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(54) **PLATELET GLYCOPROTEIN IB ALPHA
FUSION POLYPEPTIDES AND METHODS OF
USE THEREOF**

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435/325; 530/350; 536/23.5

(57) **ABSTRACT**

The present invention provides compositions and methods for treating or preventing vascular-associated disorders.

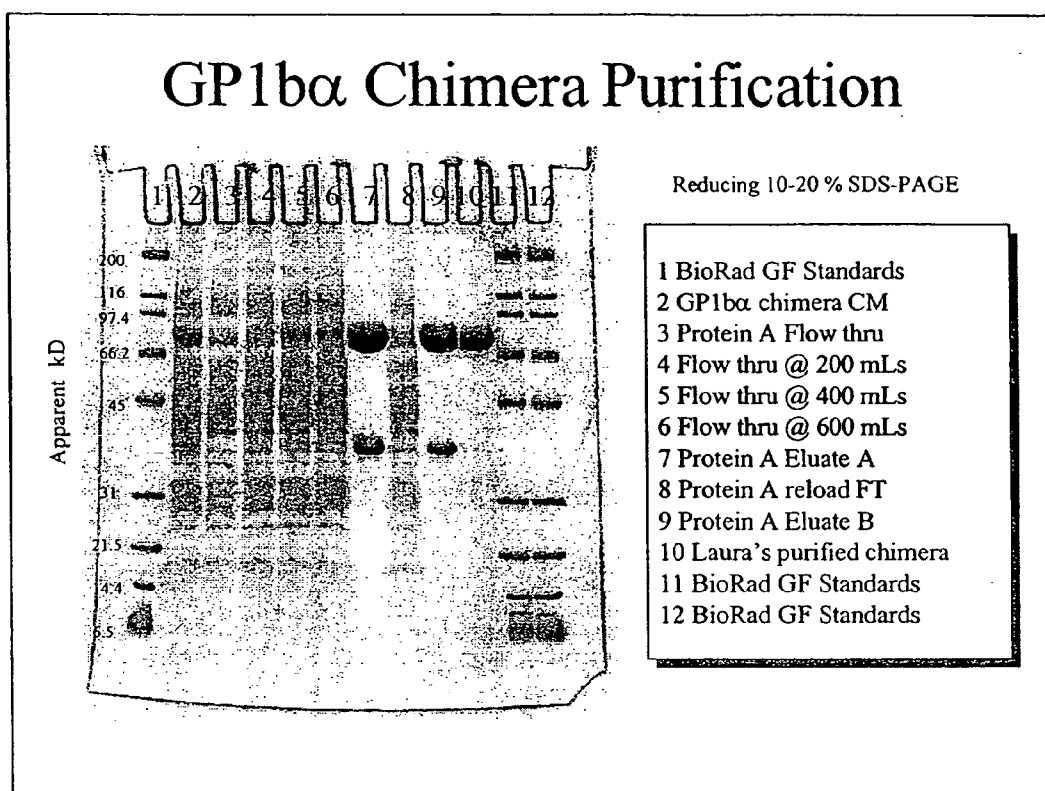


FIG. 1

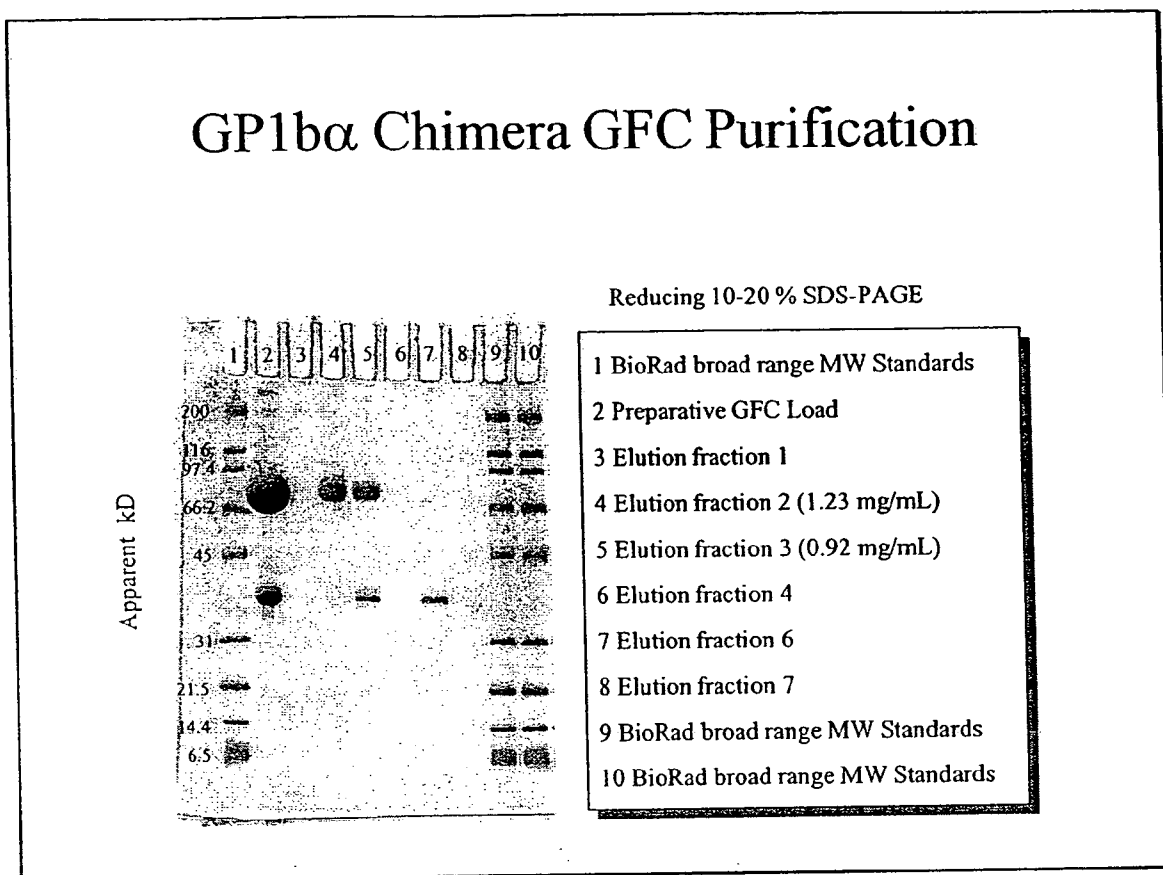


FIG. 2

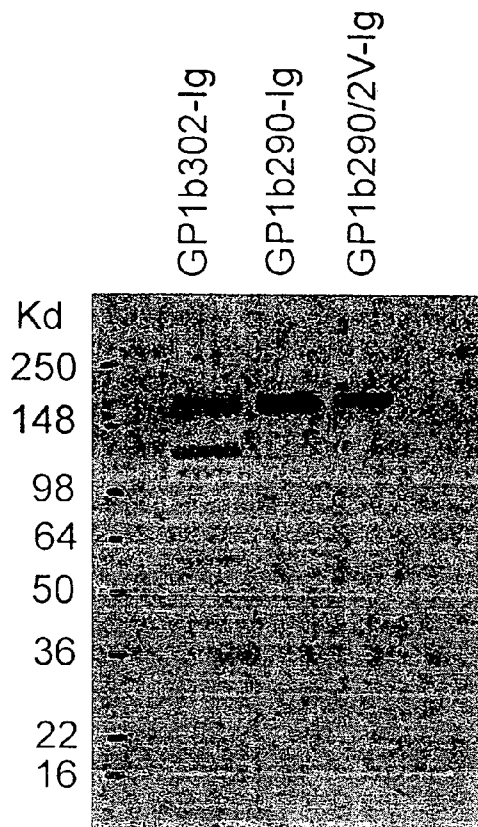


FIG. 3

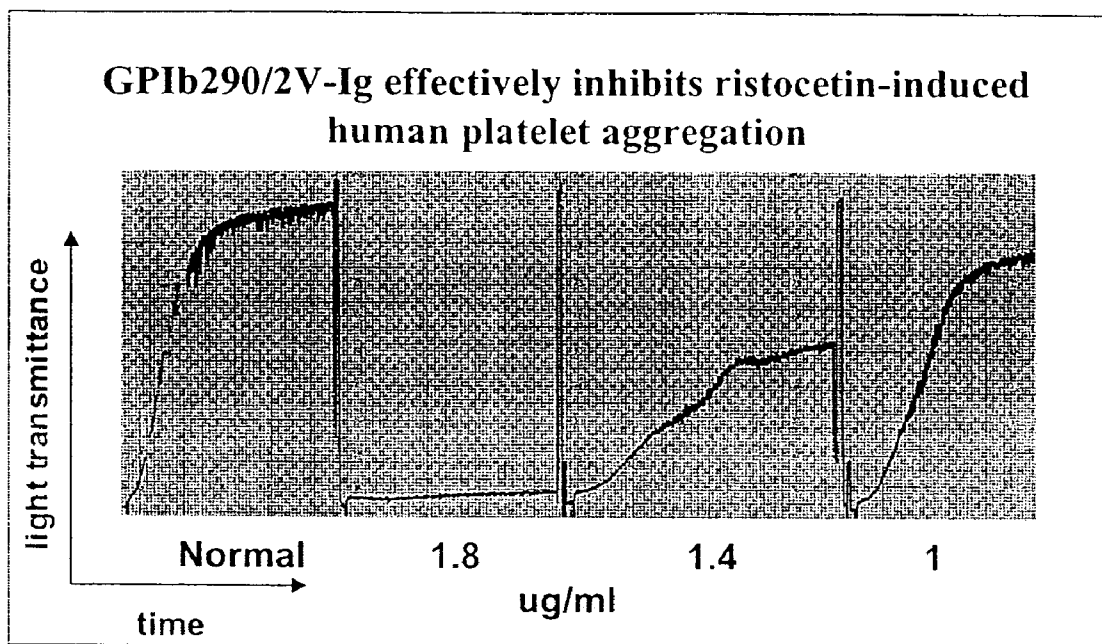


Fig 4

Effect of GPIIb/IIIa (GPIIb290/2V-Ig) in a canine coronary cyclic flow (Folts) model at various doses

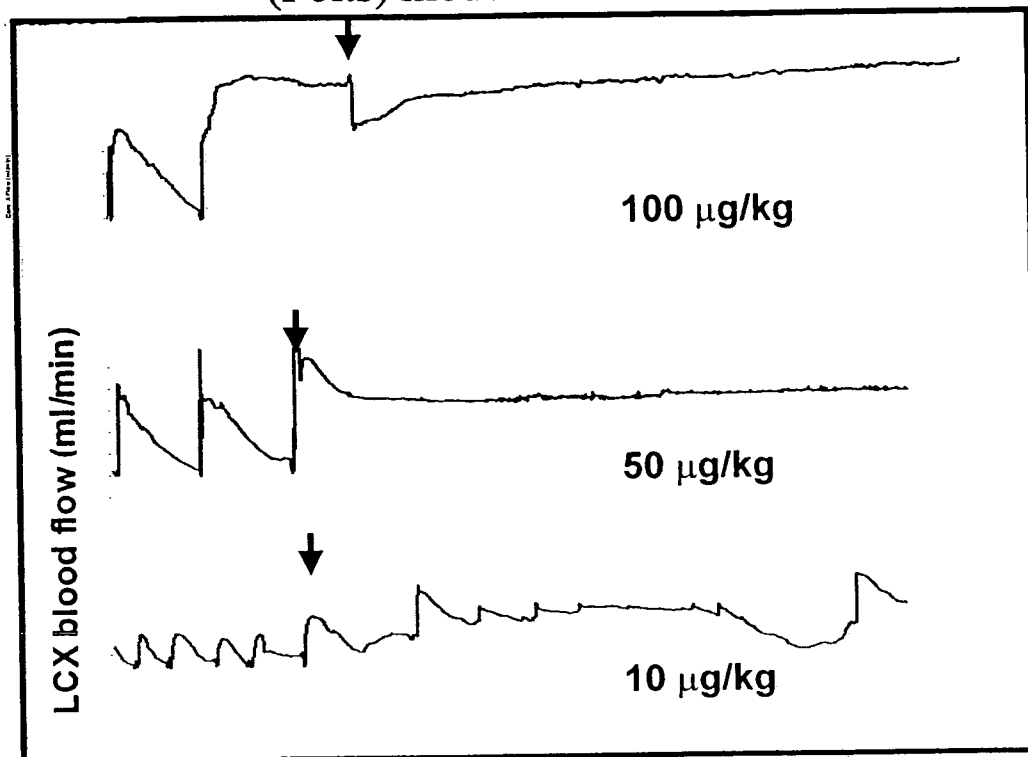


Fig 5

Injured coronary artery:

Blocking subendothelial-bound vWF with GPIb-Ig prevents initial platelet adherence and subsequent thrombotic events

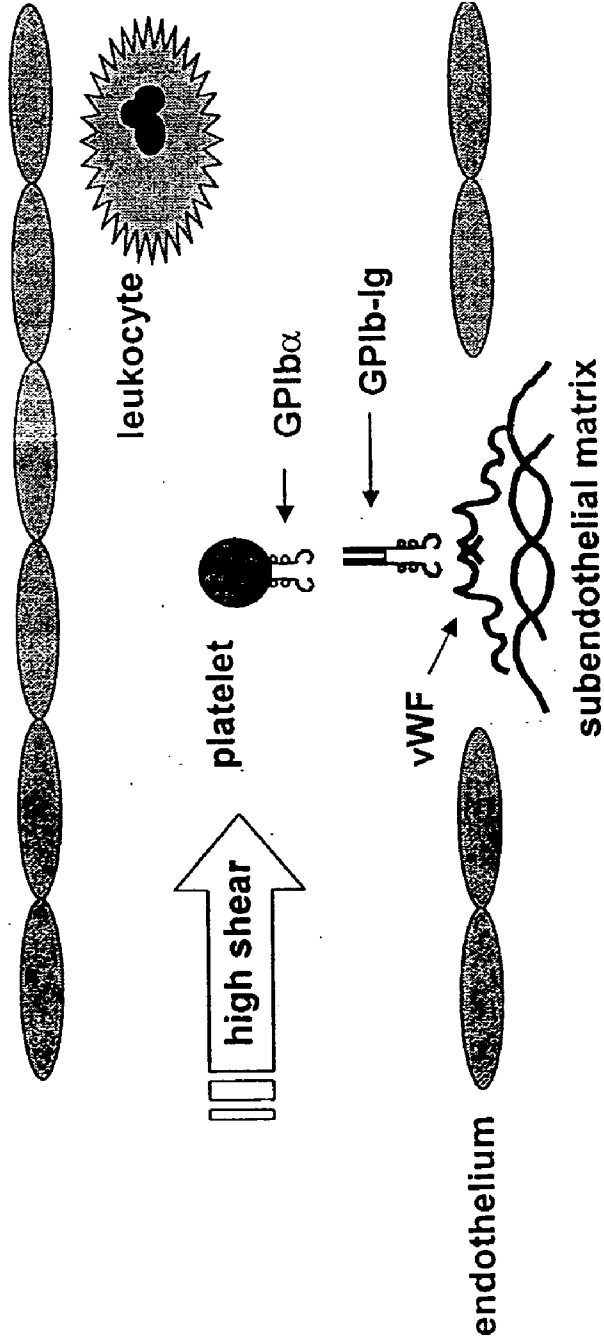


Fig. 6

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PLATELET GLYCOPROTEIN IB ALPHA FUSION POLYPEPTIDES AND METHODS OF USE THEREOF

RELATED U.S. APPLICATION

[0001] This application claims priority to U.S. Ser. No. 60/266,838 filed Feb. 6, 2001, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to generally to compositions and methods for treating or preventing vascular-associated disorders and more particularly to compositions including platelet glycoprotein IB α -derived polypeptides and methods of using same.

BACKGROUND OF THE INVENTION

[0003] The deleterious effects of vascular-associated disorders such as stroke, heart attack, and arteroseclerosis are thought to be caused, at least in part, by the inappropriate triggering of a vascular inflammation and repair response. The vascular inflammation and repair response involves adhesive interactions between various cell types normally found freely circulating in blood. Examples of such interactions the interaction that can occur between platelets, leukocytes and the inner wall of blood vessels (i.e., the vascular endothelium). Under conditions of high fluid shear forces, platelets adhere to the endothelium via an interaction between the glycoprotein (GP) Ib-IX-V complex on their surface and von Willebrand factor (vWF) present on exposed vessel subendothelium. In contrast, leukocytes can adhere either directly to activated endothelium or indirectly by first adhering to vWF-immobilized platelets. In both instances, leukocyte cell surface molecules that bind to either the selectins or integrins classes of adhesion receptors mediate these adhesion events. Leukocyte-platelet adhesion

is thought to occur, in part, via interaction of the leukocyte surface integrin molecule, Mac1 and the GP1b component of the platelet surface GPIb-IX-V complex.

[0004] In response to vascular disturbances such as arterosclerotic plaque rupture or mechanical injury, e.g., such as that caused by angioplasty, stent placement, ischemic damage or stenosis, leukocytes and platelets can accumulate at a vascular lesion site and provide multiple adhesive substrates for one another. This accumulation of leukocytes and platelets lead to the local production of factors including, e.g., mitogens, cytokines and chemokines, causing the further undesirable progression of a vascular disease.

SUMMARY OF THE INVENTION

[0005] The invention is based in part on the discovery of glycoprotein-Ib α -derived fusion proteins that inhibit the adherence of platelets to leukocytes. Accordingly, the glycoprotein-Ib α -derived fusion proteins can be used to treat vascular conditions associated with vascular inflammation, thrombosis, atherosclerosis, and angioplasty-related restenosis. The polypeptides, referred to herein as glycoprotein Ib α fusion polypeptides.

[0006] In one aspect, the invention provides a glycoprotein Ib α fusion polypeptide that includes a first polypeptide, comprising at least a region of a glycoprotein Ib α polypeptide, operably linked to a second polypeptide. The second polypeptide is preferably to form a multimer, e.g., a dimer. In preferred embodiments, the second polypeptide comprising at least a region of an immunoglobulin polypeptide. In some embodiments, the fusion protein includes the sequences of GP1b302-Ig (SEQ ID NO: 1), Gp1b302/2A-Ig (SEQ ID NO:2), GP1b302/4X-Ig (SEQ ID NO:3), GP1b290 Ig (SEQ ID NO:4), GP1b290/2V-Ig (SEQ ID NO:5), or GP1b290/1A-Ig (SEQ ID NO:6), or a fragment, homolog, analog or derivative thereof. The sequences of these polypeptides are provided below:

GP1b302/Ig
MPLLLLLLLLLPSPLPHPHICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLA (SEQ ID NO: 1)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDLDSHNQLQSLPLLGQTLPALTVLDVSNRNLTS

LPLGALRGLGELQELYLKGNELKTLPPGLLTPTPKLEKLSLANNNLTELPAGLLNGLNLDLTL

QENSLYTIPKGFSGHLLPFAFLHGNPWCNCEIILYFRRWLQDNAENVVVKQGVVVKAMTSNVA

SVQCDNSDKFPVYKYPGKGCPTLGDGDTLDYDYPEEDTEGDKVRAVTRVVKFPTKARPHTCPP

CPAPEALGAPSVFLFPKPKDITLMSRTPVETCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE

EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPVPPIEKTIISKAKGQPREPQVYITLPPSREEM

TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV

SCSVMHEALHNHYTQKSLSLSPGK

GP1b302/2A-Ig
MPLLLLLLLLLPSPLPHPHICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLA (SEQ ID NO: 2)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDLDSHNQLQSLPLLGQTLPALTVLDVSNRNLTS

LPLGALRGLGELQELYLKGNELKTLPPGLLTPTPKLEKLSLANNNLTELPAGLLNGLNLDLTL

QENSLYTIPKGFSGHLLPFAFLHGNPWCNCEIILYFRRWLQDNAENVVVKQGVVVKAMTSNVA

SVQCDNSDKFPVYKYPGKGCPTLGDGDTLDYDYPEEDTEGDKVAATATVVKFPTKARPHTCPP

-continued

CPAPEALGAPSVFLFPPKPKD~~TL~~MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPVP~~IE~~KTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ~~Q~~GNVF
SCSVMHEALHNNHTQKSLSLSPGK

GP1b302/4X-Ig
MPLLLLLLLLLPSPLPHHPICEVSKVASHLEVNCDKRNLTALPPDLPKD~~TT~~ILHLS~~EN~~LLYTFSLA (SEQ ID NO: 3)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDSLHNQLQSLPLLGQTLPALTVLDVSNR~~LT~~S
LPLGALRGLGELQELYLKGNE~~LK~~TLPPGLLTPTPKLEKLSLANN~~N~~TELPA~~GL~~LNGL~~EN~~LD~~T~~LLL
QENSLYTI~~PK~~GF~~FG~~SHLLPFAFLHGNP~~W~~LCNCEILYFRRWLQDNAENVYVWQVVDVKA~~V~~TSNVA
SVQCDNSDKFPVYKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVA~~A~~TAVVKFPTKARPHTC~~PP~~
CPAPEALGAPSVFLFPPKPKD~~TL~~MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPVP~~IE~~KTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ~~Q~~GNVF
SCSVMHEALHNNHTQKSLSLSPGK

GP1b290-Ig
MPLLLLLLLLLPSPLPHHPICEVSKVASHLEVNCDKRNLTALPPDLPKD~~TT~~ILHLS~~EN~~LLYTFSLA (SEQ ID NO: 4)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDSLHNQLQSLPLLGQTLPALTVLDVSNR~~LT~~S
LPLGALRGLGELQELYLKGNE~~LK~~TLPPGLLTPTPKLEKLSLANN~~N~~TELPA~~GL~~LNGL~~EN~~LD~~T~~LLL
QENSLYTI~~PK~~GF~~FG~~SHLLPFAFLHGNP~~W~~LCNCEILYFRRWLQDNAENVYVWQGV~~D~~VKAMTSNVA
SVQCDNSDKFPVYKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVRPHTC~~PP~~CPAPEALGAPSVF
LFPPKPKD~~TL~~MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPVP~~IE~~KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ~~Q~~GNVFS~~CS~~V~~M~~HEALHNNY
TQKSLSLSPGK

GP1b290/2V-Ig
MPLLLLLLLLLPSPLPHHPICEVSKVASHLEVNCDKRNLTALPPDLPKD~~TT~~ILHLS~~EN~~LLYTFSLA (SEQ ID NO: 5)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDSLHNQLQSLPLLGQTLPALTVLDVSNR~~LT~~S
LPLGALRGLGELQELYLKGNE~~LK~~TLPPGLLTPTPKLEKLSLANN~~N~~TELPA~~GL~~LNGL~~EN~~LD~~T~~LLL
QENSLYTI~~PK~~GF~~FG~~SHLLPFAFLHGNP~~W~~LCNCEILYFRRWLQDNAENVYVWQVVDVKA~~V~~TSNVA
SVQCDNSDKFPVYKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVRPHTC~~PP~~CPAPEALGAPSVF
LFPPKPKD~~TL~~MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPVP~~IE~~KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ~~Q~~GNVFS~~CS~~V~~M~~HEALHNNY
TQKSLSLSPGK

GP1b290/1A-Ig
MPLLLLLLLLLPSPLPHHPICEVSKVASHLEVNCDKRNLTALPPDLPKD~~TT~~ILHLS~~EN~~LLYTFSLA (SEQ ID NO: 6)

TLMPYTRLTQNLNDRCELTKLQVDGTLFVLGTLDSLHNQLQSLPLLGQTLPALTVLDVSNR~~LT~~S
LPLGALRGLGELQELYLKGNE~~LK~~TLPPGLLTPTPKLEKLSLANN~~N~~TELPA~~GL~~LNGL~~EN~~LD~~T~~LLL
QENSLYTI~~PK~~GF~~FG~~SHLLPFAFLHGNP~~W~~LCNCEILYFRRWLQDNAENVYVWQGV~~D~~VAA~~M~~TSNVA
SVQCDNSDKFPVYKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVRPHTC~~PP~~CPAPEALGAPSVF

-continued

LFPPKPKDITLMSRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL

TVLHQDWLNGKEYKCKVSNKALPVP IEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG

FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSTMHEALHNNY

TQKSLSLSPGK

[0007] Also provided by the invention is a method of inhibiting leukocyte adhesion to a biological tissue contacting a leukocyte with a glycoprotein Iba fusion polypeptide according to the invention. The leukocyte is contacted in an amount sufficient to inhibit adherence of the leukocyte and the biological tissue

[0008] In another aspect, the invention provides a method of treating a disorder associated with platelet activation. The method includes administering to a subject an effective amount of a glycoprotein Iba fusion polypeptide.

[0009] Also included in the invention is a nucleic acid encoding a glycoprotein Iba fusion polypeptide, as well as a vector containing glycoprotein Iba fusion polypeptide-encoding nucleic acids described herein, and a cell containing the vectors or nucleic acids described herein.

[0010] Also included in the invention are pharmaceutical compositions that include the glycoprotein Iba fusion polypeptides, as well as antibodies that specifically recognize the glycoprotein Iba fusion polypeptides.

[0011] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0012] Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIG. 1** is an illustration of a coomassie blue stained gel showing the purification of a GP1b302-Ig fusion protein secreted from CHO cells stably transfected with a mammalian expression vector containing a GP1b302-Ig coding region. Lanes 7,9 show protein A eluates containing tryptic fragments (lower band of approximately 38 kD). Lane 10 is protein A eluate after gel filtration column (GFC) as described in **FIG. 2**.

[0014] **FIG. 2** is an illustration of a gel showing the purification of a protein A eluted GP1b302-Ig fusion protein by gel filtration column (GFC). GFC enables separation of upper band (intact fusion protein, lane 4) from lower band (tryptic cleavage fragment, lane 7).

[0015] **FIG. 3** is an illustration of a western blot of conditioned cell culture medium demonstrating the extent of

proteolysis for various GP1b-Ig fusion proteins secreted from stability transfected CHO cells.

[0016] **FIG. 4** is a chart depicting an UV spectrum measuring platelet aggregation.

[0017] **FIG. 5** is a chart showing the effect of a single bolus injection of a GP1b290/2V-Ig fusion protein at various concentrations on mean LCX flow patterns during *in vivo* Folts model experiments. Arrow shows time of drug injection.

[0018] **FIG. 6** is a schematic illustration depicting an injured coronary artery with high fluid shear blood flow.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The invention provides fusion proteins containing glycoprotein Iba protein-immunoglobulin fusion proteins that are useful for inhibiting adherence of platelets and leukocytes to biological tissues, such as for example the vascular endothelium. The fusion proteins of the invention, or nucleic acids encoding these fusion proteins, can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a glycoprotein Iba ligand (such as Von Willebrand Factor, Mac-1, P-selectin or thrombin) and a glycoprotein Iba protein on the surface of a cell, such as a platelet. Inhibition of binding suppresses glycoprotein Iba protein-mediated platelet aggregation and associated signal transduction *in vivo*.

[0020] The glycoprotein Iba protein-immunoglobulin fusion proteins can be used to modulate the bioavailability of a glycoprotein Iba protein cognate ligand. Inhibition of the glycoprotein Iba protein ligand/glycoprotein Iba protein interaction are useful therapeutically for, *inter alia*, the treatment of vascular inflammation and other vascular disorders associated with platelet activation.

[0021] Glycoprotein Iba Fusion Polypeptides

[0022] In various aspects the invention provides fusion proteins that include a first polypeptide containing at least a portion of a glycoprotein Iba polypeptide operatively linked to a second polypeptide. As used herein, a glycoprotein Iba "fusion protein" or "chimeric protein" includes at least a portion of a glycoprotein Iba polypeptide operatively linked to a non-glycoprotein Iba polypeptide. A "glycoprotein Iba polypeptide" refers to a polypeptide having an amino acid sequence corresponding to at least a portion of a glycoprotein Iba polypeptide, whereas a "non-glycoprotein Iba polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the glycoprotein Iba protein, e.g., a protein that is different from the glycoprotein Iba polypeptide or fragment and that is derived from the same or a

different organism. Within a glycoprotein Iba fusion protein the glycoprotein Iba polypeptide can correspond to all or a portion of an Iba protein.

[0023] In one embodiment, a glycoprotein Iba fusion protein comprises at least one biologically active portion of a glycoprotein Iba protein. In another embodiment, a glycoprotein Iba fusion protein comprises at least two biologically active portions of a glycoprotein Iba protein. In yet another embodiment, a glycoprotein Iba fusion protein comprises at least three biologically active portions of a glycoprotein Iba protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the first and second polypeptides are chemically linked (most typically via a covalent bond such as a peptide bond) in a manner that allows for at least one function associated with a glycoprotein Iba polypeptide. When used to refer to nucleic acids encoding a glycoprotein Iba fusion polypeptide, the term operatively linked means that a nucleic acid encoding the glycoprotein Iba polypeptide and the non-glycoprotein Iba polypeptide are fused in-frame to each other. The non-glycoprotein Iba polypeptide can be fused to the N-terminus or C-terminus of the glycoprotein Iba polypeptide.

[0024] In a further embodiment, the glycoprotein Iba fusion protein may be linked to one or more additional moieties. For example, the glycoprotein Iba fusion protein may additionally be linked to a GST fusion protein in which the glycoprotein Iba fusion protein sequences are fused to the C-terminus of the GST (i.e., glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of glycoprotein Iba fusion protein.

[0025] In another embodiment, the fusion protein includes a heterologous signal sequence (i.e., a polypeptide sequence that is not present in a polypeptide encoded by a glycoprotein Iba nucleic acid) at its N-terminus. For example, the native glycoprotein Iba signal sequence can be removed and replaced with a signal sequence from another protein. In certain host cells (e.g., mammalian host cells), expression and/or secretion of glycoprotein Iba can be increased through use of a heterologous signal sequence. 10 An chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, e.g., by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that encode a fusion moiety (e.g., an Fc region of an immunoglobulin heavy chain). A glycoprotein Iba encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the immunoglobulin protein.

[0026] In various embodiments, the glycoprotein Iba fusion polypeptide includes the amino acid sequence of one or more of SEQ ID NOs: 1-6.

[0027] Glycoprotein Iba fusion polypeptides may exist as oligomers, such as dimers or trimers. Preferably the glycoprotein Iba fusion polypeptide is a dimer.

[0028] The first polypeptide, and/or nucleic acids encoding the first polypeptide, can be constructed using GP Iba encoding sequences are known in the art and are described in, e.g. European Patent Application Publication No. 0 317 278 A2, and Lopez et al. 84:5615-19, 1987. Other sources for GP Iba polypeptides and nucleic acids encoding GP Iba polypeptides include GenBank Accession Nos. BAB12038 and AB038516, D85894 and BAA12911, respectively (human sequences), and GenBank Accession No. AAC53320 and U91967, respectively, and are incorporated herein by reference in their entirety.

[0029] In some embodiments, the GP Ib α polypeptide moiety is provided as a variant GP Ib α polypeptide having a mutation in the naturally-occurring GP Ib α sequence (wild type) that results in higher affinity (relative to the non-mutated sequence) binding of the GP Ib α polypeptide to a leukocyte cell surface molecule. For example, the mutant polypeptide may bind with higher affinity to Von Willebrand factor (vWF). This increased reactivity, or hyperresponsiveness, can be assessed using low concentrations of ristocetin. Alternately, any other suitable means for determining the reactivity of the polypeptide with vWF can also be utilized to identify polypeptides which are "more" reactive with vWF, i.e. more reactive than naturally-occurring wild-type GP Iba. Examples of GP Ib α polypeptide variants that bind with higher affinity to vWF include GP Iba variants that include sequence alterations in the hinge region of a GP Iba polypeptide. The hinge region is defined as the region including residues 220 to 310 and is reported to be a major binding site for vWF within the GP Ib α polypeptide. Mutations in the hinge region include those at residue 233, which in the wild-type GP Ib α encodes glycine. A substitution of valine for glycine 233 is preferred, but other amino acids could also be substituted. A second site for mutation at the hinge region is at residue 239, which in the wild-type GP Ib α encodes methionine. A substitution of valine for glycine 239 is preferred, but other amino acids can also be substituted. In addition, hinge region variants of GP Ib α polypeptides suitable for use in a fusion polypeptide of the invention have mutations at residue both positions 233 and 239. (see e.g., Dong et al., JBC 275:36 27663-27670 (2000)) Thus, the invention includes fusion proteins that have a substitution at position 239, e.g., an M239V substitution of a variant GP Ib α polypeptide. Also within the invention is a fusion protein having a substitution at position 233, e.g., G233V, and a fusion protein that includes a variant GP Ib α polypeptide with positions at both 233 and 239, e.g., a G233V and M239V substitution.

[0030] In some embodiments, the GP Ib α polypeptide moiety is provided as a variant GP Ib α polypeptide having mutations in the naturally-occurring GP Ib α sequence (wild type) that results in a GP Ib α sequence more resistant to proteolysis (relative to the non-mutated sequence). Tryptic cleavage sites in the naturally-occurring GP Ib α sequence have been described. (see e.g. Titani et al., PNAS 84: 5610-5614, (1987))

[0031] In some embodiments, the first polypeptide includes full-length GP Ib α polypeptide. Alternatively, the first polypeptide comprise less than full-length GP Ib α polypeptide. For example the first polypeptide less than 600 amino acids in length, e.g., less than or equal to 500, 250, 150, 100, 50, or 25 amino acids in length.

[0032] Examples of a first polypeptide include a polypeptide which includes the amino acid sequence of any of the GP Ib α polypeptide sequences of GP1b302 (SEQ ID NO:7), GP1b302/2A (SEQ ID NO:8) GP1b/4X (SEQ ID NO:9), GP1b290 (SEQ ID NO:10), GB1b290/2V (SEQ ID NO: 11) and GB1b290/1A (SEQ ID NO: 12).

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 7)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVVDVKAMTSNVASVQCDNSDKFPV

YKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVRATRTRVVKFPPTKA

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 8)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVVDVKAMTSNVASVQCDNSDKFPV

YKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVAATATVVKFPPTKA

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 9)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVVDVKAVTSNVASVQCDNSDKFPV

KYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVAATATVVKFPPTKA

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 10)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVVDVKAMTSNVASVQCDNSDKFPV

YKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVR

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 11)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVVDVKAVTSNVASVQCDNSDKFPV

YKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVR

HPICEVSKVASHLEVNCDKRNLTALPPDLPKDTTILHLSENLLYTFSLATLMPYTRLTQNLNDR (SEQ ID NO: 12)

CELTKLQVDGTLPVLTGLDLSHNQLQSLPLLGQTLPALTVLDVSNRSLPLGALRGLGELQE

LYLKGNELKTLPPGLLTPTPKLEKLSLANNLTELPAAGLNLENLDTLLLQENSLYTIKGGFF

GSHLLPFAFLHGNPWLNCNCEILYFRRWLQDNAENVYVWKQGVDDVAAMTSNVASVQCDNSDKFPV

YKYPGKGCPTLGDEGDTLDYDYYPEEDTEGDKVR

[0033] A signal peptide that can be included in the fusion protein is MPLLLLLLLPSPLHP (SEQ ID NO: 13). If desired, one or more amino acids can additionally be inserted between the first polypeptide moiety comprising the GP Ib α moiety and the second polypeptide moiety.

[0034] The second polypeptide is preferably soluble. In some embodiments, the second polypeptide enhances the half-life, (e.g., the serum half-life) of the linked polypeptide. In some embodiments, the second polypeptide includes a sequence that facilitates association of the fusion polypeptide with a second GP Ib α polypeptide. In preferred embodiments, the second polypeptide includes at least a region of an immunoglobulin polypeptide. Immunoglobulin fusion polypeptides are known in the art and are described in e.g., U.S. Pat. Nos. 5,516,964; 5,225,538; 5,428,130; 5,514,582; 5,714,147; and 5,455,165.

[0035] In some embodiments, the second polypeptide comprises a full-length immunoglobulin polypeptide. Alter-

polypeptide includes the heavy chain of an immunoglobulin polypeptide. More preferably the second polypeptide includes the Fc region of an immunoglobulin polypeptide.

[0036] In another aspect of the invention the second polypeptide has less effector function than the effector function of a Fc region of a wild-type immunoglobulin heavy chain. Fc effector function includes for example, Fc receptor binding, complement fixation and T cell depleting activity. (see for example, U.S. Pat. No. 6,136,310) Methods of assaying T cell depleting activity, Fc effector function, and antibody stability are known in the art. In one embodiment the second polypeptide has low or no affinity for the Fc receptor. In an alternative embodiment, the second polypeptide has low or no affinity for complement protein C1q.

[0037] A preferred second polypeptide sequence includes the amino acid sequence of SEQ ID NO: 12. This sequence includes a Fc region. Underlined amino acids are those that differ from the amino acid found in the corresponding position of the wild-type immunoglobulin sequence:

```
HTCPPCPAPALGAPSVFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK (SEQ ID NO: 14)
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPVIIEKTIISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMEALHNHYTQKSLSLSPGK
```

natively, the second polypeptide comprise less than full-length immunoglobulin polypeptide, e.g., a heavy chain, light chain, Fab, Fab₂, Fv, or Fc. Preferably, the second

[0038] DNA sequences encoding fusion polypeptides of SEQ ID NOs: 1-6 are disclosed below as sequences SEQ ID NOs: 15-20, respectively:

GP1b302-Ig nucleotide sequence

```
atgcctctcctcctcttctgctgctcctgctgccaagcccttacaccccccccatctgtgaggt (SEQ ID NO: 15)
ctccaaagtggccagccacctagaagtgaactgtgacaagaggaatctgacagcgctgcctccag
acctgcccgaagacacaacatcctccacctgagtgagaacctcctgtacaccttctcctggca
acctgatgccttacactcgctcactcagctgaacctagataggtgagctcaccagctcca
ggtcgatgggacgctgcccagtgctggggaccctggatctatcccacaatcagctgcaaacctgc
ccttgctagggcagacactgctgctcaccgtcctggacgtctccttcaaccggctgacctgc
ctgcctcttggtgccctgctggtcttggcgaactccaagagctctacctgaaaggcaatgagct
gaagaccctgccccaggctcctgacgcccacccaagctggagaagctcagctctggctaaca
acaactgactgagctccccgctgggtcctgaaatgggtggagaatctcgacaccttctcctc
caagagaactcgctgtatacaataccaaaggctttttgggtcccacctcctgcttttctt
tctccacgggaacccctggttatgcaactgtgagatcctctatcttctcgtcgtgctgcaggaca
atgctgaaaatgtctacgtatggaagcaaggtgtggacgtcaaggccatgacctataacgtggcc
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aggtgctgcccacaaggactgtggtcaagttccccaccaaagcgggcccacacatgccaccg
tgcccagcacctgaagccctggggcaccgtcagctctcctctccccccaaaaccaaggacac
cctcatgatctcccgaccctgaggtcacatgcgtggtggtgagctgagccagaagacctg
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aggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggag
gagcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagtcctccatcgagaaaaccatct
ccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatcccgggaggagatg
accaagaaccaggtcagcctgacctgctgtcaaggcttctatcccagcgacatcgccgtgga
gtgggagagcaatgggcagccggagaacaaactacaagaccacgcctcccgtgctggactccgacg
gccccctctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaaagctcttc
tcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctcc
gggtaaa

GP1b302/2A-Ig nucleotide sequence

atgcctctcctcctcttctgctgctcctgctgccaagccccttacacccccacccatctgtgaggt (SEQ ID NO:16)
ctccaaagtgccagccacacacaggaagtgactgtgacaagaggaatctgacagcgtcctccag
acctgccaaagacacaaccatcctccacctgagtgagaacctcctgtacacctctcctctggca
acctgatgccttacactcgcctcactcagctgaacctagataggtgagctcaccaagctcca
ggtcgatgggacgctgcccagtgctggggaccctggatctatcccacaatcagctgcaaagcctgc
cctgctagggcagacactgctgctcaccgtcctggacgtctccttcaaccggctgacctcg
ctgcctcttgggtgccctgctggtcttggcgaactccaagagctctacctgaaaggcaatgagct
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acaacttgactgagctccccgctcctgaatgggctggagaatctcgacaccttctcctc
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tctccagggaaacccctggtatgcaactgtgagatcctctatcttctcgtcgctggctgcaggaca
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ccttggatgaaaggtgacacagacctatagattactaccagaagaggacactgagggcgata
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ccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatcccgggaggagatg
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gccccctctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaaagctcttc
tcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctcc
gggtaaa

GP1b302/4X-Ignucleotide sequence

atgcctctcctcctccttctgctgctcctgctgccaagccccttacacccccacccatctgtgaggt (SEQ ID NO: 17)

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ctccaaagtggccagccacctagaaagtgaactgtgacaagaggaatctgacagcgtgcctccag
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gccccttctcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttc
tcatgctcctgatgatgaggtctgcacaaccactacacgcagaagagcctctcctgtctcc
gggtaaa

GP1b290-Ig nucleotide sequence

atgctctctcctccttctgctgctcctgctgccaagcccttacacccccaccatctgtgaggt (SEQ ID NO: 18)
ctccaaagtggccagccacctagaaagtgaactgtgacaagaggaatctgacagcgtgcctccag
acctgcccgaagacacaacacctccacctgagtgagaacctcctgtacaccttctccctggca
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gcaggtggcagcaggggaactctctcatgctccgtgatgcatgaggtctctgcacaaccactac
acgcagaagagcctctccctgctctccgggtaaa

GP1b290/2V-Ig nucleotide sequence

atgctctcctcctcttggctgctcctgctgccaaagcccttacacccccaccatctgtgaggt (SEQ ID NO: 19)
ctccaaagtgccagccacctagaagtgaactgtgacaagaggaatctgacagcgtcctccag
acctgcccgaagacacaaccatcctccacctgagtgagaacctcctgtacacctctcctggca
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cacgctcccgtgctgactccgagccctctctctctacagcaagctcaccgtggacaaga
gcaggtggcagcaggggaactctctcatgctccgtgatgcatgaggtctctgcacaaccactac
acgcagaagagcctctccctgctctccgggtaaa

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GP1b290/1A-Ig nucleotide sequence

atgcctctcctcctcttctgtctcctgctgccaagcccttacacccccacccatctgtgaggt (SEQ ID NO: 20)
 ctccaaagtggccagccacctagaagtgaactgtgacaagaggaatctgacagcgctgctccag
 acctgccaaagacacaaccatcctccacctgagtgagaacctcctgtacaccttctcctggca
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 ggtcgatgggacgctgccagtgctggggaccctggatctatcccacaatcagctgcaaagcctgc
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 cagcctcccgtgctggaactccgagggcccttcttctctacagcaagctcaccgtggacaaga
 gcaggtggcagcaggggaactcttctcatgctcctgatgcatgaggtctgacacaaccactac
 acgcagaagagcctctccctgtctccgggtaaa

[0039] Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding glycoprotein I α fusion polypeptides, or derivatives, fragments, analogs or homologs thereof. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as “expression vectors”.

In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0040] The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, “operatively-linked” is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide

sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell).

[0041] The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (e.g., glycoprotein I β fusion polypeptides, mutant forms of glycoprotein I β fusion polypeptides, etc.).

[0042] The recombinant expression vectors of the invention can be designed for expression of glycoprotein I β fusion polypeptides in prokaryotic or eukaryotic cells. For example, glycoprotein I β fusion polypeptides can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

[0043] Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant protein; (ii) to increase the solubility of the recombinant protein; and (iii) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[0044] Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann et al., (1988) *Gene* 69:301-315) and pET 11d (Studier et al., GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

[0045] One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. See, e.g., Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (see, e.g., Wada, et al., 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

[0046] In another embodiment, the glycoprotein I β fusion polypeptide expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, et al., 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz et al., 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (In Vitrogen Corp, San Diego, Calif.).

[0047] Alternatively, glycoprotein I β fusion polypeptide can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, et al., 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

[0048] In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, et al., 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, e.g., Chapters 16 and 17 of Sambrook, et al., MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

[0049] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, et al., 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477), pancreas-specific promoters (Edlund, et al., 1985. *Science* 230: 912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Devel-

opmentally-regulated promoters are also encompassed, e.g., the murine hox promoters (Kessel and Gruss, 1990. *Science* 249: 374-379) and the α -fetoprotein promoter (Campes and Tilghman, 1989. *Genes Dev.* 3: 537-546).

[0050] The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to NOV glycoprotein Iba fusion polypeptide mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see, e.g., Weintraub, et al., "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

[0051] Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0052] A host cell can be any prokaryotic or eukaryotic cell. For example, glycoprotein Iba fusion polypeptides can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as human, Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[0053] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (*MOLECULAR CLONING: A LABORATORY MANUAL*, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

[0054] For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a

selectable marker (e.g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding glycoprotein Iba fusion polypeptides or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

[0055] A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) glycoprotein Iba fusion polypeptides. Accordingly, the invention further provides methods for producing glycoprotein Iba fusion polypeptides using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding glycoprotein Iba fusion polypeptides has been introduced) in a suitable medium such that glycoprotein Iba fusion polypeptides is produced. In another embodiment, the method further comprises isolating glycoprotein Iba fusion polypeptide from the medium or the host cell.

[0056] The fusion polypeptides may be isolated and purified in accordance with conventional conditions, such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis or the like. For example, the immunoglobulin fusion proteins may be purified by passing a solution through a column which contains immobilized protein A or protein G which selectively binds the Fc portion of the fusion protein. See, for example, Reis, K. J., et al., *J. Immunol.* 132:3098-3102 (1984); PCT Application, Publication No. WO87/00329. The fusion polypeptide may be eluted by treatment with a chaotropic salt or by elution with aqueous acetic acid (1 M).

[0057] Alternatively, fusion polypeptides according to the invention can be chemically synthesized using methods known in the art. Chemical synthesis of polypeptides is described in, e.g., A variety of protein synthesis methods are common in the art, including synthesis using a peptide synthesizer. See, e.g., *Peptide Chemistry, A Practical Textbook*, Bodasnsky, Ed. Springer-Verlag, 1988; Merrifield, *Science* 232: 241-247 (1986); Barany, et al, *Intl. J. Peptide Protein Res.* 30: 705-739 (1987); Kent, *Ann. Rev. Biochem.* 57:957-989 (1988), and Kaiser, et al, *Science* 243: 187-198 (1989). The polypeptides are purified so that they are substantially free of chemical precursors or other chemicals using standard peptide purification techniques. The language "substantially free of chemical precursors or other chemicals" includes preparations of peptide in which the peptide is separated from chemical precursors or other chemicals that are involved in the synthesis of the peptide. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of peptide having less than about 30% (by dry weight) of chemical precursors or non-peptide chemicals, more preferably less than about 20% chemical precursors or non-peptide chemicals, still more preferably less than about 10% chemical precursors or non-peptide chemicals, and most preferably less than about 5% chemical precursors or non-peptide chemicals.

[0058] Chemical synthesis of polypeptides facilitates the incorporation of modified or unnatural amino acids, including D-amino acids and other small organic molecules. Replacement of one or more L-amino acids in a peptide with the corresponding D-amino acid isoforms can be used to increase the resistance of peptides to enzymatic hydrolysis, and to enhance one or more properties of biologically active peptides, i.e., receptor binding, functional potency or duration of action. See, e.g., Doherty, et al., 1993. *J. Med. Chem.* 36: 2585-2594; Kirby, et al., 1993. *J. Med. Chem.* 36:3802-3808; Morita, et al., 1994. *FEBS Lett.* 353: 84-88; Wang, et al., 1993. *Int. J. Pept. Protein Res.* 42: 392-399; Fauchere and Thiunieu, 1992. *Adv. Drug Res.* 23: 127-159.

[0059] Introduction of covalent cross-links into a peptide sequence can conformationally and topographically constrain the polypeptide backbone. This strategy can be used to develop peptide analogs of the fusion polypeptides with increased potency, selectivity and stability. Because the conformational entropy of a cyclic peptide is lower than its linear counterpart, adoption of a specific conformation may occur with a smaller decrease in entropy for a cyclic analog than for an acyclic analog, thereby making the free energy for binding more favorable. Macrocyclization is often accomplished by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [e.g., with $K_3Fe(CN)_6$ at pH 8.5](Samson et al., *Endocrinology*, 137: 5182-5185 (1996)), or between two amino acid side chains. See, e.g., DeGrado, *Adv. Protein Chem.* 39: 51-124 (1988). Disulfide bridges are also introduced into linear sequences to reduce their flexibility. See, e.g., Rose, et al., *Adv. Protein Chem.* 37: 1-109 (1985); Mosberg et al., *Biochem Biophys Res Commun.* 106: 505-512 (1982). Furthermore, the replacement of cysteine residues with penicillamine (Pen, 3-mercapto-(D) valine) has been used to increase the selectivity of some opioid-receptor interactions. Lipkowski and Carr, *Peptides: Synthesis, Structures, and Applications*, Gutte, ed., Academic Press pp. 287-320 (1995).

[0060] Pharmaceutical Compositions Including Glycoprotein Iba Fusion Polypeptides or Nucleic Acids Encoding Same

[0061] The glycoprotein Iba fusion proteins, or nucleic acid molecules encoding these fusion proteins, (also referred to herein as "Therapeutics" or "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional

media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0062] The active agents disclosed herein can also be formulated as liposomes. Liposomes are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

[0063] Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

[0064] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0065] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. 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. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Pro-

longed absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0066] Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a glycoprotein Iba fusion protein) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. 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, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0067] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0068] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0069] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0070] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0071] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers

can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0072] In some embodiments, oral or parenteral compositions are formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0073] The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see, e.g., U.S. Pat. No. 5,328,470) or by stereotactic injection (see, e.g., Chen, et al., 1994. *Proc. Natl. Acad. Sci. USA* 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

[0074] Sustained-release preparations can be prepared, if desired. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

[0075] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0076] Methods of Inhibiting Adherence of in a Biological System

[0077] Also included in the invention are methods of inhibiting adherence of a blood cell to a biological tissue in

a biological system. The method includes adding to a biological system a fusion polypeptide of the invention in an amount sufficient to inhibit adherence of a blood cell to the biological tissue.

[0078] The blood cell can be for example, a leukocyte, platelet or red blood cell. The leukocyte can be any leukocyte that is capable of adhering to a biological tissue. In various aspects the leukocyte is a granulocyte, (i.e., neutrophil, basophil or eosinophil), monocyte (i.e., macrophage) or lymphocyte (e.g., T-lymphocyte, B-lymphocyte, tumor infiltrating lymphocytes or natural killer cell). In some embodiments, the leukocytes express a $\beta 2$ integrin, e.g. Mac-1. Alternately, the leukocyte expresses a selectin ligand.

[0079] Also included in the inventions are methods of inhibiting adherence of a protein to a biological tissue in a biological system. The method includes adding to a biological system a fusion polypeptide of the invention in an amount sufficient to inhibit adherence of the protein to the biological tissue.

[0080] The protein can be membrane associated (e.g., covalently, non-covalently, ionically). Alternatively, the protein can be in a soluble form (i.e., in solution). The protein is von Willibrand Factor, thrombin, P-selectin or glycoprotein Iba.

[0081] As used herein a "biological tissue" is meant to include one or more cells with or without intracellular substances (e.g., extracellular matrix proteins, polysaccharides and proteoglycans. A biological tissue also includes solely extracellular matrix substances, such as the subendothelium connective tissue matrix. In some aspects the biological tissue is the vascular endothelium. The biological tissue can be one or more platelets or leukocytes. In various aspects the biological tissue is complexed with a component of the GP Ib-IX-V complex such as glycoprotein Ib α , Mac-1, P-selectin, thrombin or a von Willibrand Factor. By "complexed" is meant that the biological tissue contains a soluble form of a component of the GP Ib-IX-V complex. Alternatively, "complexed" is meant that the biological tissue contains a cell that expresses a component of the GP Ib-IX-V complex.

[0082] As used herein a biological system is meant to include any system that comprises biological components, e.g., cells, proteins, carbohydrates, lipids or nucleic acids. The biological system can be an in vivo, ex vivo or in vitro system.

[0083] By "adherence" is meant to include any leukocyte-biological interaction, e.g., rolling, firm attachments or specific interaction.

[0084] Inhibition of adherence of a blood cell or protein to a biological tissue can be measured using methods known in the art. For example, assays for detecting binding of glycoprotein Iba to a biological tissue are described in Simon et al., J. Exp. Med. 192:193-204, 2000, and references cited therein. In various embodiments, binding of a GP Ib α fusion protein inhibits binding of a blood cell or protein to a biological tissue by at least 30%, 50%, 75%, 90%, 95%, 99% or 99.9%.

[0085] Adherence can also be assessed in condition of greater or less than physiological flow conditions, including static conditions and serial application of static and shear

conditions. Adherence can be determined for example colorimetrically, fluorometrically, by flow cytometry or using a parallel plate flow chamber assay.

[0086] Also included in the invention are methods of treating platelet activation associated disorders in a subject by administering to a subject a biologically-active therapeutic compound (hereinafter "Therapeutic"). Alternatively, the subject is also administered one or more of the following acetylsalicylic acid, e.g., aspirin heparin, e.g., unfractionated or low-molecular weight heparins, glycoprotein IIb/IIIa antagonists, clopidogrel, P-selectin antagonists, thrombin inhibitors or thrombolytic enzymes.

[0087] The subject can be e.g., any mammal, e.g., a human, a primate, mouse, rat, dog, cat, cow, horse, pig.

[0088] The Therapeutics include, e.g.: (i) any one or more of the glycoprotein Iba fusion polypeptides, and derivative, fragments, analogs and homologs thereof; (ii) antibodies directed against the glycoprotein Iba fusion polypeptides; and (iii) nucleic acids encoding a glycoprotein Iba fusion polypeptide, and derivatives, fragments, analogs and homologs thereof.

[0089] Essentially, any disorder, which is etiologically linked to platelet activation, is considered amenable to prevention or to treatment. The disorder can be, e.g., vascular inflammation, atherosclerosis, restenosis (e.g., angioplasty-related restenosis) and/or a condition associated with thrombotic disease, e.g., angina, (i.e., stable angina and unstable angina) acute myocardial infarction, stroke, venous thrombosis or arterial thrombosis.

[0090] The invention will be further illustrated in the following non-limiting examples.

EXAMPLE 1

Production and Purification of Recombinant GP1B-IG Fusion Proteins

[0091] Three GP1b-Ig fusion proteins, GP1b302-Ig (SEQ ID NO: 1), GP1b290 Ig (SEQ ID NO:4), and GP1b290/2V-Ig (SEQ ID NO:5), were produced by recombinant methods and purified. Chinese hamster ovary (CHO) cells lacking dihydrofolate reductase (DHFR) activity were stably transfected with linearized plasmid DNA consisting of a mammalian expression vector directing the transcription of a GP1b-Ig coding regions in polycistronic fashion with a DHFR selectable marker gene. Candidate expressing cells were selected in medium containing increasing concentrations of methotrexate (MTX) essentially as described in Kaufman et al. *Nucleic Acids Res.* (1991) 19:4485-90. For collection of GP1b-Ig conditioned medium, CHO cells were grown to near confluent levels on 5-20 culture dishes (150 mm diameter), the cell monolayer was washed twice with PBS and cells were cultured for approximately 24 hrs in medium lacking fetal bovine serum. The medium was then collected and cells discarded.

[0092] CHO cell condition media (CM) was adjusted to 50 mM Tris pH8.0, 200 mM NaCl, filtered through a 0.2 μ m filter, and applied to a Poros Protein A column. The column was washed with 10 column volumes of 50 mM Tris pH 8.0, 200 mM NaCl and eluted with Pierce IgG elution buffer. The protein peak was followed by absorbance at 280 nm. The pH of the elute was adjusted with 0.1 volumes of 1 M Tris, pH

8.0. The protein was then concentrated and the buffer exchanged by finger dialysis (25 kD MWCO) against TBS (10 mM Tris, pH 8.0, 150 mM NaCl). The concentrated protein was then further purified by gel filtration chromatography on a TosoHaas G3000SW column run in TBS.

[0093] The purified protein was analyzed by Western Blots. Briefly, 13 microliters of CHO cell conditioned medium was loaded per lane on a 4-20% reducing SDS PAGE gel. Western transfer was performed using Electrobolt apparatus and nitrocellulose membrane (Novex, San Diego, Calif.). The primary detection antibody was monoclonal API, and secondary antibody was an HRP-conjugated goat anti-murine IgG (GT1, Brookfield, Wis.). HRP detection was via ECL system (Amersham-Pharmacia Biotech).

EXAMPLE 2

In Vitro Inhibition of Platelet Aggregation

[0094] The ability of the glycoprotein Ib α polypeptide-immunoglobulin fusion polypeptide to inhibit platelet aggregation in vitro, was determined. Platelet rich plasma (PRP) from freshly drawn, citrate blood was prepared by differential centrifugation for 10 minutes at 900 rpm. 0.4 mls of PRP (3×10^8 /ml) was preincubated for 5 minutes at 37° C. with various concentrations of GP1b290/2v-Ig. Ristocetin was added to 1.5 mg/ml to induce platelet aggregation. Aggregation was measured using a Sienco DP247E aggregometer. Aggregation was quantified and recorded on a chart recorder by monitoring the increase in light transmittance with stirring at 1000 rpm. As illustrated in FIG. 4, GP1b290/2v-Ig inhibited ristocetin induced platelet aggregation.

EXAMPLE 3

In Vivo Inhibition of Repetitive Coronary Artery Thrombosis

[0095] The ability of a glycoprotein Ib α GPIb290/2V-Ig polypeptide-immunoglobulin fusion polypeptide to inhibit coronary artery thrombosis in vivo was determined using the procedure described by Folts at al., Circulation 54:365-70, 1976.

[0096] Mongrel dogs, weighing 20-25 kg, were anesthetized with sodium pentobarbital (30 mg/kg i.v.), then intu-

bated and ventilated with room air using a respirator. Venous and arterial catheters were placed. The heart was approached by left thoracotomy through the fifth intercostal space. The pericardium was opened and sutured to the wound edges to provide a cradle without displacing the heart. About 2cm of the left circumflex coronary artery (LCX) was isolated. Mean and dynamic LCX flow was continuously monitored using a perivascular ultrasonic flow probe placed proximally on the artery. After a stabilization period, the endothelium of the LCX was injured by squeezing with a hemostat. A plastic constrictor was placed distal and overlying the area of injured endothelium to provide approximately 70-80% vessel stenosis. When blood flow decreased to zero, the blood flow was restored by shaking the constrictor to dislodge aggregated platelets. This decrease and restoration of blood flow are termed CFRs. At least five consecutive CFRs were recorded prior to administering the test drug.

[0097] Representative results are shown in FIG. 5. The tracings indicate that increasing amounts of glycoprotein Ib α GPIb290/2V-Ig resulted in higher blood flow. These results demonstrate that glycoprotein Ib α GPIb290/2V-Ig inhibits thrombosis in the animal model.

[0098] A schematic illustration depicting an injured coronary artery with high fluid shear blood flow is presented in FIG. 6. The figure depicts an injured coronary artery with high fluid shear blood flow. The vessel has a segment of damaged endothelium that exposes subendothelial matrix proteins, including immobilized vWF. In the presence of GPIb alpha fusion polypeptide (GPIb-Ig), the vWF binding site is blocked, thereby preventing platelet adherence via the platelet-bound GPIb alpha within the GPIb-V-IX complex. Lukocyte capture is also diminished.

Other Embodiments

[0099] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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	420		425		430														
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu				
	435						440					445							
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys				
	450					455					460								
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser				
465				470						475					480				
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp				
				485					490					495					
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser				
			500					505					510						
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala				
		515					520					525							
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
	530					535					540								

<210> SEQ ID NO 2
 <211> LENGTH: 544
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(544)
 <223> OTHER INFORMATION: GP1b302/2A-Ig

<400> SEQUENCE: 2

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

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Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 225 230 235 240
 Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
 245 250 255
 Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 260 265 270
 Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 275 280 285
 Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 290 295 300
 Val Ala Ala Thr Ala Thr Val Val Lys Phe Pro Thr Lys Ala Arg Pro
 305 310 315 320
 His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser
 325 330 335
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 340 345 350
 Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp Pro
 355 360 365
 Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 370 375 380
 Lys Thr Lys Pro Arg Glu Glu Tyr Asn Ser Thr Tyr Arg Val Val
 385 390 395 400
 Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 405 410 415
 Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Val Pro Ile Glu Lys Thr
 420 425 430
 Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 435 440 445
 Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 450 455 460
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 465 470 475 480
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 485 490 495
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 500 505 510
 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 515 520 525
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 530 535 540

<210> SEQ ID NO 3
 <211> LENGTH: 544
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(544)
 <223> OTHER INFORMATION: GP1b302/4X-Ig
 <400> SEQUENCE: 3

Met Pro Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
 1 5 10 15

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His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
 20 25 30

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
 35 40 45

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
 50 55 60

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
 65 70 75 80

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
 85 90 95

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
 100 105 110

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
 115 120 125

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
 130 135 140

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
 145 150 155 160

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
 165 170 175

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
 180 185 190

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
 195 200 205

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
 210 215 220

Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 225 230 235 240

Glu Asn Val Tyr Val Trp Lys Gln Val Val Asp Val Lys Ala Val Thr
 245 250 255

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 260 265 270

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 275 280 285

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 290 295 300

Val Ala Ala Thr Ala Thr Val Val Lys Phe Pro Thr Lys Ala Arg Pro
 305 310 315 320

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser
 325 330 335

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 340 345 350

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 355 360 365

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 370 375 380

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 385 390 395 400

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 405 410 415

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Val Pro Ile Glu Lys Thr

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            420              425              430
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
      435                      440              445

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
      450                      455              460

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
      465                      470              475              480

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
      485                      490              495

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
      500                      505              510

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
      515                      520              525

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      530                      535              540

<210> SEQ ID NO 4
<211> LENGTH: 531
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(531)
<223> OTHER INFORMATION: GP1b290-Ig

<400> SEQUENCE: 4

Met Pro Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
  1                    5              10              15

His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
      20              25              30

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
      35              40              45

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
      50              55              60

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
      65              70              75              80

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
      85              90              95

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
      100             105             110

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
      115             120             125

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
      130             135             140

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
      145             150             155             160

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
      165             170             175

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
      180             185             190

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
      195             200             205

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
      210             215             220

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Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 225 230 235 240

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
 245 250 255

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 260 265 270

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 275 280 285

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 290 295 300

Val Arg Pro His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly
 305 310 315 320

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Asp Thr Leu Met
 325 330 335

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 340 345 350

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 355 360 365

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 370 375 380

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 385 390 395 400

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Val Pro Ile
 405 410 415

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 420 425 430

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 435 440 445

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 450 455 460

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 465 470 475 480

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 485 490 495

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 500 505 510

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 515 520 525

Pro Gly Lys
 530

<210> SEQ ID NO 5
 <211> LENGTH: 531
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(531)
 <223> OTHER INFORMATION: GP1b290/2V-Ig
 <400> SEQUENCE: 5

Met Pro Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
 1 5 10 15

-continued

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

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          420          425          430
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    435          440          445

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    450          455          460

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    465          470          475          480

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
    485          490          495

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
    500          505          510

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    515          520          525

Pro Gly Lys
    530

<210> SEQ ID NO 6
<211> LENGTH: 531
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(531)
<223> OTHER INFORMATION: GP1b290/1A-Ig

<400> SEQUENCE: 6

Met Pro Leu Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
  1          5          10          15

His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
    20          25          30

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
    35          40          45

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
    50          55          60

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
    65          70          75          80

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
    85          90          95

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
    100          105          110

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
    115          120          125

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
    130          135          140

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
    145          150          155          160

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
    165          170          175

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
    180          185          190

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
    195          200          205

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
    210          215          220

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Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 225 230 235 240
 Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Ala Ala Met Thr
 245 250 255
 Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 260 265 270
 Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 275 280 285
 Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 290 295 300
 Val Arg Pro His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly
 305 310 315
 Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Asp Thr Leu Met
 325 330 335
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 340 345 350
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 355 360 365
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 370 375 380
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 385 390 395
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Val Pro Ile
 405 410 415
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 420 425 430
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 435 440 445
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 450 455 460
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 465 470 475
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 485 490 495
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 500 505 510
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 515 520 525
 Pro Gly Lys
 530

<210> SEQ ID NO 7
 <211> LENGTH: 302
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(302)
 <223> OTHER INFORMATION: GP1b302
 <400> SEQUENCE: 7

His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
 1 5 10 15

-continued

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
 20 25 30
 Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
 35 40 45
 Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
 50 55 60
 Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
 65 70 75 80
 Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
 85 90 95
 Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
 100 105 110
 Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
 115 120 125
 Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
 130 135 140
 Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
 145 150 155 160
 Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
 165 170 175
 Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
 180 185 190
 Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
 195 200 205
 Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 210 215 220
 Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
 225 230 235 240
 Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 245 250 255
 Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 260 265 270
 Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 275 280 285
 Val Arg Ala Thr Arg Thr Val Val Lys Phe Pro Thr Lys Ala
 290 295 300

<210> SEQ ID NO 8
 <211> LENGTH: 302
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(302)
 <223> OTHER INFORMATION: GP1b302/2A

<400> SEQUENCE: 8

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

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      50              55              60
Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
 65                    70                    75                    80
Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
                    85                    90                    95
Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
                    100                    105                    110
Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
                    115                    120                    125
Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
                    130                    135                    140
Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
                    145                    150                    155                    160
Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
                    165                    170                    175
Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
                    180                    185                    190
Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
                    195                    200                    205
Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
                    210                    215                    220
Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
                    225                    230                    235                    240
Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
                    245                    250                    255
Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
                    260                    265                    270
Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
                    275                    280                    285
Val Ala Ala Thr Ala Thr Val Val Lys Phe Pro Thr Lys Ala
                    290                    295                    300

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<210> SEQ ID NO 9
<211> LENGTH: 301
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(301)
<223> OTHER INFORMATION: GP1b/4X

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<400> SEQUENCE: 9

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

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Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
 100 105 110
 Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
 115 120 125
 Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
 130 135 140
 Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
 145 150 155 160
 Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
 165 170 175
 Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
 180 185 190
 Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
 195 200 205
 Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 210 215 220
 Glu Asn Val Tyr Val Trp Lys Gln Val Val Asp Val Lys Ala Val Thr
 225 230 235 240
 Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 245 250 255
 Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp Thr
 260 265 270
 Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys Val
 275 280 285
 Ala Ala Thr Ala Thr Val Val Lys Phe Pro Thr Lys Ala
 290 295 300

<210> SEQ ID NO 10
 <211> LENGTH: 290
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(290)
 <223> OTHER INFORMATION: GP1b290

<400> SEQUENCE: 10

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

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Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
   130                               135                               140

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
  145                               150                               155                               160

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
                               165                               170                               175

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
                               180                               185                               190

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
   195                               200                               205

Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
   210                               215                               220

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
  225                               230                               235                               240

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
                               245                               250                               255

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
   260                               265                               270

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
   275                               280                               285

Val Arg
   290

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<210> SEQ ID NO 11
<211> LENGTH: 290
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(290)
<223> OTHER INFORMATION: GB1b290/2V

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<400> SEQUENCE: 11

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His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
   1                               5                               10                               15

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
   20                               25                               30

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
   35                               40                               45

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
   50                               55                               60

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
   65                               70                               75                               80

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
   85                               90                               95

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
  100                               105                               110

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
  115                               120                               125

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
   130                               135                               140

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
  145                               150                               155                               160

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr

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	165		170		175									
Leu Leu Leu	Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe													
	180					185						190		
Gly Ser His	Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu													
	195					200						205		
Cys Asn Cys	Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala													
	210					215						220		
Glu Asn Val	Tyr Val Trp Lys Gln Val Val Asp Val Lys Ala Val Thr													
	225					230						235		240
Ser Asn Val	Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val													
						245						250		255
Tyr Lys Tyr	Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp													
						260								270
Thr Asp Leu	Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys													
						275								285
Val Arg														
	290													

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<210> SEQ ID NO 12
<211> LENGTH: 290
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(290)
<223> OTHER INFORMATION: GB1b290/1A
    
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<400> SEQUENCE: 12

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

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Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 210 215 220

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Ala Ala Met Thr
 225 230 235 240

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 245 250 255

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 260 265 270

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 275 280 285

Val Arg
 290

<210> SEQ ID NO 13
 <211> LENGTH: 16
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(16)
 <223> OTHER INFORMATION: Signal Peptide

<400> SEQUENCE: 13

Met Pro Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
 1 5 10 15

<210> SEQ ID NO 14
 <211> LENGTH: 224
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: DOMAIN
 <222> LOCATION: (1)..(224)

<400> SEQUENCE: 14

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser
 1 5 10 15

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 20 25 30

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 35 40 45

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 50 55 60

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 65 70 75 80

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 85 90 95

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Val Pro Ile Glu Lys Thr
 100 105 110

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 115 120 125

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 130 135 140

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 145 150 155 160

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

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

<210> SEQ ID NO 15
 <211> LENGTH: 1632
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

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atgcctctcc tctctctgct gctcctgctg ccaagccctt tacaccccca ccccatctgt    60
gaggctctcca aagtggccag ccacctagaa gtgaactgtg acaagaggaa tctgacagcg    120
ctgcctccag acctgccgaa agacacaacc atcctccacc tgagtgagaa cctcctgtac    180
accttctccc tggcaaccct gatgccttac actcgcctca ctcagctgaa cctagatagg    240
tgcgagctca ccaagctcca ggtcgatggg acgctgccag tgctggggac cctggatcta    300
tcccacaatc agctgcaaag cctgcctctg ctagggcaga cactgcctgc tctcaccgtc    360
ctggacgtct cttcaaccg gctgacctcg ctgcctcttg gtgccctgcg tggctctggc    420
gaactccaag agctctacct gaaaggcaat gagctgaaga ccctgcccc agggctcctg    480
acgcccacac ccaagctgga gaagctcagt ctggctaaca acaacttgac tgagctcccc    540
gtgggctccc tgaatgggct ggagaatctc gacacccttc tcctccaaga gaactcgtg    600
tatacaatac caaagggctt ttttgggtcc cacctcctgc cttttgcttt tctccacggg    660
aaccctggtt tatgcaactg tgagatcctc tattttcgtc gctggctgca ggacaatgct    720
gaaaatgtct acgtatggaa gcaagggtg gacgtcaagg ccatgacctc taactgggcc    780
agtgtgcagt gtgacaatc agacaagttt cccgtctaca aataccagg aaaggggtgc    840
cccacccttg gtgatgaagg tgacacagac ctatatgatt actaccaga agaggacact    900
gagggcgata aggtgcgtgc cacaaggact gtggtcaagt tccccacaa agcgcggccg    960
cacacatgcc caccgtgcc agcacctgaa gccctggggg caccgtcagt ctctctcttc   1020
ccccaaaac ccaaggacac cctcatgac tcccggacc ctgaggtcac atgctgtggtg   1080
gtggacgtga gccacgaaga cctgaggtc aagttcaact ggtacgtgga cggcgtggag   1140
gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta cctgtgtggtc   1200
agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc   1260
tccaacaaag ccctcccagt cccatcgag aaaaccatct ccaaagcaa agggcagccc   1320
cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc   1380
agcctgacct gcctggtcaa aggcctctat cccagcgaca tcgccgtgga gtgggagagc   1440
aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggcccc   1500
ttctctctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaactctctc   1560
tcatgctccc tgatgcatga ggctctgcac aaccactaca cgagaagag cctctcctctg   1620
tctccgggta aa                                     1632
  
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<210> SEQ ID NO 16
<211> LENGTH: 1632
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16
atgcctctcc tcctcttgct gctcctgctg ccaagcccct tacacccccca ccccatctgt    60
gaggctctcca aagtggccag ccacctagaa gtgaactgtg acaagaggaa tctgacagcg    120
ctgcctccag acctgccgaa agacacaacc atcctccacc tgagtgagaa cctcctgtac    180
accttctccc tggcaaccct gatgccttac actcgcctca ctcagctgaa cctagatagg    240
tgcgagctca ccaagctcca ggtcagatgg acgctgccag tgctggggac cctggatcta    300
tcccacaatc agctgcaaag cctgcctctg ctagggcaga cactgcctgc tctcaccgtc    360
ctggacgtct cttcaaccg gctgacctcg ctgcctcttg gtgccctgcg tggctctggc    420
gaactccaag agctctacct gaaaggcaat gagctgaaga ccctgcccc agggctcctg    480
acgcccacac ccaagctgga gaagctcagt ctggctaaca acaacttgac tgagctcccc    540
gctgggctcc tgaatgggct ggagaatctc gacacccttc tcctccaaga gaactcgtg    600
tatacaatac caaagggctt ttttgggtcc cacctcctgc cttttgcttt tctccacggg    660
aaccctggt tatgcaactg tgagatcctc tattttcgtc gctggctgca ggacaatgct    720
gaaaatgtct acgtatggaa gcaaggtgtg gacgtcaagg ccatgacctc taactgggcc    780
agtgtgcagt gtgacaatc agacaagttt cccgtctaca aataccagg aaaggggtgc    840
cccacccttg gtgatgaagg tgacacagac ctatatgatt actaccaga agaggacact    900
gagggcgata aggtgctgc cacagcgact gtggtcaagt tccccacaa agcgcggccg    960
cacacatgcc caccgtgcc agcacctgaa gccctggggg caccgtcagt ctctctcttc    1020
ccccaaaac ccaaggacac cctcatgac tcccggaacc ctgaggtcac atgctgtgtg    1080
gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag    1140
gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtgtgc    1200
agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtaca gtgcaaggtc    1260
tccaacaaag ccctcccagt cccatcgag aaaaccatct ccaagccaa agggcagccc    1320
cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc    1380
agcctgacct gcctgtgcaa aggcctctat cccagcgaca tcgccgtgga gtgggagagc    1440
aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggcccc    1500
ttcttctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaactcttc    1560
tcatgctccg tgatgcatga ggctctgcac aaccactaca cgagaagag cctctcctg    1620
tctccgggta aa    1632

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<210> SEQ ID NO 17
<211> LENGTH: 1632
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17
atgcctctcc tcctcttgct gctcctgctg ccaagcccct tacacccccca ccccatctgt    60
gaggctctcca aagtggccag ccacctagaa gtgaactgtg acaagaggaa tctgacagcg    120
ctgcctccag acctgccgaa agacacaacc atcctccacc tgagtgagaa cctcctgtac    180

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accttctccc tggcaaccct gatgccttac actcgcctca ctcagctgaa cctagatagg 240
tgcgagctca ccaagctcca ggtcgatggg acgctgccag tgctggggac cctggatcta 300
tcccacaatc agctgcaaag cctgccttg ctagggcaga cactgcctgc tctcaccgtc 360
ctggacgtct ccttcaaccg gctgacctg ctgcctcttg gtgccctgcg tggctctggc 420
gaactccaag agctctacct gaaaggcaat gagctgaaga ccctgcccc agggtcctg 480
acgcccacac ccaagctgga gaagctcagt ctggctaaca acaacttgac tgagctcccc 540
gctgggctcc tgaatgggct ggagaatctc gacacccttc tcctccaaga gaactcgtg 600
tatacaatac caaagggctt ttttgggtcc cacctcctgc cttttgcttt tctccacggg 660
aaccctggt tatgcaactg tgagatcctc tattttcgtc gctggctgca ggacaatgct 720
gaaaatgtct acgtatggaa gcaagtggg gacgtcaagg ccgtgacctc taactgggcc 780
agtgtgcagt gtgacaatc agacaagttt cccgtctaca aataccagg aaaggggtgc 840
cccacccttg gtgatgaagg tgacacagac ctatatgatt actaccaga agaggacct 900
gagggcgata aggtgctgc cacagcgact gtggtcaagt tccccacaa agcgcggccg 960
cacacatgcc caccgtgcc agcacctgaa gccctggggg caccgtcagt ctctctctc 1020
ccccaaaac ccaaggacac cctcatgatc tcccgaccct ctgaggtcac atgcgtggtg 1080
gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag 1140
gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc 1200
agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtaca gtgcaaggtc 1260
tccaacaaag ccctcccagt cccatcgag aaaaccatct ccaagccaa agggcagccc 1320
cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc 1380
agcctgacct gcctggtcaa aggcctctat cccagcgaca tcgccgtgga gtgggagagc 1440
aatgggcagc cggagaacaa ctacaagacc acgctcccg tgctggactc cgacggcccc 1500
ttctctctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaactctctc 1560
tcatgctccg tgatgcatga ggctctgcac aaccactaca cgagaagag cctctcctg 1620
tctccgggta aa 1632

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<210> SEQ ID NO 18

<211> LENGTH: 1593

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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atgcctctcc tcctcttctg gctcctgctg ccaagcccct tacaccccca ccccatctgt 60
gaggtctcca aagtggccag ccacctagaa gtgaactgtg acaagaggaa tctgacagcg 120
ctgcctccag acctgccgaa agacacaacc atcctccacc tgagttagaa cctcctgtac 180
accttctccc tggcaaccct gatgccttac actcgcctca ctcagctgaa cctagatagg 240
tgcgagctca ccaagctcca ggtcgatggg acgctgccag tgctggggac cctggatcta 300
tcccacaatc agctgcaaag cctgccttg ctagggcaga cactgcctgc tctcaccgtc 360
ctggacgtct ccttcaaccg gctgacctg ctgcctcttg gtgccctgcg tggctctggc 420
gaactccaag agctctacct gaaaggcaat gagctgaaga ccctgcccc agggtcctg 480
acgcccacac ccaagctgga gaagctcagt ctggctaaca acaacttgac tgagctcccc 540

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gctgggctcc tgaatgggct ggagaatctc gacacccttc tcctccaaga gaactcgctg 600
tatacaatac caaagggtct ttttgggtcc cacctcctgc cttttgcttt tctccacggg 660
aaccctggt tatgcaactg tgagatcctc tattttcgtc gctggctgca ggacaatgct 720
gaaaatgtct acgtatggaa gcaagggtg gacgtcaagg ccatgacctc taactgggcc 780
agtgtgcagt gtgacaatc agacaagttt cccgtctaca aataccagg aaaggggtgc 840
cccacccttg gtgatgaagg tgacacagac ctatatgatt actaccaga agaggacact 900
gagggcgata aggtgcggcc gcacacatgc ccaccgtgcc cagcacctga agcctgggg 960
gcaccgtcag tcttctctt cccccaaaa cccaaggaca ccctcatgat ctcccgacc 1020
cctgaggtca catgctgtgt ggtggactg agccacgaag acctgaggt caagttcaac 1080
tggtactggt acggcgtgga ggtgcataat gccaaagaca agccgaggga ggagcagtac 1140
aacgacagt accgtgtgtt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1200
aaggagtaca agtgcaaggt ctccaacaaa gccctccag tcccatcga gaaaaccatc 1260
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgagg 1320
gagatgacca agaaccaggt cagcctgacc tgctgtgtca aaggcttcta tcccagcgac 1380
atcgccgtgg agtgggagag caatgggag ccggagaaca actacaagac cagcctccc 1440
gtgctggact ccgacggccc cttcttctc tacagcaagc tcaccgtgga caagagcagg 1500
tggcagcagg ggaactgtt ctcatgctc gtgatgcatg aggtcttga caaccactac 1560
acgcagaaga gcctctcct gtctccgggt aaa 1593

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<210> SEQ ID NO 19
<211> LENGTH: 1593
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 19

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atgctctctc tcctcttctg gctcctgctg ccaagcccct tacaccccca ccccatctgt 60
gaggtctcca aagtggccag ccacctagaa gtgaactgtg acaagaggaa tctgacagcg 120
ctgctccag acctgcccga agacacaacc atcctccacc tgagtggaaa cctcctgtac 180
accttctccc tggcaacct gatgccttac actcgcctca ctcagetgaa cctagatagg 240
tgcgagctca ccaagctcca ggtcgtatgg acgctgccag tgctggggac cctggatcta 300
tcccacaate agctgcaaag cctgcctctg ctagggcaga cactgcctgc tctcaccgtc 360
ctggactct cttcaaccg gctgaactcg ctgcctctg gtgccctggt tggctctggc 420
gaactccaag agctctacct gaaaggcaat gagctgaaga ccctgcccc agggctcctg 480
acgccacac ccaagctgga gaagctcagt ctggctaaca acaacttgac tgagctcccc 540
gctgggctcc tgaatgggct ggagaatctc gacacccttc tcctccaaga gaactcgctg 600
tatacaatac caaagggtct ttttgggtcc cacctcctgc cttttgcttt tctccacggg 660
aaccctggt tatgcaactg tgagatcctc tattttcgtc gctggctgca ggacaatgct 720
gaaaatgtct acgtatggaa gcaagggtg gacgtcaagg ccgtgacctc taactgggcc 780
agtgtgcagt gtgacaatc agacaagttt cccgtctaca aataccagg aaaggggtgc 840
cccacccttg gtgatgaagg tgacacagac ctatatgatt actaccaga agaggacact 900
gagggcgata aggtgcggcc gcacacatgc ccaccgtgcc cagcacctga agcctgggg 960

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gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 1020
cctgagggtca catgctgtgt ggtggacgtg agccacgaag accctgaggt caagttcaac 1080
tggtacgtgg acggcgtgga ggtgcataat gccaaagaaa agccgcggga ggagcagtag 1140
aacagcacgt accgtgtgtt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1200
aaggagtaca agtgcaaggt ctccaacaaa gccctcccag tccccatcga gaaaaccatc 1260
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgggag 1320
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 1380
atgcccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1440
gtgctggact ccgacggccc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1500
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1560
acgcagaaga gcctctcctt gtctccgggt aaa 1593

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<210> SEQ ID NO 20

<211> LENGTH: 1593

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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1-28. (canceled)

29. A method of inhibiting adherence of a platelet to von Willebrand Factor in a subject, the method comprising administering to a subject in need thereof a polypeptide comprising the amino acid sequence of SEQ ID NO:5 in an amount sufficient to inhibit adherence of said platelet to von Willebrand Factor.

30-46. (canceled)

47. A method of treating a disorder associated with platelet activation in a subject, the method comprising administering to a subject in need thereof a polypeptide comprising the amino acid sequence of SEQ ID NO:5.

48. The method of claim 47, wherein said disorder is associated with thrombotic disease.

49. The method of claim 47, wherein said disorder is ischemic heart disease, angina, acute myocardial infarction, stroke, venous thrombosis, atherosclerosis, restenosis, vascular inflammation or arterial thrombosis.

50. The method of claim 47, wherein said disorder is angina.

51. The method of claim 50, wherein said angina is unstable angina.

52. The method of claim 47, wherein said subject is a human.

53. The method of claim 47, further comprising administering to said subject a compound selected from the group consisting of acetylsalicylic acid, heparin, a glycoprotein IIb/IIIa antagonist, clopidogrel, a P-selectin antagonist, a thrombin inhibitor and a thrombolytic enzyme.

54. The method of claim 47, wherein said disorder is ischemic heart disease.

55. The method of claim 47, wherein said disorder is acute myocardial infarction.

56. The method of claim 47, wherein said disorder is stroke.

57. The method of claim 47, wherein said disorder is venous thrombosis.

58. The method of claim 47, wherein said disorder is atherosclerosis.

59. The method of claim 47, wherein said disorder is arterial thrombosis.

60. The method of claim 47, wherein said disorder is restenosis.

61. The method of claim 60, wherein said restenosis is angioplasty-related restenosis.

62. The method of claim 50, wherein said angina is stable angina.

63. The method of claim 47, wherein said disorder is vascular inflammation.

64. The method of claim 47, further comprising administering to said subject acetylsalicylic acid.

65. The method of claim 47, further comprising administering to said subject heparin.

66. The method of claim 47, further comprising administering to said subject a glycoprotein IIb/IIIa antagonist.

67. The method of claim 47, further comprising administering to said subject clopidogrel.

68. The method of claim 47, further comprising administering to said subject a P-selectin antagonist.

69. The method of claim 47, further comprising administering to said subject a thrombin inhibitor.

70. The method of claim 47, further comprising administering to said subject a thrombolytic enzyme.

71. The method of claim 29, wherein said subject is a human.

72. The method of claim 29, wherein said subject is a primate.

73. The method of claim 47, wherein said subject is a primate.

74. The method of claim 47, wherein said polypeptide is a multimeric polypeptide.

75. The method of claim 74, wherein said multimeric polypeptide is a dimer.

76. The method of claim 47, wherein said polypeptide consists essentially of the amino acid sequence of SEQ ID NO:5.

77. The method of claim 47, wherein said polypeptide consists of the amino acid sequence of SEQ ID NO:5.

78. A method of inhibiting adherence of a platelet to von Willebrand Factor in a human, the method comprising administering to a human in need thereof a polypeptide that consists of the amino acid sequence of SEQ ID NO:5, wherein the polypeptide blocks von Willebrand Factor binding sites preventing platelet adherence whereby allowing for a reduced amount of restrained blood flow.

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