQAP GKGLEWVSSISSSSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARGDSYMYDVWGQGLTVTVSS (SEQ ID NO: 44)
TP-2C7	DIQMTQSPSSLSASVGDRTITCRASQDIRNNLAWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCQQRNGFPLTFGGQGTKVEIKRT (SEQ ID NO: 46)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIQ SPGRGLEWLGIIYYRSKWYNYHAYSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARSNWSGYFDYWGQGLTVTVSS (SEQ ID NO: 48)
TP-2D7	DIVMTQSPSLPVTPEPASISCRSSQSLHNSGYTYSWY LQKPGQSPQLLIYLGSNRASGVDRFSGSGSGTDFTLKISR VEAEDVGYYCQYDNAPITFGQGTKVEIKRT (SEQ ID NO: 50)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIQ SPGRGLEWLGIIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARFGDTNRNGTDVWGQGLTVTVSS (SEQ ID NO: 52)
TP-2E3	DIALTQPASVSGSPGQSITISCTGTSSDIGGNYVSWYQQH PGKAPKLLMIYGVNRPVSGVSNRFSKSGKSGNTASLTISGLQA EDEADYYCASSADKFTMSIVFGGGKTLTVLGQ (SEQ ID NO: 54)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIQ SPGRGLEWLGMIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARVNQYTSDDYWGQGLTVTVSS (SEQ ID NO: 56)
TP-2E5	DIQMTQSPSSLSASVGDRTITCRASQPIYNSLSWYQQKPG KAPKLLIYGVSNLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCLQVDNLPITFGQGTKVEIKRT (SEQ ID NO: 58)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWSWIQ SPGRGLEWLGMIYFYSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARVNANGYYAYVDLWGQGLTVTVS S (SEQ ID NO: 60)
TP-2F9	DIVLTQSPATLSLSPGERATLSCRASQSVSSQYLAWYQQKP GQAPRLIIYAASSRATGVPARFSGSGSGTDFTLTISLLEPE DFAVYYCQQDSNLPATFGQGTKVEIKRT (SEQ ID NO: 62)	QVQLVESGGGLVQPGGSLRLSCAASGFTFYKYAMHWVRQAP GKGLEWVSGIQYDGSYTYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARYYCKCVDLWGQGLTVTVSS (SEQ ID NO: 64)
TP-2G2	DIELTQPPSVSVAPGQTARISCSGDNIRKIFYVHWYQQKPGQ APVLVIYGTNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSKFNITVFGGKTLTVLGQ (SEQ ID NO: 66)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWRQAP GKGLEWVSAILSDGSSTSYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARYPDWGWYTDVWGQGLTVTVSS (SEQ ID NO: 68)
TP-2G4	DIELTQPPSVSVAPGQTARISCSGDALRKHYVYWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDKPYPILVFGGKTLTVLGQ (SEQ ID NO: 70)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAP GKGLEWVSNISYSGSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARVGYGYGFDYWGQGLTVTVSS (SEQ ID NO: 72)
TP-2G5	DIVLTQSPATLSLSPGERATLSCRASQNVSSNYLAWYQQKP GQAPRLIIYDASNRATGVPARFSGSGSGTDFTLTISLLEPE DFAVYYCQQFYDSPQTFGGQGTKVEIKRT (SEQ ID NO: 74)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWSWIQ SPGRGLEWLGFIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARHNPDLGFDYWGQGLTVTVSS (SEQ ID NO: 76)
TP-2G6	DIVLTQSPATLSLSPGERATLSCRASQYVTSSYLAWYQQKP GQAPRLIIYGSSSRATGVPARFSGSGSGTDFTLTISLLEPE FATYYCQQYSSSPITFGQGTKVEIKRT (SEQ ID NO: 78)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSSSAAWSWIQ SPGRGLEWLGIIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARHSMVGFVDWGQGLTVTVSS (SEQ ID NO: 80)
TP-2G7	DIELTQPPSVSVAPGQTARISCSGDNLTYYVHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQTYDSNNESIVFGGKTLTVLGQ (SEQ ID NO: 82)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAP GKGLEWVSNISSSSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARKGGGEHGFPSDIWGQGLTVTVSS (SEQ ID NO: 84)
TP-2G9	DIALTQPASVSGSPGQSITISCTGTSSDLGGFNTVSWYQQH PGKAPKLLMIYSVSRPVGVSNNRFSKSGKSGNTASLTISGLQA EDEADYYCQSYDLNNLVFGGKTLTVLGQ (SEQ ID NO: 86)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMTWVRQAP GKGLEWVSAIKSDGSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARNDSCGFVDWGQGLTVTVSS (SEQ ID NO: 88)
TP-2H10	DIVLTQSPATLSLSPGERATLSCRASQSVSSFYLAWYQQKP GQAPRLIIYGSSSRATGVPARFSGSGSGTDFTLTISLLEPE DFATYYCQQYDSTPSTFGQGTKVEIKRT (SEQ ID NO: 90)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNGAAGWIQ SPGRGLEWLGFIYYRSKWYNSYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARQDGMGMDSWGQGLTVTVSS (SEQ ID NO: 92)
TP-3A2	DIELTQPPSVSVAPGQTARISCSGDNIGSRAYWYQQKPGQ APVVVIYDSDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCAAIFYARTVFGGKTLTVLGQ (SEQ ID NO: 94)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYYLSWVRQAP GKGLEWVSGISYNGSSTNYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARMWRYSLGADSWGQGLTVTVSS (SEQ ID NO: 96)
TP-3A3	DIELTQPPSVSVAPGQTARISCSGDNIGSKYVHWYQQKPGQ APVVVIYDSDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWDKSEGYVFGGKTLTVLGQ (SEQ ID NO: 98)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNNAISWVRQAP GKGLEWVSAINSSSSSTSYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARGHHRGHSWASFIDYWGQGLTVTVSS (SEQ ID NO: 100)

Clone	VL	VH
TP-3A4	DIELTQPPSVSVAPGQTARISCSGDNLRDKYASWYQQKPGQ APVLVIYKSKSERPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSSYTLNPNLNLYVFGGGTKLTVLGQ (SEQ ID NO: 102)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAP KGLEWVSSISYDSSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARYGGMDYWGQGTLLTVSS (SEQ ID NO: 104)
TP-3B3	DIELTQPPSVSVAPGQTARISCSGDNLRKYAHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSAYAMGSSPVFGGGTKLTVLGQ (SEQ ID NO: 106)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAP KGLEWVSNISYMGSNNTYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARGLFPGYFDYWGQGTLLTVSS (SEQ ID NO: 108)
TP-3B4	DIQMTQSPSSLSASVGDRTITCRASQNIISNYLNWYQQKPG KAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCQQYGNPFTFGQGTKVEIKRT (SEQ ID NO: 110)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNGAAWGWRQ SPGRGLEWLGHIYYRSKWYNSYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARWGGIHDGDIYFDYWGQGTLLTV SS (SEQ ID NO: 112)
TP-3C1	DIALTQPPASVSGSPGQSITISCTGTSSDLGGFNTVSWYQQH PGKAPKLMISVSSRPSGVSNRFGSGSKSGNTASLTISGLQA EDEADYYCQSYDLNNLVFGGGTKLTVLGQ (SEQ ID NO: 86)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMHWVRQAP KGLEWVSGISYSSSFTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARALGGVDYWGQGTLLTVSS (SEQ ID NO: 136)
TP-3C2	DIQMTQSPSSLSASVGDRTITCRASQISITNYLNWYQQKPG KAPKLLIYDVSNLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCQQYSGYPLTFGQGTKVEIKRT (SEQ ID NO: 114)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSSSAAWSWIRQ SPGRGLEWLGMIYYRSKWYNHYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARGGSGVMDVWGQGTLLTVSS (SEQ ID NO: 116)
TP-3C3	DIQMTQSPSSLSASVGDRTITCRASQISINPYLNWYQQKPG KAPKLLIYAASNLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCQQLDNRSITFGQGTKVEIKRT (SEQ ID NO: 118)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWRQ SPGRGLEWLGVIYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARARAKKSGGFDYWGQGTLLTVSS (SEQ ID NO: 120)
TP-3D3	DIELTQPPSVSVAPGQTARISCSGDSLGSKFAHWYQQKPGQ APVLVIYDSDNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSTYTSRSHSYVFGGGTKLTVLGQ (SEQ ID NO: 122)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYASWVRQAPG KGLEWVSGISGDSNTHYADSVKGRFTISRDNKNTLYLQM NSLRAEDTAVYYCARYDNFYFDVWGQGTLLTVSS (SEQ ID NO: 124)
TP-3E1	DIELTQPPSVSVAPGQTARISCSGDNIGSYAYWYQQKPGQ APVLVIYDDSNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYDSTGLLVFGGGTKLTVLGQ (SEQ ID NO: 126)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSNYAMTWVRQAP KGLEWVSVISSVGSNTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARPTKAGRTWWGPMYMDVWGQGTLLTV SS (SEQ ID NO: 128)
TP-3F1	DIELTQPPSVSVAPGQTARISCSGDNIGSYFASWYQQKPGQ APVLVIYDDSNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCEGSNVFGGGTKLTVLGQ (SEQ ID NO: 130)	QVQLVQSGAEVKKPGESLKISCKSGSYFTDYWIGWVRQMP KGLEWMGIIQPSDSDNTYSPSPGQVTTISADKISTAYLQ WSSLKASDTAMYYCARFMWWGKYDSGFDVWGQGTLLTVSS (SEQ ID NO: 132)
TP-3F2	DIELTQPPSVSVAPGQTARISCSGDNLPKSVYWYQQKPGQ APVLVIYDSDNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSWTSRPMVFGGGTKLTVLGQ (SEQ ID NO: 134)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMHWVRQAP KGLEWVSGISYSSSFTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARALGGVDYWGQGTLLTVSS (SEQ ID NO: 136)
TP-3G1	DIQMTQSPSSLSASVGDRTITCRASQGISSYLHWYQQKPG KAPKLLIYGASTLQSGVPSRFSGSGSGTDFTLTISLQPED FATYYCQQQNGYPFTFGQGTKVEIKRT (SEQ ID NO: 138)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSGCGWWRQ SPGRGLEWLGIIYYRSKWYNAYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARYLGSNFYVYSDVWGQGTLLTVS S (SEQ ID NO: 140)
TP-3G3	DIQMTQSPSSLSASVGDRTITCRASQNIHSHLNWYQQKPG KAPKLLIYDASSLQSGVPSRFSGSGSGTDFTLTISLQPED FAVYYCQQYYDYPLTFGQGTKVEIKRT (SEQ ID NO: 142)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMSWVRQAP KGLEWVSSISSSSNTYYGDSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARMHYKGMDIWGQGTLLTVSS (SEQ ID NO: 144)
TP-3H2	DIELTQPPSVSVAPGQTARISCSGDKLGKYAYWYQQKPGQ APVLVIYGDSCRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSSAAGSTVFGGGTKLTVLGQ (SEQ ID NO: 146)	QVQLVESGGGLVQPGGSLRLSCAASGFTFNSYYMSWVRQAP KGLEWVSNISSSGSNNTYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARVHYGDFDWGQGTLLTVSS (SEQ ID NO: 148)
TP-4A7	DIELTQPPSVSVAPGQTARISCSGDALGSKFAHWYQQKPGQ APVLVIYDDSERPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQAYDSGLLYVFGGGTKLTVLGQ (SEQ ID NO: 150)	QVQLVESGGGLVQPGGSLRLSCAASGFTFRNYAMNWVRQAP KGLEWVSVISGSSSYTYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARADLPYMFVDYWGQGTLLTVSS (SEQ ID NO: 152)
TP-4A9	DIELTQPPSVSVAPGQTARISCSGDALGKYASWYQQKPGQ APVLVIYGDNRKPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYTTRSLVFGGGTKLTVLGQ (SEQ ID NO: 154)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMWVRQAP KGLEWVSLISGVSSSYTYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARSYLGFDVWGQGTLLTVSS (SEQ ID NO: 156)
TP-4B7	DIVMTQSPSLSLPVTPEPASISCRSSQSLVFSNGNTYLNWY LQKPGQSPQLLIYKSNRASGVDPDRFSGSGSGTDFTLKISR VEAEDGVVYCYQYDSYPLTFGQGTKVEIKRT (SEQ ID NO: 158)	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWSWIRQ SPGRGLEWLGIIYKRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARWHSKHWGFDYWGQGTLLTVSS (SEQ ID NO: 160)

Clone	VL	VH
TP-4E8	DIELTQPPSVSVAPGQTARISCSGDALGSKYVSWYQQKPGQ APVLVIYGDNKRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQSYTSLNQVFGGGTKLTVLGQ (SEQ ID NO: 162)	QVQLVESGGGLVQPGGSLRLSCAASGFTTFNDYAMSWVRQAP GKGLEWVSLIESVSSSTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARTIGVLWDDVWGQGLTVTVSS (SEQ ID NO: 164)
TP-4G8	DIELTQPPSVSVAPGQTARISCSGDKLGSKSVHWYQQKPGQ APVLVIYRDTDRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCQTYDYILNVFGGGTKLTVLGQ (SEQ ID NO: 166)	QVQLVESGGGLVQPGGSLRLSCAASGFTTFSTYAMHWVRQAP GKGLEWVSTISGYGSFTYYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARNRKYGMNDNWGQGLTVTVSS (SEQ ID NO: 168)
TP-4H8	DIELTQPPSVSVAPGQTARISCSGDSIGKKYVHWYQQKPGQ APVLVIYGDNNRPSGIPERFSGSNSGNTATLTISGTQAEDE ADYYCSTADSVITYKNVFGGGTKLTVLGQ (SEQ ID NO: 170)	QVQLVESGGGLVQPGGSLRLSCAASGFTTFSDHAMHWVRQAP GKGLEWVSVIEYSGSKTNYADSVKGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARGDYYPYLVFAIWGQGLTVTVSS (SEQ ID NO: 172)

Cross-reactivity to mouse TFPI

[0081] 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

[0082] 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/ml chloramphenicol 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 EC₅₀ and binding affinity of Anti-TFPI antibodies

[0083] Purified Fab antibodies were used to determine EC₅₀ of anti-TFPI antibodies to human or mouse TFPI. EC₅₀ 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.

[0084] As shown in Table 3, the 24 anti-TFPI Fabs showed various EC₅₀ 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).

[0085] 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).

Antibody clones	Binding EC ₅₀ (nM)		Affinity (nM)	
	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

[0086] 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

[0087] 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, CT), 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

[0088] 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

[0089] 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 propagation, 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 CaCl₂ (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.

[0090] An exemplary result of ROTEM assay in detecting the effect of anti-TFPI antibodies in shortening blood clotting time is shown in Fig. 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

[0091] 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 ($R^2 = 0.258$).

[0092] 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
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

[0093] 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

[0094] 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 EC₅₀ 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

[0095] 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

[0096] 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 hemophilic blood

[0097] 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 patients. Figure 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

[0098] 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, CA) 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, MA). A HRP conjugated donkey anti-mouse antibody (Pierce, Rockford, IL) 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, IL). 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.

[0099] Table 5. The domains bound by antibodies as determined by Western blots and ELISA

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

[00100] 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 than a restrictive sense. Furthermore, all articles, books, patent applications and patents referred to herein are incorporated herein by reference in their entireties.

We claim:

1. A therapeutic composition comprising:
 - a) an isolated human monoclonal IgG antibody that binds specifically to the Kunitz 1 and Kunitz 2 domain of tissue factor pathway inhibitor (TFPI).
2. The composition of claim 1, wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 305, a CDR-2 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 348, and a CDR-3 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 391.
3. The composition of claim 1 further comprising Factor VIII or Factor IX in the substantial absence of Factor VII.
4. The composition of claim 1, wherein the antibody has a binding affinity to human TFPI by Biacore assay of about 1.25 to 1140 nM.
5. The composition of claim 1 wherein the antibody is formulated in combination a dose of 10 to 100 mg in a pharmaceutically acceptable carrier for injection.
6. The composition of claim 1, wherein the CDR-2 region has at least 85% homology to SEQ ID NO. 348.
7. The composition of claim 1, wherein the CDR-3 region has at least 85% homology to SEQ ID NO. 391.
8. The composition of claim 1, wherein the antibody is a fragment of a single chain.
9. The composition of claim 1, wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 305, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 348, and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 391.

10. The composition of claim 1, wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 305, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 348 and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 391, and wherein the antibody light chain has CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 176, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 219 and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 262.

11. The composition of claim 1, wherein the antibody heavy chain is comprised of an amino acid sequence as shown in SEQ ID NO. 16.

12. The composition of claim 8, wherein the light chain is comprised of an amino acid sequence as shown in SEQ ID NO. 14.

13. The composition of claim 1, wherein the antibody has a binding affinity to human TFPI by Biacore assay of about 1.25 nM.

14. The composition of claim 3, wherein the composition formulated in a dose of 10 to 100 mg of the human antibody in a pharmaceutically acceptable carrier for injection.

15. A therapeutic composition comprising in combination:

a) an isolated human monoclonal IgG antibody that binds specifically to the Kunitz 1 and Kunitz 2 domain of tissue factor pathway inhibitor (TFPI), and wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 341, a CDR-2 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 384, and a CDR-3 region comprised of an amino acid sequence having at least 80% homology with SEQ ID NO. 427.

16. The composition of claim 15, further comprising Factor VIII or Factor IX in the substantial absence of Factor VII.

17. The composition of claim 16, wherein the antibody has a binding affinity to human TFPI by Biacore assay of about 15.7 nM.

18. The composition of claim 16, wherein the composition is formulated in a dose of 10 to 100 mg of the human antibody in a pharmaceutically acceptable carrier for injection.

19. The composition of claim 15, whereas the CDR-1 region has at least 85% homology to SEQ ID NO. 341.

20. The composition of claim 15, wherein the CDR-2 region has at least 85% homology to SEQ ID NO. 384.

21. The composition of claim 15, wherein the CDR-3 region has at least 85% homology to SEQ ID NO. 427.

22. The composition of claim 15, wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 341, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 384 and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 427.

23. The composition of claim 15, wherein the antibody heavy chain is comprised of an amino acid sequence as shown in SEQ ID NO. 160.

24. The composition of claim 15, wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 341, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 384 and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 427, and wherein the antibody light chain has CDR-1 region comprised of an amino acid sequence as shown in SEQ ID NO. 212, a CDR-2 region comprised of an amino acid sequence as shown in SEQ ID NO. 255 and a CDR-3 region comprised of an amino acid sequence as shown in SEQ ID NO. 298

25. The composition of claim 15, wherein the antibody heavy chain is comprised of an amino acid sequence as shown in SEQ ID NO. 160, and the antibody light chain is comprised of an amino acid sequence as shown in SEQ ID NO. 158.

26. A therapeutic composition comprising:

an isolated human monoclonal IgG antibody that binds specifically to the Kunitz 1 and the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI), wherein the antibody heavy chain has a CDR-1 region comprised of an amino acid sequence having at least 80% homology to a sequence selected from the group consisting of SEQ ID NOS. 302-344, a CDR-2 region comprised of an amino acid sequence selected from the group consisting of SEQ ID NOS. 345-387, and CDR-3 region selected from the group consisting of SEQ ID NOS. 388-430.

27. The composition of claim 28, wherein the antibody has a binding affinity to human TFPI by Biacore assay of about 1.25 to 1140 nM.

28. The composition of claim 28, wherein the antibody is formulated in a dose of 10 to 100 mg in a pharmaceutically acceptable carrier for injection.

29. The composition of claim 28, wherein the antibody light chain has CDR-1 region comprised of amino acid having at least about 80% homology to a sequence selected from the group consisting of SEQ ID NOS. 173-215, a CDR-2 region comprised of an amino acid sequence selected from the group consisting of SEQ ID NOS. 216-258, and a CDR-3 region selected from the group consisting of SEQ ID NOS. 259-301.

30. The use of an isolated human monoclonal IgG antibody of any of claims 1-29, for the manufacture of a medicament for treating a coagulation deficiency.

31. The use of the antibody claim 30, wherein the coagulation deficiency is hemophilia A or hemophilia B.

32. The use of claim 31 further comprising the Factor VIII or Factor IX in the substantial absence of Factor VII.

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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

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50

5560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65707580

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Asn Gly Gly Leu Ile Asp Val Trp Gly Gln Gly Thr Leu Val
100105110

Thr Val Ser Ser
115

<210> 25
<211> 330
<212> DNA
<213> Homo sapiens

<400> 25
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ctgagctgca gagcgagcca gaatattggt tctaattatc tggcttggtta ccagcagaaa 120
ccagggtcaag caccgctctt attaattttat ggtgcttcta ctcgtgcaac tgggggtcccg 180
gcgcgttttta acggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcggttta ttattgccag cagcttaatt ctattcctgt tacctttggc 300
caggggtacga aagttgaaat taaacgtacg 330

<210> 26
<211> 110
<212> PRT
<213> Homo sapiens

<400> 26
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
151015
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Ile Gly Ser Asn
202530
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
354045
Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Asn
505560
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65707580
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Asn Ser Ile Pro
859095

MSB7329PCT_Sequence_Listing_ST25.txt

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

<210> 27
<211> 374
<212> DNA
<213> Homo sapiens

<400> 27
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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcatgatct attatcgtag caagtggat 180
aactcttatg cgggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtactatgt ctaagtatgg tggtcctggt atggatgttt ggggccaagg caccctggtg 360
acggtttagct cagc 374

<210> 28
<211> 124
<212> PRT
<213> Homo sapiens

<400> 28
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 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> 29
<211> 330
<212> DNA

MSB7329PCT_Sequence_Listing_ST25.txt

<213> Homo sapiens
<400> 29
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tcgtgtagcg gcgatgctct tggctattat 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> 30
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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> 31
<211> 355
<212> DNA
<213> Homo sapiens

<400> 31
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gctgcgcggc ctccggattt accttttcta attattctat gacttgggtg cgccaagccc 120
ctgggaaggg tctcgagtgg gtgagcggta tctcttataa tggtagcaat acctattatg 180
cggatagcgt gaaaggccgt tttaccattt cacgtgataa ttcgaaaaac acctgtatc 240
tgcaaataaa cagcctgcgt gcggaagata cggccgtgta ttattgcgcg cgtatttatt 300
atatgaatct tcttgctggt tggggccaag gcaccctggt gacggttagc tcagc 355

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 32
<211> 118
<212> PRT
<213> Homo sapiens

<400> 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> 33
<211> 327
<212> DNA
<213> Homo sapiens

<400> 33
gatatcgaac tgaccagcc gccttcagtg agcggtgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgataatct tcgtggttat tatgcttctt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatg gatgaggat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtcttgg gattctcctt atgttcatgt gtttgccggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 34
<211> 109
<212> PRT
<213> Homo sapiens

<400> 34
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
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1 5 10 15

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> 35
<211> 353
<212> DNA
<213> Homo sapiens

<400> 35
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agctgcaaag cctccggata tacctttact ggtaattcta tgcattgggt ccgccaagcc 120
cctgggcagg gtctcgagt gatgggcact atctttccgt atgatggcac tacgaagtac 180
gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat 240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcdc gcgtggtgtt 300
cattcttatt ttgattattg gggccaaggc accctggtga cggtagctc agc 353

<210> 36
<211> 117
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 37
<211> 327
<212> DNA
<213> Homo sapiens

<400> 37
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60
attacctgca gagcgagcca gtctattcgt tcttatctgg cttggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttataag gcttctaatt tgcaaagcgg ggtcccgtcc 180
cgtttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccatcag tattctgatt ctcctgttac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 38
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt
105

100

<210> 39
<211> 365
<212> DNA
<213> Homo sapiens

<400> 39
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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcattgatc atcatcgtag caagtggat 180
aacgattatg cgggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttattcct ctattgggtca tatggattat tggggccaag gcaccctggt gacggttagc 360
tcagc 365

<210> 40
<211> 121
<212> PRT
<213> Homo sapiens

<400> 40
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 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> 41
<211> 330
<212> DNA
<213> Homo sapiens

MSB7329PCT_Sequence_Listing_ST25.txt

<400> 41
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tcgtgtagcg gcgattctat tggttcttat tatgctcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatgat ttattatgat tctaagcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccaggcttat actggtcagt ctatttctcg tgtgtttggc 300
ggcggcacga agttaaccgt tcttggccag 330

<210> 42
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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> 43
<211> 353
<212> DNA
<213> Homo sapiens

<400> 43
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt taccttttct 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

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 44
<211> 117
<212> PRT
<213> Homo sapiens

<400> 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> 45
<211> 327
<212> DNA
<213> Homo sapiens

<400> 45
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attacctgca gagcgagcca ggatattcgt aataatctgg cttggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatgct gcttcttctt tgcaaagcgg ggtcccgtcc 180
cgtttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccagcag cgtaatgggtt ttcctcttac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 46
<211> 109
<212> PRT
<213> Homo sapiens

<400> 46

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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 47
<211> 365
<212> DNA
<213> Homo sapiens

<400> 47
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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcattatct attatcgtag caagtggat 180
aaccattatg cggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttctaatt ggtctgggta ttttgattat tggggccaag gcaccctggt gacgggtagc 360
tcagc 365

<210> 48
<211> 121
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 49
<211> 342
<212> DNA
<213> Homo sapiens

<400> 49
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attagctgca gaagcagcca aagcctgctt cattctaata gctataactta tctgtcttgg 120
taccttcaaa aaccagggtca aagcccgag ctattaattt atcttggttc taatcgtgcc 180
agtgggggtcc cggatcggtt tagcggctct ggatccggca ccgattttac cctgaaaatt 240
agccgtgtgg aagctgaaga cgtgggcgtg tattattgcc agcagtatga taatgctcct 300
attacctttg gccagggtac gaaagttgaa attaaacgta cg 342

<210> 50
<211> 114
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

105110

Arg Thr

<210> 51

<211> 371

<212> DNA

<213> Homo sapiens

<400> 51

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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120

cagtctcctg ggcgtggcct cgagtggctg ggccttatct attatcgtag caagtggat 180

aacgattatg cgggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240

cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

cgttttggtg atactaatcg taatgggtact gatgtttggg gcccaaggcac cctggtgacg 360

gtttagctcag c 371

<210> 52

<211> 123

<212> PRT

<213> Homo sapiens

<400> 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> 53

MSB7329PCT_Sequence_Listing_ST25.txt

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

<400> 53
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tcgtgtacgg gtactagcag cgatattggg ggttataatt atgtgtcttg gtaccagcag 120
catcccggga aggcgccgaa acttatgatt tatgggtgta attatcgtcc ctcaggcgtg 180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
caagcggaag acgaagcgga ttattattgc tcttctgctg ataagtttac tatgtctatt 300
gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> 54
<211> 113
<212> PRT
<213> Homo sapiens

<400> 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

Gln

<210> 55
<211> 306
<212> DNA
<213> Homo sapiens

<400> 55
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ccagtctcct gggcgtggcc tcgagtggct gggcatgac tattatcgta gcaagtggta 120
taacgattat gcggtgagcg tgaaaagccg gattaccatc aaccggata cttcgaaaaa 180

MSB7329PCT_Sequence_Listing_ST25.txt

ccagtttagc ctgcaactga acagcgtgac cccggaagat acggccgtgt attattgcgc 240
gcgtgttaat cagtatactt cttctgatta ttggggccaa ggcaccctgg tgacggtttag 300
ctcagc 306

<210> 56
<211> 121
<212> PRT
<213> Homo sapiens

<400> 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> 57
<211> 327
<212> DNA
<213> Homo sapiens

<400> 57
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60
attacctgca gagcgagcca gcctatttat aattctctgt cttggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatggg gtttctaatt tgcaaagcgg ggtcccgtcc 180
cgtttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccttcag gttgataatc ttcctattac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 58
<211> 109

MSB7329PCT_Sequence_Listing_ST25.txt

<212> PRT
<213> Homo sapiens
<400> 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> 59
<211> 374
<212> DNA
<213> Homo sapiens
<400> 59
caggtgcaat tgcaacagtc tgggtccgggc 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 ctaatgggta ttatgcttat gttgatcttt ggggccaagg caccctggtg 360
acggtttagct cagc 374

<210> 60
<211> 124
<212> PRT
<213> Homo sapiens
<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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
100 105 110

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

<210> 61
<211> 330
<212> DNA
<213> Homo sapiens

<400> 61
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ctgagctgca gagcgagcca gtctgtttct tctcagtatc tggcttggtta ccagcagaaa 120
ccagggtcaag caccgctctt attaattttat gctgcttctt ctcgtgcaac tgggggtcccg 180
gcgcgttttta gcggctcttg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcggttta ttattgccag caggattcta atcttcctgc tacctttggc 300
caggggtacga aagttgaaat taaacgtacg 330

<210> 62
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Ser Asn Leu Pro

859095

Ala Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100105110

<210> 63

<211> 351

<212> DNA

<213> Homo sapiens

<400> 63

caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgctctg 60

agctgcgcgg cctccggatt taccttttat aagtatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggg 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> 64

<211> 117

<212> PRT

<213> Homo sapiens

<400> 64

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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Tyr Lys Tyr

202530

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

354045

Ser Gly Ile Gln Tyr Asp Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val

505560

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

65707580

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

859095

Ala Arg Tyr Tyr Cys Lys Cys Val Asp Leu Trp Gly Gln Gly Thr Leu

100105110

Val Thr Val Ser Ser

115

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 65
<211> 327
<212> DNA
<213> Homo sapiens

<400> 65
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgatc 60
tcgtgtagcg gcgataatat tcgtaagttt tatgttcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttatgggtact aataagcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtccttat gattctaagt ttaatactgt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 66
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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

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

<210> 67
<211> 359
<212> DNA
<213> Homo sapiens

<400> 67
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctcg 60
agctgcgcgg cctccggatt taccttttct tcttatgcta tgaattgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgct atcctttctg atggtagctc tacctcttat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

MSB7329PCT_Sequence_Listing_ST25.txt

ctgcaaata ga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttatcct 300
gattgggggtt ggtataactga tgtttggggc caaggcaccc tgggtgacggt tagctcagc 359

<210> 68
<211> 119
<212> PRT
<213> Homo sapiens

<400> 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> 69
<211> 330
<212> DNA
<213> Homo sapiens

<400> 69

gatatcgaac tgacccagcc gccttcagtg agcgttgacac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgatgctct tcgtaagcat tatgtttatt ggtaccagca gaaaccggg 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

<210> 70
<211> 110
<212> PRT
<213> Homo sapiens

MSB7329PCT_Sequence_Listing_ST25.txt

<400> 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> 71
<211> 356
<212> DNA
<213> Homo sapiens

<400> 71
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agctgcgcgg cctccggatt taccttttct tcttatgcta tgacttgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcaat atctcttatt ctggtagcaa tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaataga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgttggg 300
tattattatg gttttgatta ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> 72
<211> 118
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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

Leu Val Thr Val Ser Ser
115

<210> 73
<211> 330
<212> DNA
<213> Homo sapiens

<400> 73
gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc 60
ctgagctgca gagcgagcca gaatgtttct tctaattatc tggcttggtta ccagcagaaa 120
ccagggtcaag caccgctctt attaattttat gatgcttcta atcgtgcaac tgggggtcccg 180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcggttta ttattgccag cagttttatg attctcctca gacctttggc 300
cagggtacga aagttgaaat taaacgtacg 330

<210> 74
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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> 75
<211> 365
<212> DNA
<213> Homo sapiens

<400> 75
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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttggtc ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggctttatct attatcgtag caagtggat 180
aacgattatg cgggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtcataatc ctgatcttgg ttttgattat tggggccaag gcaccctggt gacggtagc 360
tcagc 365

<210> 76
<211> 121
<212> PRT
<213> Homo sapiens

<400> 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> 77

MSB7329PCT_Sequence_Listing_ST25.txt

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

<400> 77
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ctgagctgca gagcgagcca gtatgttact tcttcttattc tggcttggtta ccagcagaaa 120
ccagggtcaag caccgcgtct attaatattat ggttcttctc gtgcaactgg ggtcccggcg 180
cgtttttagcg gctctggatc cggcacggat tttaccctga ccattagcag cctggaacct 240
gaagactttg cgacttatta ttgccagcag tattcttctt ctcctattac ctttggccag 300
ggtagcgaag ttgaaattaa acgtacg 327

<210> 78
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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

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

<210> 79
<211> 362
<212> DNA
<213> Homo sapiens

<400> 79
caggtgcaat tgcaacagtc tgggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60
acctgtgcga tttccggaga tagcgtgagc tcttcttctg ctgcttggtc ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcattatct attatcgtag caagtggat 180
aacgattatg cgggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

MSB7329PCT_Sequence_Listing_ST25.txt

cgtcattcta tggttggttt tgatgtttgg ggccaaggca ccctggtgac ggtagctca 360
gc 362

<210> 80
<211> 120
<212> PRT
<213> Homo sapiens

<400> 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> 81
<211> 330
<212> DNA
<213> Homo sapiens

<400> 81
gatatcgaac tgacccagcc gccttcagtg agcgttgac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgataatct tggacttat tatgttcatt ggtaccagca gaaaccggg 120
caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagacttat gattctaata atgagtctat tgtgtttggc 300
ggcggcacga agttaaccgt tcttggccag 330

<210> 82
<211> 110
<212> PRT
<213> Homo sapiens

MSB7329PCT_Sequence_Listing_ST25.txt

<400> 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> 83
<211> 368
<212> DNA
<213> Homo sapiens

<400> 83
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agctgcgcgg cctccggatt tacctttaat tcttatgcta tgtcttgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcaat atctcttcta attctagcaa tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaataga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaagggt 300
gggtggtgagc atgggtttttt tccttctgat atttggggcc aaggcaccct ggtgacgggt 360
agctcagc 368

<210> 84
<211> 122
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

354045

Ser Asn Ile Ser Ser Asn Ser Ser Asn Thr Tyr Tyr Ala Asp Ser Val

505560

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

65707580

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

859095

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

100105110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115120

<210> 85

<211> 333

<212> DNA

<213> Homo sapiens

<400> 85

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tcgtgtacgg gtactagcag cgatcttggg ggttttaata ctgtgtcttg gtaccagcag 120

catcccgga aggcgccgaa acttatgatt tattctgttt cttctcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgacat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg atcttaataa tcttgtgttt 300

ggcggcgga cgaagttaac cgttcttggc cag 333

<210> 86

<211> 111

<212> PRT

<213> Homo sapiens

<400> 86

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

151015

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Phe

202530

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

354045

Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe

505560

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

65707580

MSB7329PCT_Sequence_Listing_ST25.txt

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> 87
<211> 353
<212> DNA
<213> Homo sapiens

<400> 87
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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
tctggttggt ttgatgtttg gggccaaggc accctggtga cggttagctc agc 353

<210> 88
<211> 117
<212> PRT
<213> Homo sapiens

<400> 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> 89

MSB7329PCT_Sequence_Listing_ST25.txt

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

<400> 89
gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagcca gtctgtttct tctttttatc tggcttggtg ccagcagaaa 120
ccagggtcaag caccgcgtct attaatattat ggttcttctt ctcgtgcaac tgggggtcccg 180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagact ttgcgactta ttattgccag cagtatgatt ctactccttc tacctttggc 300
caggggtacga aagttgaaat taaacgtacg 330

<210> 90
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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

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> 91
<211> 365
<212> DNA
<213> Homo sapiens

<400> 91
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acctgtgcga tttccggaga tagcgtgagc tctaattggtg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggctttatct atcgtcgtag caagtggtat 180
aactcttatg cgggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300

MSB7329PCT_Sequence_Listing_ST25.txt

cgtcaggatg gtatgggtgg tatggattct tggggccaag gcaccctggt gacggttagc 360
tcagc 365

<210> 92
<211> 121
<212> PRT
<213> Homo sapiens

<400> 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> 93
<211> 327
<212> DNA
<213> Homo sapiens

<400> 93

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tcgtgtagcg gcgataatat tggttctcgt tatgcttatt ggtaccagca gaaaccggg 120
caggcgccag ttgttgtgat ttatgatgat tctgatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg cgctgcttat actttttatg ctcgtactgt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 94
<211> 109
<212> PRT
<213> Homo sapiens

MSB7329PCT_Sequence_Listing_ST25.txt

<400> 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> 95
<211> 359
<212> DNA
<213> Homo sapiens

<400> 95
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agctgcgcgg cctccggatt taccttttct aattattatc tttcttgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgg atctcttata atggtagctc taccaattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaa caccctgtat 240
ctgcaaata acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtatgtgg 300
cgttattctc ttggtgctga ttcttggggc caaggcaccc tggtgacggt tagctcagc 359

<210> 96
<211> 119
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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

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> 97
<211> 327
<212> DNA
<213> Homo sapiens

<400> 97
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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> 98
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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
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85

90

95

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

<210> 99
<211> 371
<212> DNA
<213> Homo sapiens

<400> 99
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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 gcgtgggtcat 300
catcgtgggtc attcttgggc ttcttttatt gattattggg gccaaaggcac cctggtgacg 360
gttagctcag c 371

<210> 100
<211> 123
<212> PRT
<213> Homo sapiens

<400> 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 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> 101

MSB7329PCT_Sequence_Listing_ST25.txt

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

<400> 101
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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
ggcggcgga cgaagttaac cggttcttggc cag 333

<210> 102
<211> 111
<212> PRT
<213> Homo sapiens

<400> 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
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> 103
<211> 347
<212> DNA
<213> Homo sapiens

<400> 103
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 60
agctgcgcgg cctccggatt taccttttct 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

MSB7329PCT_Sequence_Listing_ST25.txt

ggtatggatt attggggcca aggcaccctg gtgacgggta gctcagc 347

<210> 104
<211> 115
<212> PRT
<213> Homo sapiens

<400> 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> 105
<211> 327
<212> DNA
<213> Homo sapiens
<400> 105
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tcgtgtagcg gcgataatct tcgttctaag tatgctcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttatgggtgat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ctctgcttat gctatggggtt cttctcctgt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 106
<211> 109
<212> PRT
<213> Homo sapiens
<400> 106

MSB7329PCT_Sequence_Listing_ST25.txt

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> 107
<211> 356
<212> DNA
<213> Homo sapiens

<400> 107
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 60
agctgcgcgg cctccggatt taccttttct tcttatggta tgcattgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcaat atctcttata tgggtagcaa taccaattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtggctctt 300
tttctgggtt attttgatta ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> 108
<211> 118
<212> PRT
<213> Homo sapiens

<400> 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
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MSB7329PCT_Sequence_Listing_ST25.txt

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 Leu Phe Pro Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 109
<211> 327
<212> DNA
<213> Homo sapiens

<400> 109
gatatccaga tgacccagag cccgtctagc ctgagcgca gctgggtga tcgtgtgacc 60
attacctgca gagcgagcca gaatatttct aattatctga attggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatggc acttcttctt tgcaaagcgg ggtcccgtcc 180
cgtttttagcg gctctggatc cggcactgat ttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccagcag tatggtaata atcctactac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 110
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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

<210> 111
<211> 377
<212> DNA
<213> Homo sapiens

<400> 111
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acctgtgcga tttccggaga tagcgtgagc tctaattggtg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggccatatct attatcgtag caagtggat 180
aactcttatg cgggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttgggggtg gtattcatga tggtgatatt tattttgatt attggggcca aggcaccctg 360
gtgacgggta gctcagc 377

<210> 112
<211> 125
<212> PRT
<213> Homo sapiens

<400> 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> 113
<211> 327
<212> DNA

MSB7329PCT_Sequence_Listing_ST25.txt

<213> Homo sapiens
<400> 113
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attacctgca gagcgagcca gtctattact aattatctga attggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatgat gtttctaatt tgcaaagcgg ggtcccggtcc 180
cgtttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccagcag tattctgggtt atcctcttac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 114
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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
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> 115
<211> 362
<212> DNA
<213> Homo sapiens

<400> 115
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acctgtgcga tttccggaga tagcgtgagc tcttcttctg ctgcttggtc ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcattgatct attatcgtag caagtggat 180
aaccattatg cgggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtgggtgggt ctggtgttat ggatgtttgg ggccaaggca ccctggtgac ggtagctca 360

MSB7329PCT_Sequence_Listing_ST25.txt

gc 362

<210> 116
<211> 120
<212> PRT
<213> Homo sapiens

<400> 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> 117
<211> 327
<212> DNA
<213> Homo sapiens
<400> 117
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attacctgca gagcgagcca gtctattaat ccttatctga attggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatgct gcttctaatt tgcaaagcgg ggtcccgtcc 180
cgtttttagcg gctctggatc cggcactgat ttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccagcag cttgataatc gttctattac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 118
<211> 109
<212> PRT
<213> Homo sapiens

<400> 118

MSB7329PCT_Sequence_Listing_ST25.txt

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> 119
<211> 371
<212> DNA
<213> Homo sapiens

<400> 119
caggtgcaat tgcaacagtc tgggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60
acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcgttatct attatcgtag caagtggat 180
aacgattatg cggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgtgctcgtg ctaagaagtc tgggtggtttt gattattggg gccaaaggcac cctggtgacg 360
gtagctcag c 371

<210> 120
<211> 123
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 121
<211> 330
<212> DNA
<213> Homo sapiens

<400> 121
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tcgtgtagcg gcgattctct tggttctaag tttgctcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ctctacttat acttctcggt ctcattctta tgtgtttggc 300
ggcggcacga agttaaccgt tcttggccag 330

<210> 122
<211> 110
<212> PRT
<213> Homo sapiens

<400> 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> 123
<211> 350
<212> DNA
<213> Homo sapiens

<400> 123
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgctctg 60
agctgcgcgg cctccggatt taccttttct tcttatgctt cttgggtgcg ccaagcccct 120
gggaaggggtc tcgagtgggt gagcgggtatc 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> 124
<211> 116
<212> PRT
<213> Homo sapiens

<400> 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> 125
<211> 327
<212> DNA

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<213> Homo sapiens
<400> 125
gatatcgaac tgaccagcc gccttcagtg agcggtgcac caggtcagac cgcgcgatc 60
tcgtgtagcg gcgataatat tggttcttat tatgcttatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttatgatgat tctaatacgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtcttat gattctactg gtcttcttgt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 126
<211> 109
<212> PRT
<213> Homo sapiens

<400> 126
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp 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
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> 127
<211> 377
<212> DNA
<213> Homo sapiens

<400> 127
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt taccttttct 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
aaggctgggtc gtacttgggtg gtggggtcct tatatggatg tttggggcca aggcacctg 360

MSB7329PCT_Sequence_Listing_ST25.txt

gtgacggtta gctcagc 377

<210> 128
<211> 125
<212> PRT
<213> Homo sapiens

<400> 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> 129
<211> 312
<212> DNA
<213> Homo sapiens

<400> 129

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> 130
<211> 104
<212> PRT
<213> Homo sapiens

<400> 130

MSB7329PCT_Sequence_Listing_ST25.txt

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> 131
<211> 368
<212> DNA
<213> Homo sapiens

<400> 131
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcctttact gattattgga ttggttggtt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt atccagccgt ctgatagcga taccaattat 180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcg gcgttttatg 300
tggtggggta agtatgattc tggttttgat gtttggggcc aaggcaccct ggtgacggtt 360
agctcagc 368

<210> 132
<211> 122
<212> PRT
<213> Homo sapiens

<400> 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
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

MSB7329PCT_Sequence_Listing_ST25.txt

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> 133
<211> 327
<212> DNA
<213> Homo sapiens

<400> 133
gatatcgaac tgaccagcc gccttcagtg agcgttgac caggtcagac cgcgcgatc 60
tcgtgtagcg gcgataatct tccttctaag tctgtttatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatgat ttatggatgat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtcttgg acttctcgtc ctatggttgt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 134
<211> 109
<212> PRT
<213> Homo sapiens

<400> 134
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp 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

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

<210> 135
<211> 353
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (156)..(156)
<223> n is a, c, g, or t

<400> 135
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 60
agctgcgcgg cctccggatt taccttttct tcttattcta tgcattgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcggc atctcntatt cttctagctt tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgctctt 300
gggtggtggtg ttgattattg gggccaaggc accctggtga cggttagctc agc 353

<210> 136
<211> 117
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

115

<210> 137
<211> 327
<212> DNA
<213> Homo sapiens

<400> 137
gatatccaga tgaccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60
attacctgca gagcgagcca gggatatttct tcttatctgc attggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatggg gcttctactt tgcaaagcgg ggtcccgctcc 180
cgtttttagcg gctctggatc cggcactgat ttaccctga ccattagcag cctgcaacct 240
gaagactttg cgacttatta ttgccagcag cagaatgggt atccttttac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

<210> 138
<211> 109
<212> PRT
<213> Homo sapiens

<400> 138
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys 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> 139
<211> 374
<212> DNA
<213> Homo sapiens

<400> 139
caggtgcaat tgcaacagtc tgggtccgggc ctggtgaaac cgagccaaac cctgagcctg 60
acctgtgcga tttccggaga tagcgtgagc tctaattctg gtggttgggg ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggccttatct attatcgtag caagtggtat 180

MSB7329PCT_Sequence_Listing_ST25.txt

aacgcttatg cggtgagcgt gaaaagccgg attaccatca acccggtatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttatcttg gttctaattt ttatgtttat tctgatgttt ggggccaagg caccctggtg 360
acggtttagct cagc 374

<210> 140
<211> 124
<212> PRT
<213> Homo sapiens

<400> 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

<210> 141
<211> 327
<212> DNA
<213> Homo sapiens

<400> 141

gatatccaga tgaccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60
attacctgca gagcgagcca gaatattcat tctcatctga attggtacca gcagaaacca 120
ggtaaagcac cgaaactatt aatttatgat gcttcttctt tgcaaagcgg ggtcccgctc 180
cgtttttagcg gctctggatc cggcactgat ttaccctga ccattagcag cctgcaacct 240
gaagactttg cggtttatta ttgccagcag tattatgatt atcctcttac ctttggccag 300
ggtacgaaag ttgaaattaa acgtacg 327

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 142
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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> 143
<211> 353
<212> DNA
<213> Homo sapiens

<400> 143

caggtgcaat tgggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt taccttttct 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
tataagggtg tggaatatttg gggccaaggc accctggtga cggttagctc agc 353

<210> 144
<211> 117
<212> PRT
<213> Homo sapiens

<400> 144

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

MSB7329PCT_Sequence_Listing_ST25.txt

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> 145
<211> 324
<212> DNA
<213> Homo sapiens

<400> 145
gatatcgaac tgaccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgatc 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> 146
<211> 108
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

65707580

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Ala Ala Phe Gly Ser Thr Val

859095

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln

100105

<210> 147

<211> 350

<212> DNA

<213> Homo sapiens

<400> 147

caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 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> 148

<211> 116

<212> PRT

<213> Homo sapiens

<400> 148

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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr

202530

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

354045

Ser Asn Ile Ser Ser Ser Gly Ser Asn Thr Asn Tyr Ala Asp Ser Val

505560

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

65707580

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

859095

Ala Arg Val His Tyr Gly Phe Asp Phe Trp Gly Gln Gly Thr Leu Val

100105110

Thr Val Ser Ser

115

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 149
<211> 327
<212> DNA
<213> Homo sapiens

<400> 149
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgatc 60
tcgtgtagcg gcgatgctct tggttctaag tttgctcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatgat ttatgatgat tctgagcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccaggcttat gattctggtc ttctttatgt gtttgggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 150
<211> 109
<212> PRT
<213> Homo sapiens

<400> 150
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> 151
<211> 359
<212> DNA
<213> Homo sapiens

<400> 151
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 60
agctgcgcgg cctccggatt tacctttcgt aattatgcta tgaattgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgtt atctctggtt cttctagcta tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

MSB7329PCT_Sequence_Listing_ST25.txt

ctgcaaata acagcctgcg tgcggaagat acggccgtgt attattgcmc gcgtgctgat 300
cttccttata tggtttttga ttattggggc caaggcaccc tggtgacggt tagctcagc 359

<210> 152
<211> 119
<212> PRT
<213> Homo sapiens

<400> 152

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe 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> 153
<211> 324
<212> DNA
<213> Homo sapiens

<400> 153

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgatgctct tggtaagtat tatgcttctt ggtaccagca gaaaccggg 120
caggcgccag ttcttgatgat ttatggatgat aataagcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtcttat actactcgtt ctcttggtgtt tggcggcggc 300
acgaagttaa ccgttcttgg ccag 324

<210> 154
<211> 108
<212> PRT
<213> Homo sapiens

MSB7329PCT_Sequence_Listing_ST25.txt

<400> 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> 155
<211> 353
<212> DNA
<213> Homo sapiens

<400> 155
caggtgcaat tgggtgaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgctctg 60
agctgcgcgg cctccggatt taccttttct tcttatggta tgtcttgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcctt atctctgggt tttctagctc tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgttcttat 300
cttggttatt ttgatgtttg gggccaaggc accctgggtga cggttagctc agc 353

<210> 156
<211> 117
<212> PRT
<213> Homo sapiens

<400> 156

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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 157
<211> 342
<212> DNA
<213> Homo sapiens

<400> 157
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attagctgca gaagcagcca aagcctgggt ttttctgatg gcaataactta tctgaattgg 120
taccttcaaa aaccagggtca aagcccgag ctattaattt ataagggttc taatcgtgcc 180
agtgggggtcc cggatcgttt tagcggctct ggatccggca ccgattttac cctgaaaatt 240
agccgtgtgg aagctgaaga cgtgggcgtg tattattgcc agcagtatga ttcttatcct 300
cttacctttg gccagggtac gaaagttgaa attaaacgta cg 342

<210> 158
<211> 114
<212> PRT
<213> Homo sapiens

<400> 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> 159
<211> 371
<212> DNA
<213> Homo sapiens

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acctgtgcga tttccggaga tagcgtgagc tctaattctg ctgcttggtc ttggattcgc 120
cagtctcctg ggcgtggcct cgagtggctg ggcattatct ataagcgtag caagtggat 180
aacgattatg cgggtgagcgt gaaaagccgg attaccatca acccgatac ttcgaaaaac 240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg 300
cgttggcatt ctgataagca ttgggggttt gattattggg gccaaggcac cctggtgacg 360
gtagctcag c 371

<210> 160
<211> 123
<212> PRT
<213> Homo sapiens

<400> 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
Page 67

MSB7329PCT_Sequence_Listing_ST25.txt
120

115

<210> 161
<211> 327
<212> DNA
<213> Homo sapiens

<400> 161
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tcgtgtagcg gcgatgctct tggttctaag tatgtttctt ggtaccagca gaaacccggg 120
caggcgccag ttcttgatgat ttatggatgat aataagcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagtcttat acttattctc ttaatcaggt gtttggcggc 300
ggcacgaagt taaccgttct tggccag 327

<210> 162
<211> 109
<212> PRT
<213> Homo sapiens

<400> 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> 163
<211> 356
<212> DNA
<213> Homo sapiens

<400> 163
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agctgcgcgg cctccggatt tacctttaat gattatgcta tgtcttgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcctt atcgagtctg tttctagctc tacctattat 180

MSB7329PCT_Sequence_Listing_ST25.txt

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtactatt 300
gggtgttcttt gggatgatgt ttggggccaa ggcaccctgg tgacggttag ctcagc 356

<210> 164
<211> 118
<212> PRT
<213> Homo sapiens

<400> 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

<210> 165
<211> 324
<212> DNA
<213> Homo sapiens

<400> 165

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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> 166
<211> 108

MSB7329PCT_Sequence_Listing_ST25.txt

<212> PRT
<213> Homo sapiens
<400> 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> 167
<211> 359
<212> DNA
<213> Homo sapiens

<400> 167
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agctgcgcgg cctccggatt taccttttct 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
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<210> 168
<211> 119
<212> PRT
<213> Homo sapiens
<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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> 169
<211> 333
<212> DNA
<213> Homo sapiens

<400> 169
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caggcgccag ttcttgatgatatggtgat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ctctactgct gattctgtta ttacttataa gaatgtgttt 300
ggcggcgga cgaagttaac cggtcttggc cag 333

<210> 170
<211> 111
<212> PRT
<213> Homo sapiens

<400> 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

MSB7329PCT_Sequence_Listing_ST25.txt

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

<210> 171
<211> 362
<212> DNA
<213> Homo sapiens

<400> 171
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cctgggaagg gtctcgagtg ggtgagcgtt atcgagtatt ctggtagcaa gaccaattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgggtgat 300
tattatcctt atcttgtttt tgctatttgg ggccaaggca ccctggtgac ggtagctca 360
gc 362

<210> 172
<211> 120
<212> PRT
<213> Homo sapiens

<400> 172
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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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

MSB7329PCT_Sequence_Listing_ST25.txt

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<210> 174
<211> 11
<212> PRT
<213> Homo sapiens

<400> 174
Ser Gly Asp Asn Ile Pro Glu Lys Tyr Val His
1 5 10

<210> 175
<211> 11
<212> PRT
<213> Homo sapiens

<400> 175
Ser Gly Asp Lys Ile Gly Ser Lys Tyr Val Tyr
1 5 10

<210> 176
<211> 11
<212> PRT
<213> Homo sapiens

<400> 176
Ser Gly Asp Asn Leu Arg Asn Tyr Tyr Ala His
1 5 10

<210> 177
<211> 11
<212> PRT
<213> Homo sapiens

<400> 177
Ser Gly Asp Lys Leu Gly Lys Lys Tyr Val His
1 5 10

<210> 178
<211> 11
<212> PRT
<213> Homo sapiens

<400> 178
Ser Gly Asp Asn Leu Gly Asn Lys Tyr Ala His
1 5 10

<210> 179

MSB7329PCT_Sequence_Listing_ST25.txt

<211> 12
<212> PRT
<213> Homo sapiens

<400> 179
Arg Ala Ser Gln Asn Ile Gly Ser Asn Tyr Leu Ala
1 5 10

<210> 180
<211> 11
<212> PRT
<213> Homo sapiens

<400> 180
Ser Gly Asp Ala Leu Gly Thr Tyr Tyr Ala Tyr
1 5 10

<210> 181
<211> 11
<212> PRT
<213> Homo sapiens

<400> 181
Ser Gly Asp Asn Leu Arg Gly Tyr Tyr Ala Ser
1 5 10

<210> 182
<211> 11
<212> PRT
<213> Homo sapiens

<400> 182
Arg Ala Ser Gln Ser Ile Arg Ser Tyr Leu Ala
1 5 10

<210> 183
<211> 11
<212> PRT
<213> Homo sapiens

<400> 183
Ser Gly Asp Ser Ile Gly Ser Tyr Tyr Ala His
1 5 10

<210> 184
<211> 11
<212> PRT
<213> Homo sapiens

<400> 184
Arg Ala Ser Gln Asp Ile Arg Asn Asn Leu Ala
1 5 10

<210> 185
<211> 16
<212> PRT

MSB7329PCT_Sequence_Listing_ST25.txt

<213> Homo sapiens
<400> 185
Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Thr Tyr Leu Ser
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<210> 186
<211> 14
<212> PRT
<213> Homo sapiens
<400> 186
Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 187
<211> 11
<212> PRT
<213> Homo sapiens
<400> 187
Arg Ala Ser Gln Pro Ile Tyr Asn Ser Leu Ser
1 5 10

<210> 188
<211> 12
<212> PRT
<213> Homo sapiens
<400> 188
Arg Ala Ser Gln Ser Val Ser Ser Gln Tyr Leu Ala
1 5 10

<210> 189
<211> 11
<212> PRT
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<400> 189
Ser Gly Asp Asn Ile Arg Lys Phe Tyr Val His
1 5 10

<210> 190
<211> 11
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<213> Homo sapiens
<400> 190
Ser Gly Asp Ala Leu Arg Lys His Tyr Val Tyr
1 5 10

<210> 191
<211> 12
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MSB7329PCT_Sequence_Listing_ST25.txt

<400> 191

Arg Ala Ser Gln Asn Val Ser Ser Asn Tyr Leu Ala
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<211> 12

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<213> Homo sapiens

<400> 192

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

<210> 193

<211> 11

<212> PRT

<213> Homo sapiens

<400> 193

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

<210> 194

<211> 14

<212> PRT

<213> Homo sapiens

<400> 194

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

<210> 195

<211> 12

<212> PRT

<213> Homo sapiens

<400> 195

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

<210> 196

<211> 11

<212> PRT

<213> Homo sapiens

<400> 196

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

<210> 197

<211> 11

<212> PRT

<213> Homo sapiens

<400> 197

MSB7329PCT_Sequence_Listing_ST25.txt

Ser Gly Asp Asn Ile Gly Ser Lys Tyr Val His
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<210> 198
<211> 11
<212> PRT
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<400> 198

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

<210> 199
<211> 11
<212> PRT
<213> Homo sapiens

<400> 199

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

<210> 200
<211> 11
<212> PRT
<213> Homo sapiens

<400> 200

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

<210> 201
<211> 11
<212> PRT
<213> Homo sapiens

<400> 201

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

<210> 202
<211> 11
<212> PRT
<213> Homo sapiens

<400> 202

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

<210> 203
<211> 11
<212> PRT
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<400> 203

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

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 204
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<212> PRT
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<400> 204

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

<210> 205
<211> 11
<212> PRT
<213> Homo sapiens

<400> 205

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

<210> 206
<211> 11
<212> PRT
<213> Homo sapiens

<400> 206

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

<210> 207
<211> 11
<212> PRT
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<400> 207

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

<210> 208
<211> 11
<212> PRT
<213> Homo sapiens

<400> 208

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

<210> 209
<211> 11
<212> PRT
<213> Homo sapiens

<400> 209

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

MSB7329PCT_Sequence_Listing_ST25.txt

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<400> 210

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

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

<400> 211

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

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

<400> 212

Arg Ser Ser Gln Ser Leu Val Phe Ser Asp Gly Asn Thr Tyr Leu Asn
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<210> 213
<211> 11
<212> PRT
<213> Homo sapiens

<400> 213

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

<210> 214
<211> 11
<212> PRT
<213> Homo sapiens

<400> 214

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

<210> 215
<211> 11
<212> PRT
<213> Homo sapiens

<400> 215

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

<210> 216
<211> 7

MSB7329PCT_Sequence_Listing_ST25.txt

<212> PRT
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 <400> 216

Gly Asp Ser Lys Arg Pro Ser
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 <211> 7
 <212> PRT
 <213> Homo sapiens
 <400> 217

Gly Asp Asn Asn Arg Pro Ser
 1 5

<210> 218
 <211> 6
 <212> PRT
 <213> Homo sapiens
 <400> 218

Asp Ser Asn Arg Pro Ser
 1 5

<210> 219
 <211> 7
 <212> PRT
 <213> Homo sapiens
 <400> 219

Tyr Asp Asn Asn Arg Pro Ser
 1 5

<210> 220
 <211> 7
 <212> PRT
 <213> Homo sapiens
 <400> 220

Gly Asp Asp Lys Arg Pro Ser
 1 5

<210> 221
 <211> 7
 <212> PRT
 <213> Homo sapiens
 <400> 221

Tyr Asp Asn Lys Arg Pro Ser
 1 5

<210> 222
 <211> 7
 <212> PRT
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MSB7329PCT_Sequence_Listing_ST25.txt

<400> 222
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1 5

<210> 223
<211> 7
<212> PRT
<213> Homo sapiens

<400> 223
Gly Asp Met Asn Arg Pro Ser
1 5

<210> 224
<211> 7
<212> PRT
<213> Homo sapiens

<400> 224
Glu Asp Asn Asn Arg Pro Ser
1 5

<210> 225
<211> 7
<212> PRT
<213> Homo sapiens

<400> 225
Lys Ala Ser Asn Leu Gln Ser
1 5

<210> 226
<211> 7
<212> PRT
<213> Homo sapiens

<400> 226
Tyr Asp Ser Lys Arg Pro Ser
1 5

<210> 227
<211> 7
<212> PRT
<213> Homo sapiens

<400> 227
Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 228
<211> 7
<212> PRT
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<400> 228

MSB7329PCT_Sequence_Listing_ST25.txt

Leu Gly Ser Asn Arg Ala Ser
1 5

<210> 229
<211> 7
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<213> Homo sapiens
<400> 229

Gly Val Asn Tyr Arg Pro Ser
1 5

<210> 230
<211> 7
<212> PRT
<213> Homo sapiens
<400> 230

Gly Val Ser Asn Leu Gln Ser
1 5

<210> 231
<211> 7
<212> PRT
<213> Homo sapiens
<400> 231

Ala Ala Ser Ser Arg Ala Thr
1 5

<210> 232
<211> 7
<212> PRT
<213> Homo sapiens
<400> 232

Gly Thr Asn Lys Arg Pro Ser
1 5

<210> 233
<211> 7
<212> PRT
<213> Homo sapiens
<400> 233

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> 234
<211> 7
<212> PRT
<213> Homo sapiens
<400> 234

Asp Ala Ser Asn Arg Ala Thr

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5

<210> 235
<211> 6
<212> PRT
<213> Homo sapiens

<400> 235

Gly Ser Ser Arg Ala Thr
1 5

<210> 236
<211> 7
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<213> Homo sapiens

<400> 236

Gly Asp Asn Asn Arg Pro Ser
1 5

<210> 237
<211> 7
<212> PRT
<213> Homo sapiens

<400> 237

Ser Val Ser Ser Arg Pro Ser
1 5

<210> 238
<211> 7
<212> PRT
<213> Homo sapiens

<400> 238

Gly Ser Ser Ser Arg Ala Thr
1 5

<210> 239
<211> 7
<212> PRT
<213> Homo sapiens

<400> 239

Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 240
<211> 7
<212> PRT
<213> Homo sapiens

<400> 240

Glu Asp Ser Asp Arg Pro Ser
1 5

MSB7329PCT_Sequence_Listing_ST25.txt

<210> 241
 <211> 7
 <212> PRT
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<400> 241

Ser Lys Ser Glu Arg Pro Ser
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<210> 242
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 242

Gly Asp Asn Asn Arg Pro Ser
 1 5

<210> 243
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 243

Gly Thr Ser Ser Leu Gln Ser
 1 5

<210> 244
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 244

Asp Val Ser Asn Leu Gln Ser
 1 5

<210> 245
 <211> 7
 <212> PRT
 <213> Homo sapiens

<400> 245

Ala Ala Ser Asn Leu Gln Ser
 1 5

<210> 246
 <211> 7
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Gln Gln Tyr Tyr Asp Tyr Pro Leu Thr
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Gln Gln Tyr Asp Ser Tyr Pro Leu Thr
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Gln Ser Tyr Thr Tyr Ser Leu Asn Gln Val
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MSB7329PCT_Sequence_Listing_ST25.txt

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Lys Ser

MSB7329PCT_Sequence_Listing_ST25.txt

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Lys Ser

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Lys Ser

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MSB7329PCT_Sequence_Listing_ST25.txt

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Gly

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Gly

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Lys Ser

MSB7329PCT_Sequence_Listing_ST25.txt

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Lys Ser

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MSB7329PCT_Sequence_Listing_ST25.txt

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Gly

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Lys Ser

MSB7329PCT_Sequence_Listing_ST25.txt

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Lys Ser

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MSB7329PCT_Sequence_Listing_ST25.txt

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Gly

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Lys Ser

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Gly

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Gly

MSB7329PCT_Sequence_Listing_ST25.txt

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Gly

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Gly

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Thr Ile Ser Gly Tyr Gly Ser Phe Thr Tyr Tyr Ala Asp Ser Val Lys
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