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(54) **METHODS AND COMPOSITIONS FOR THE TREATMENT OF WOUNDS**

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(51) **Int. Cl.**

A61K 38/00 (2006.01)

C07K 5/00 (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC **C07K 14/78** (2013.01); **A61K 9/0024** (2013.01); **A61K 9/7007** (2013.01); **A61K 38/00** (2013.01);

(Continued)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Thea D’Ambrosio

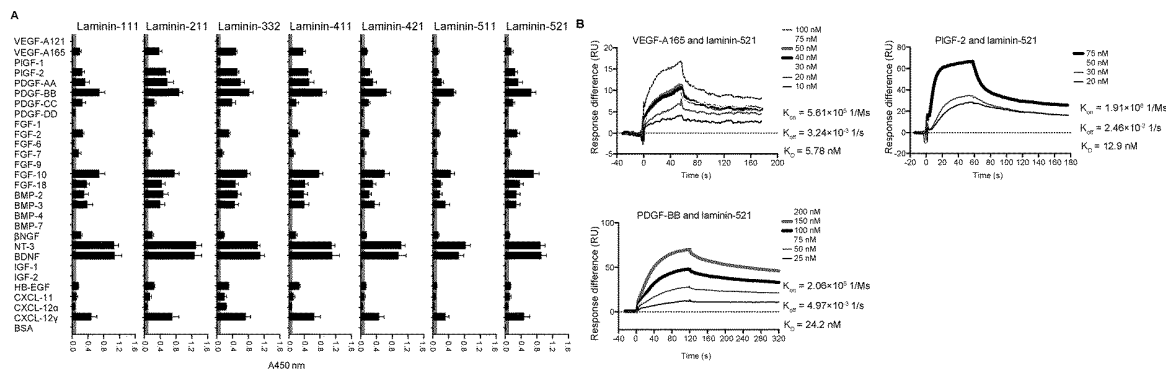
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(57) **ABSTRACT**

The methods and compositions described herein address the need in the art by providing peptides and polypeptides comprising a growth factor binding domain. In some embodiments, the peptides have an amino acid sequence that is at least 80% identical to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70, or a fragment thereof; wherein the peptide is less than 300 amino acids in length.

16 Claims, 31 Drawing Sheets

Specification includes a Sequence Listing.



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C07K 16/00 (2006.01)
C07K 17/00 (2006.01)
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A61K 38/17 (2006.01)
A61K 38/18 (2006.01)
C07K 14/475 (2006.01)
A61P 17/02 (2006.01)
A61K 38/16 (2006.01)
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A61L 27/22 (2006.01)
C07K 16/18 (2006.01)
A61K 9/00 (2006.01)
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- (52) **U.S. Cl.**
 CPC **A61K 38/18** (2013.01); **A61K 38/39** (2013.01); **A61K 47/6435** (2017.08); **A61K 47/6903** (2017.08); **A61L 27/22** (2013.01); **A61P 17/02** (2018.01); **C07K 14/475** (2013.01); **C07K 14/70546** (2013.01); **C07K 14/8121** (2013.01); **C07K 16/18** (2013.01); **A61L 2300/412** (2013.01); **C07K 2317/55** (2013.01); **C07K 2319/70** (2013.01)

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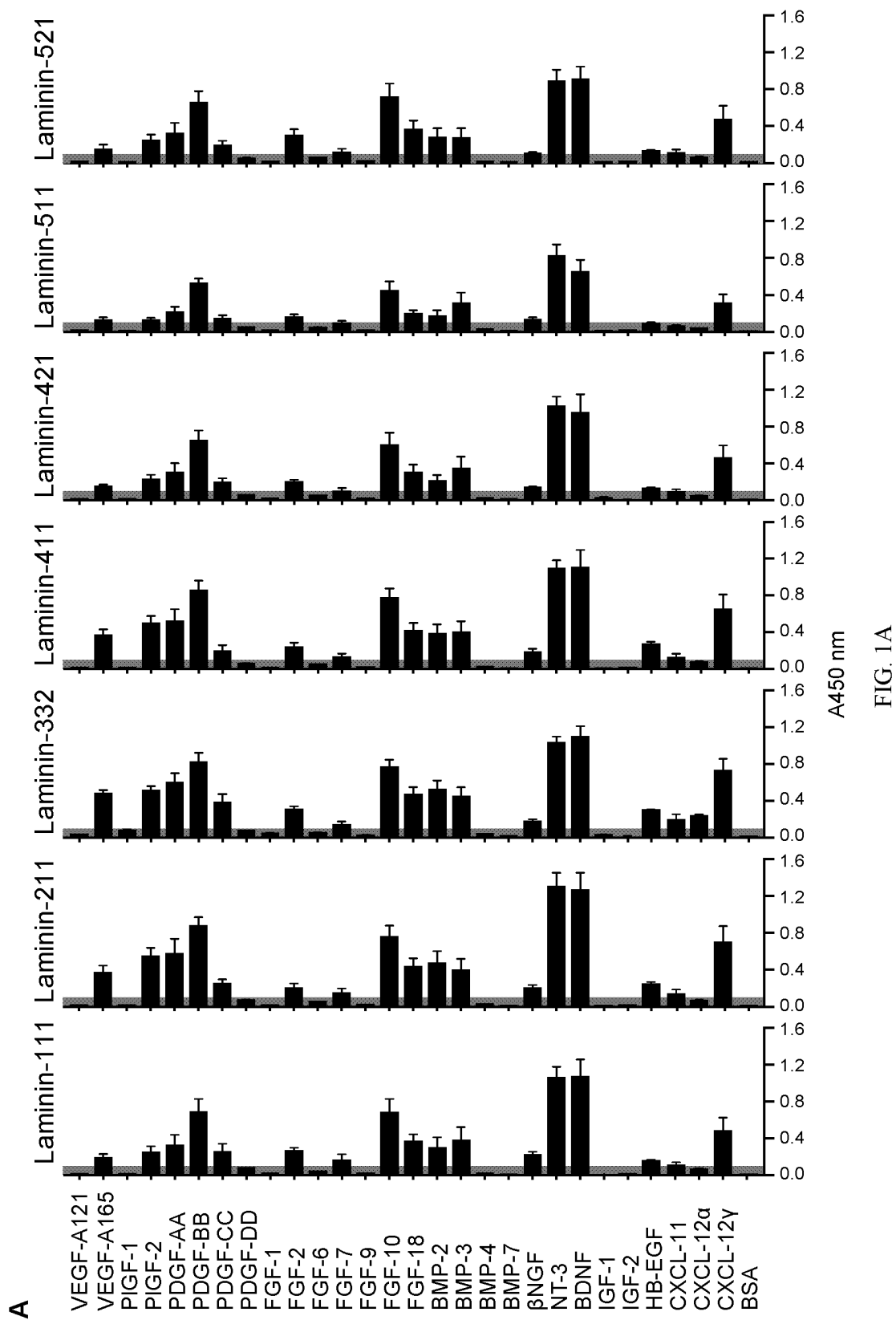
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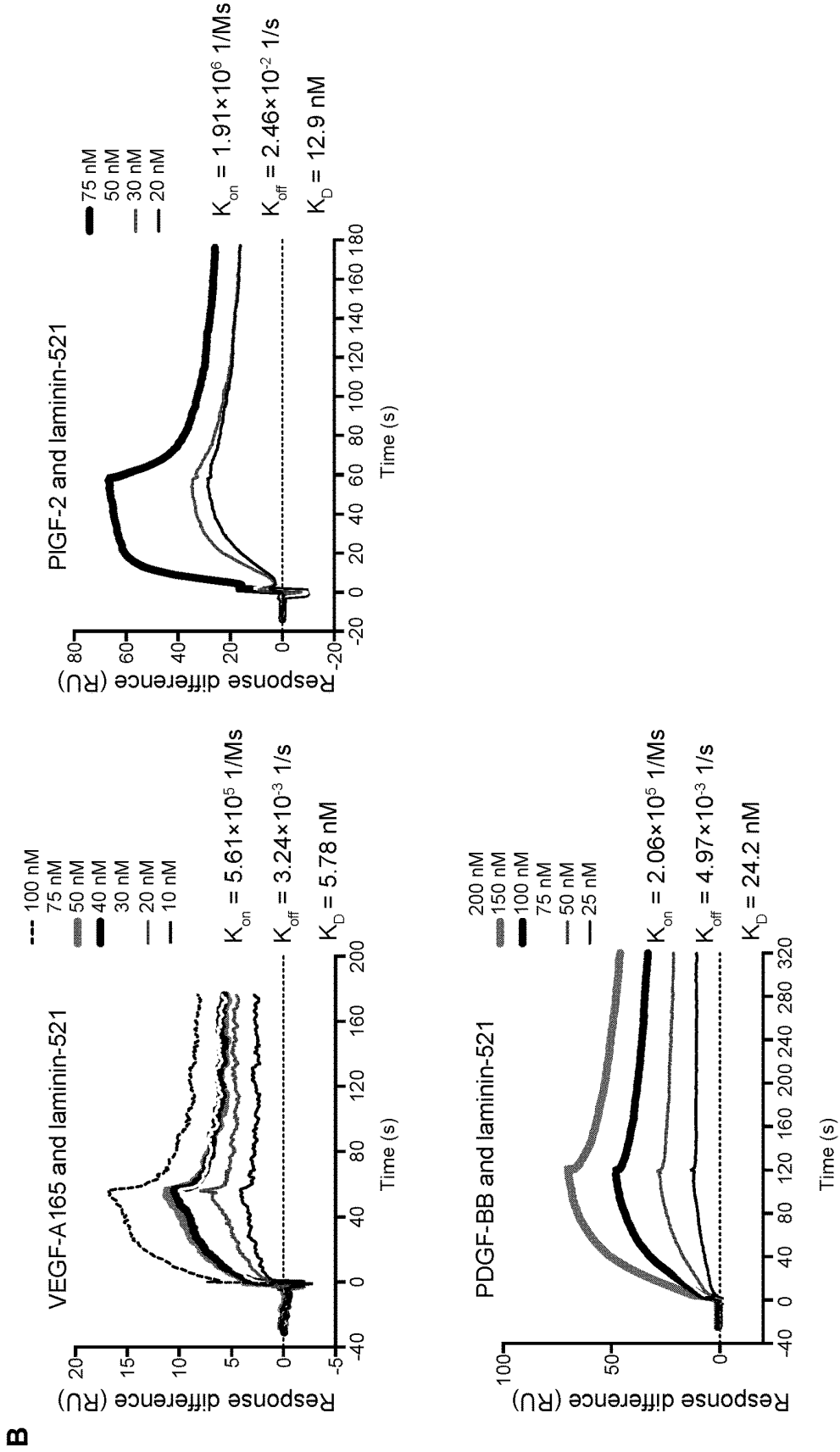


FIG. 1B

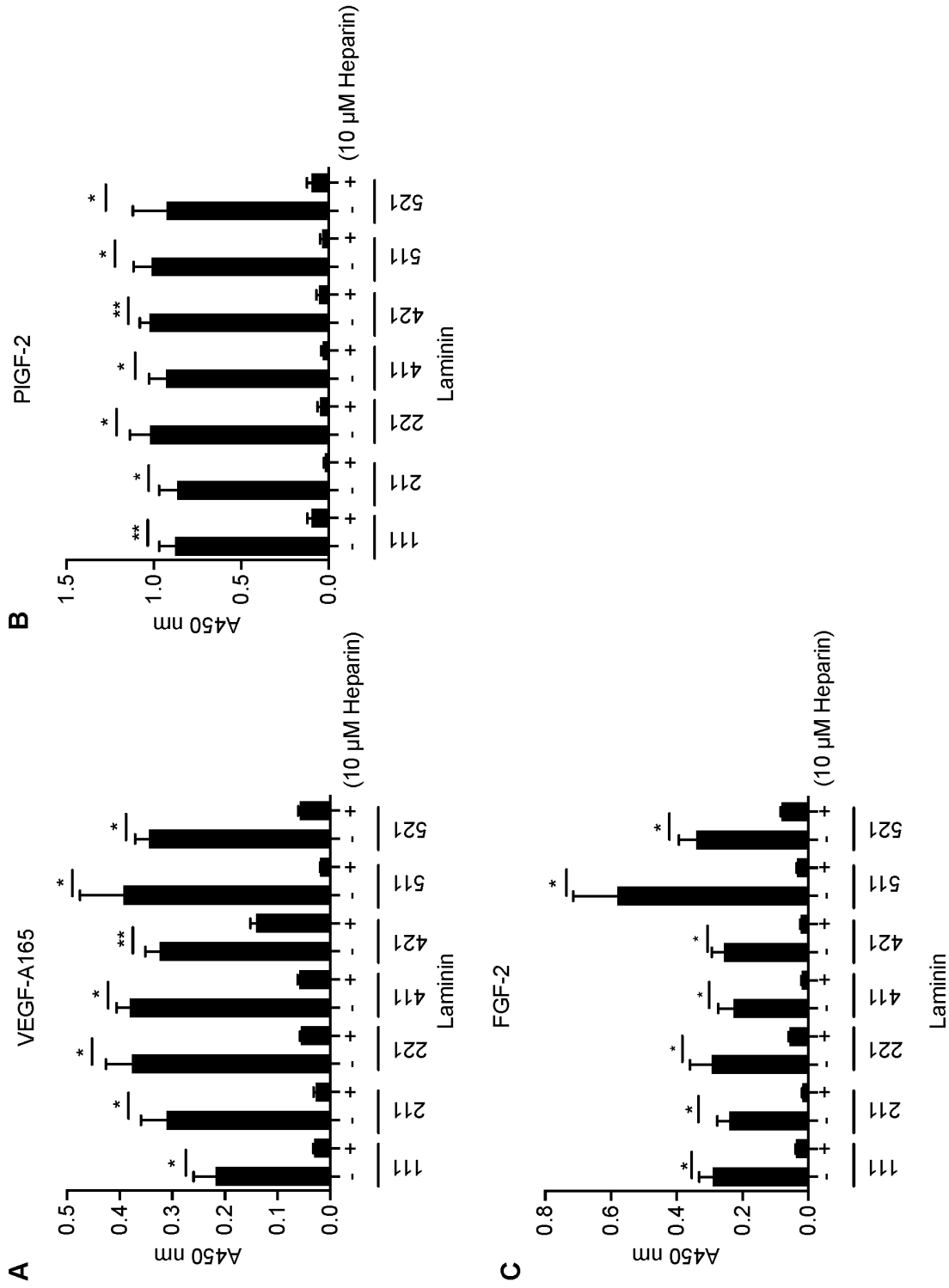


FIG. 2A-C

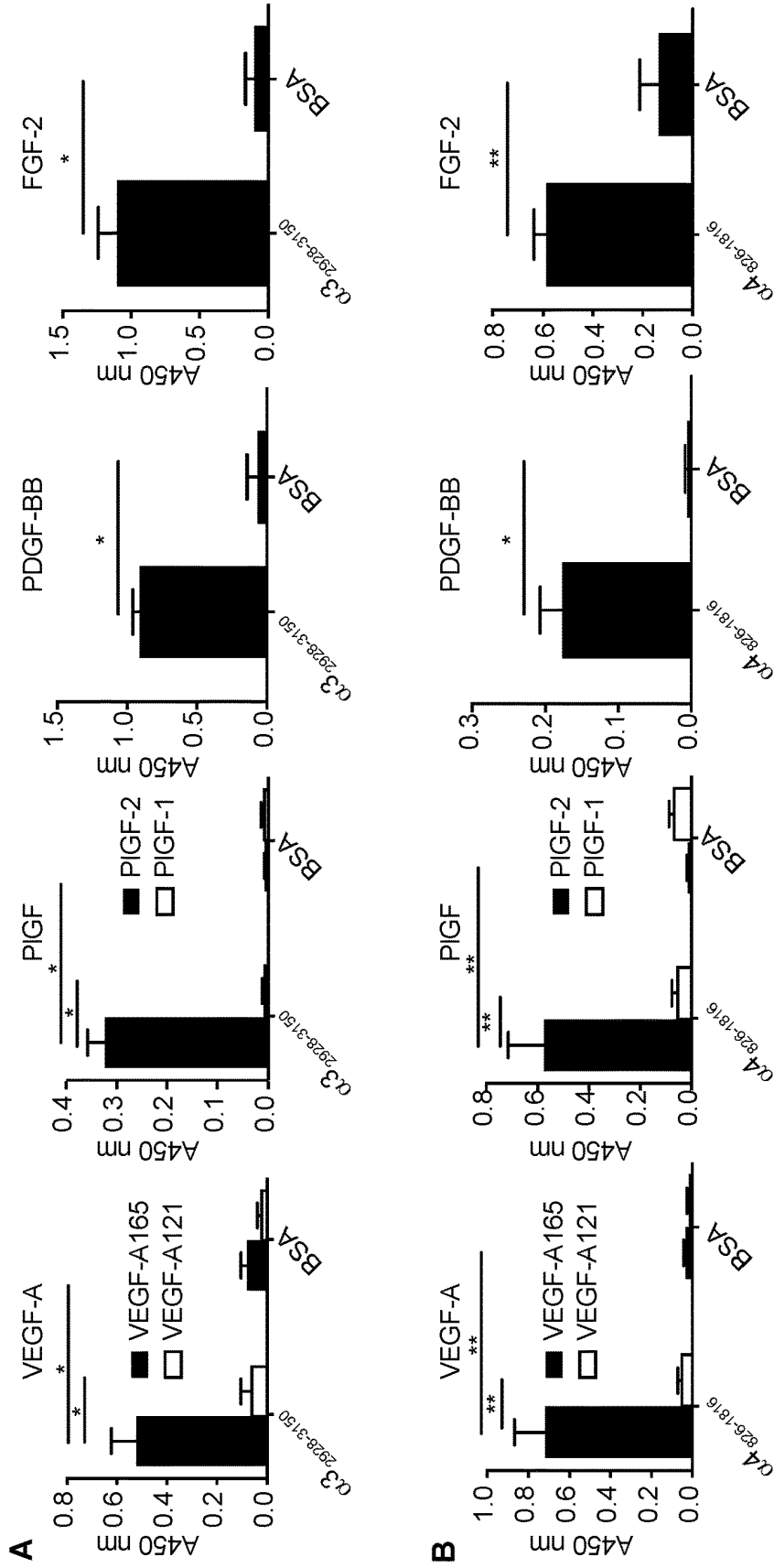


FIG. 3 A-B

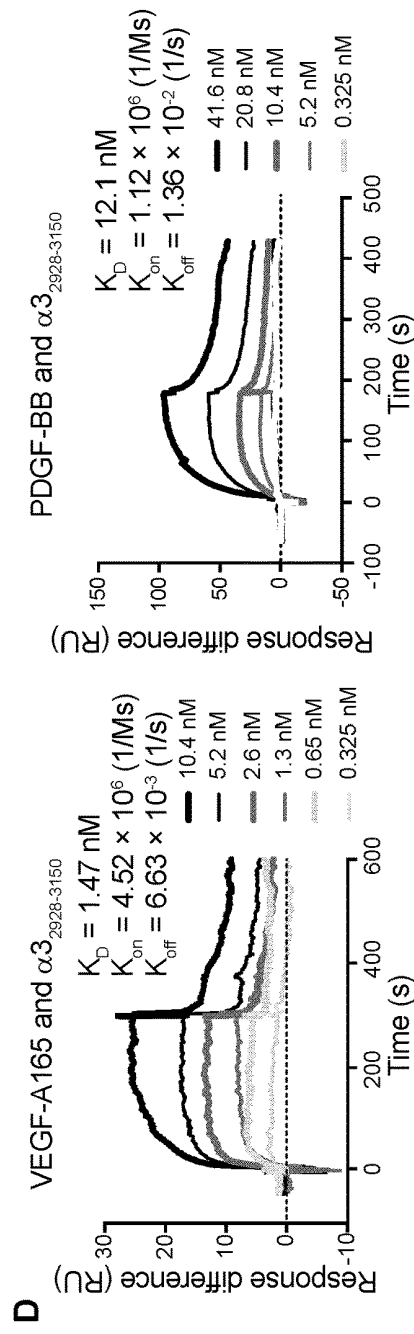
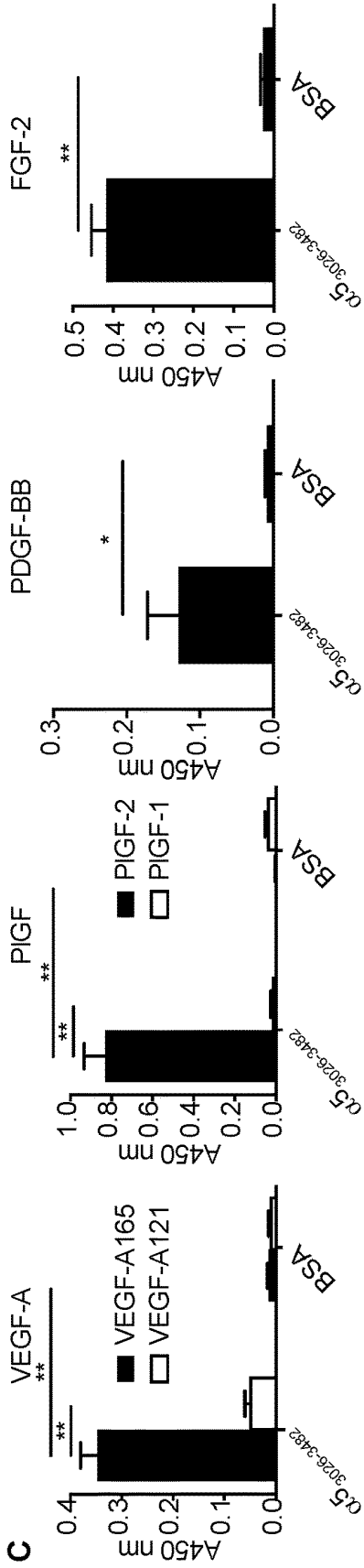


FIG. 3C-D

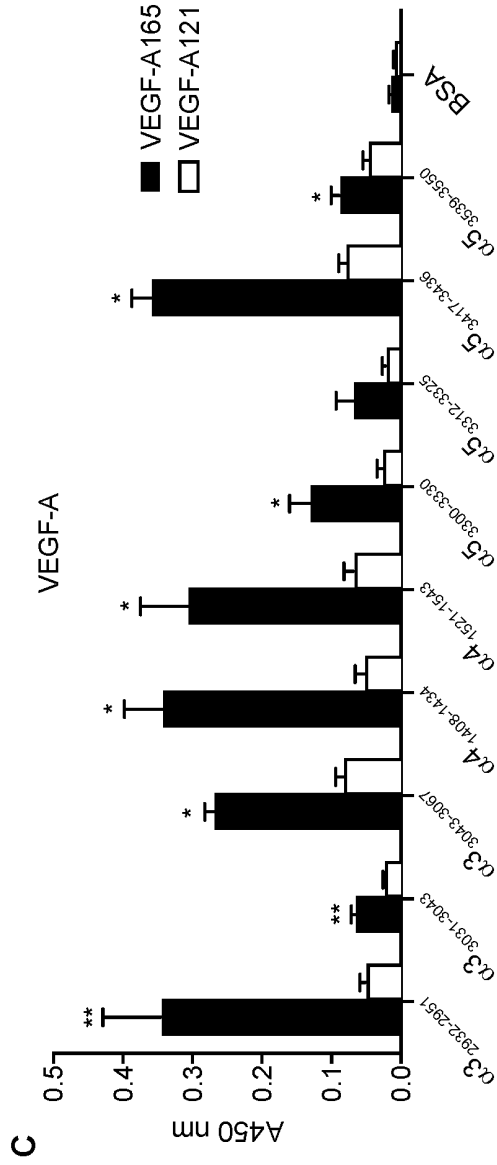
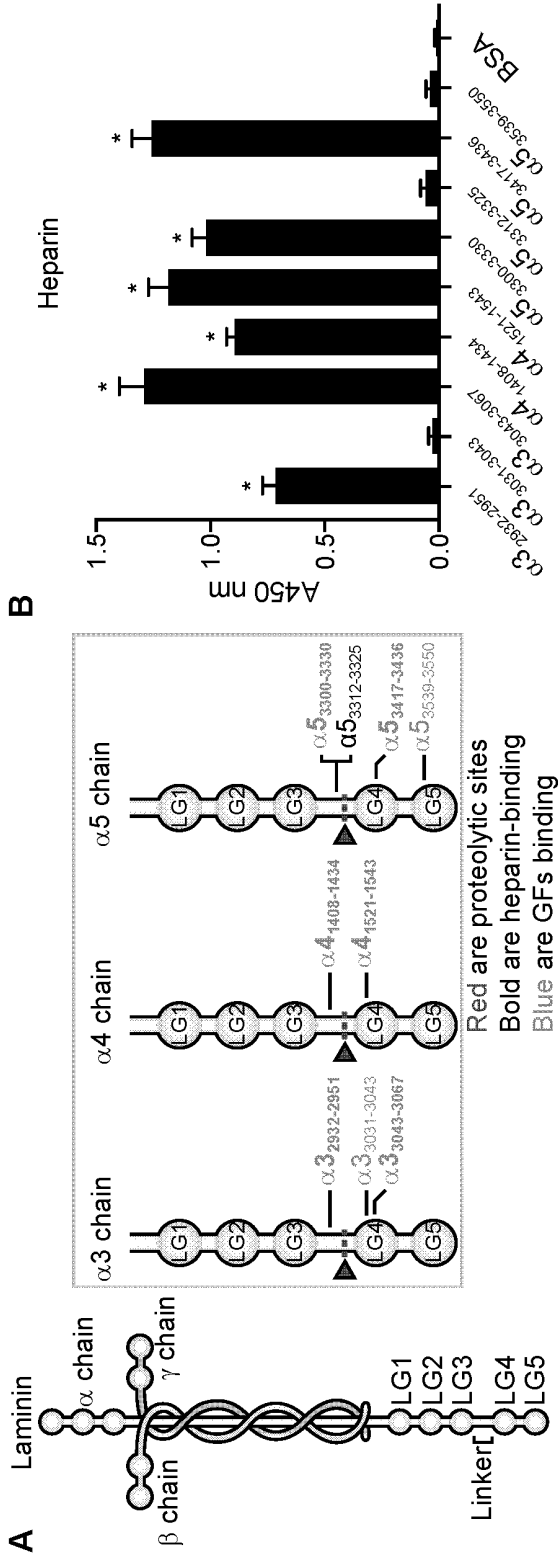


FIG. 4A-C

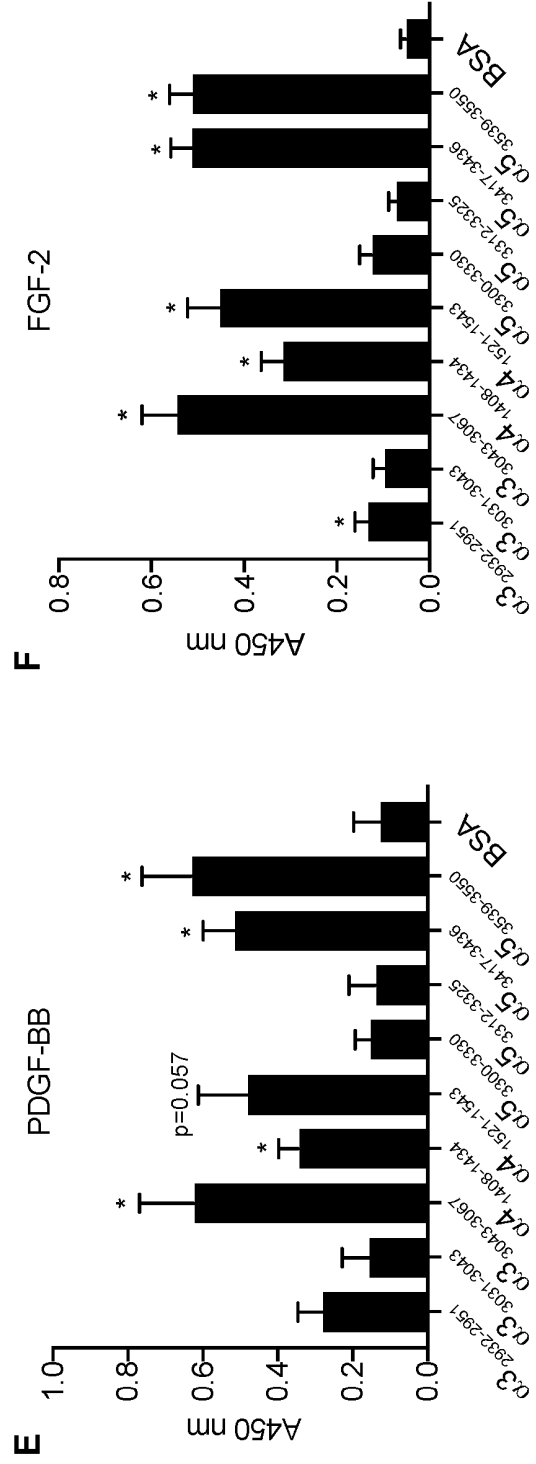
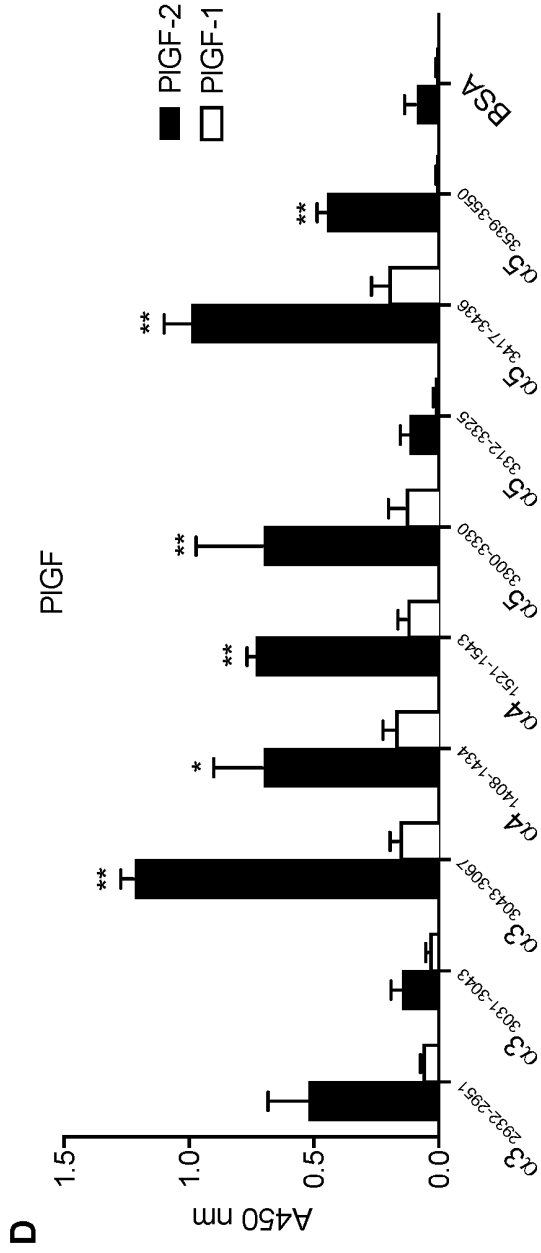


FIG. 4D-F

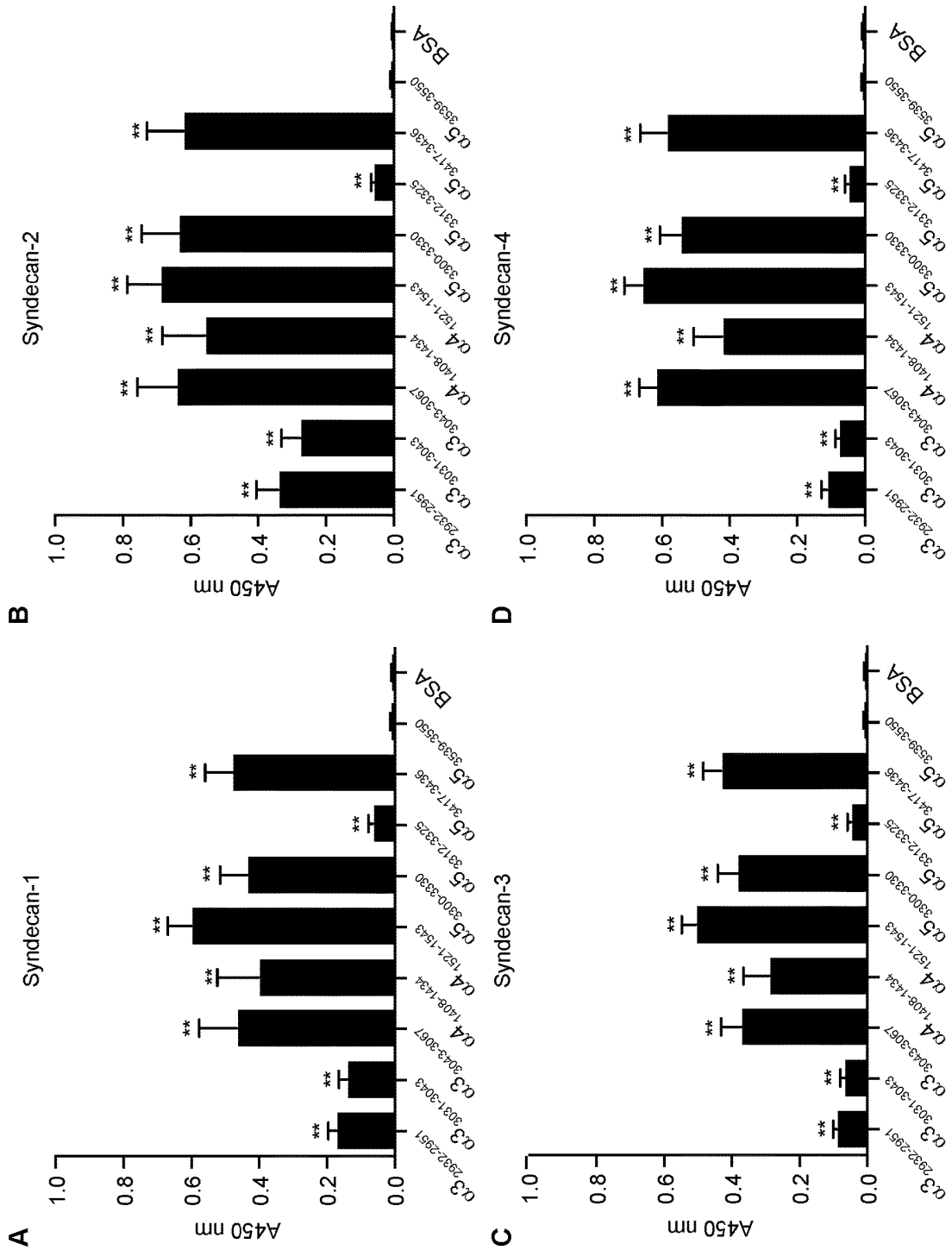


FIG. 5A-D

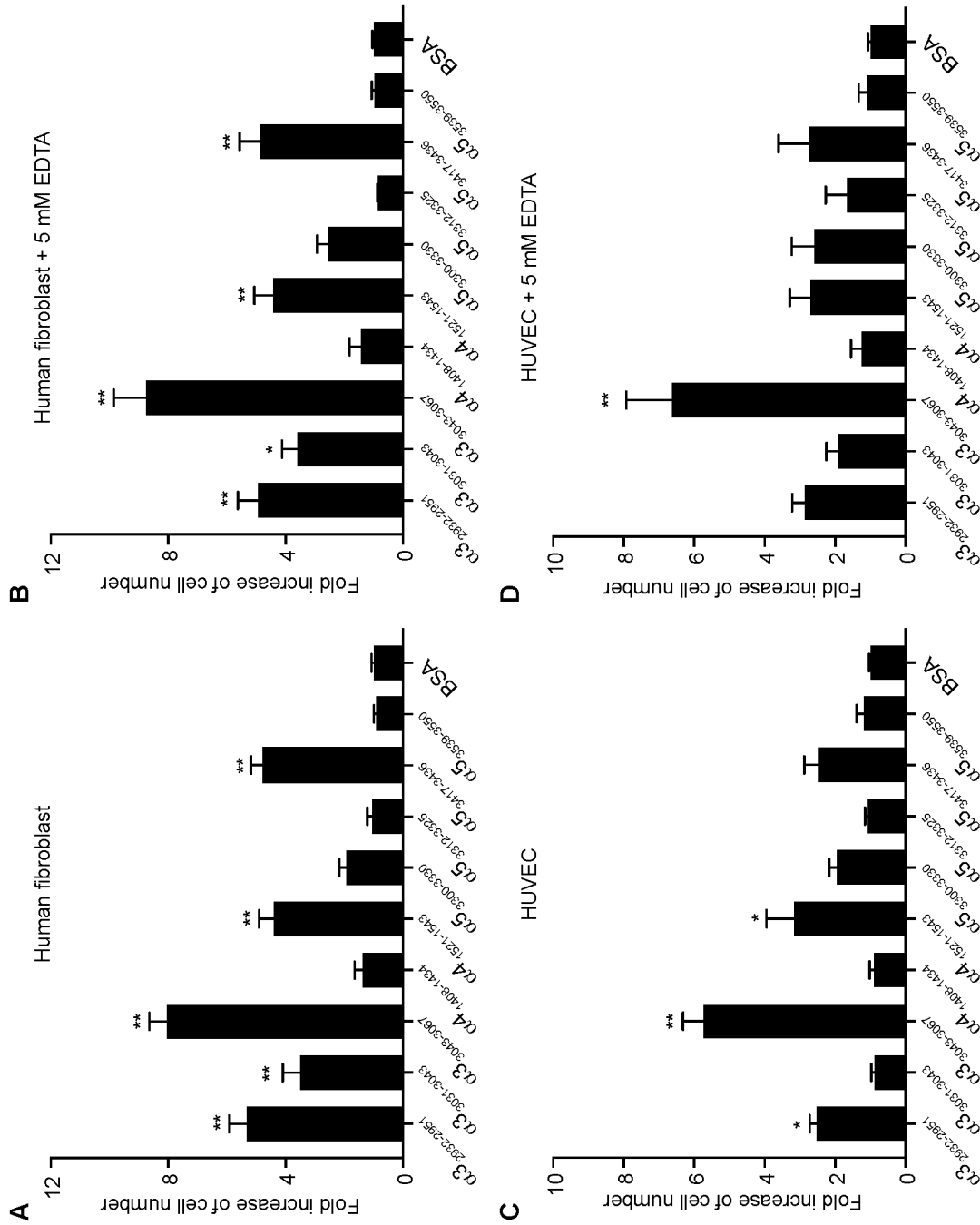


FIG. 6A-D

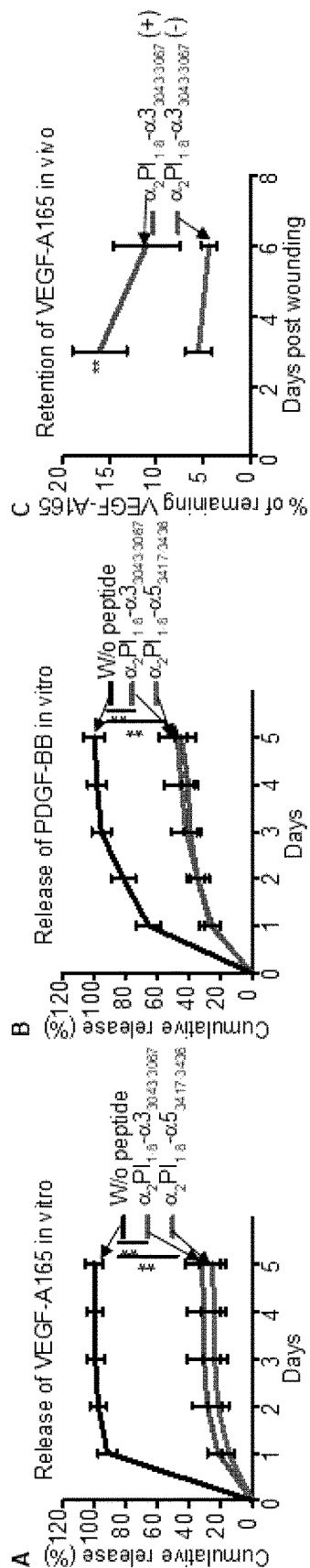


FIG. 7A-C

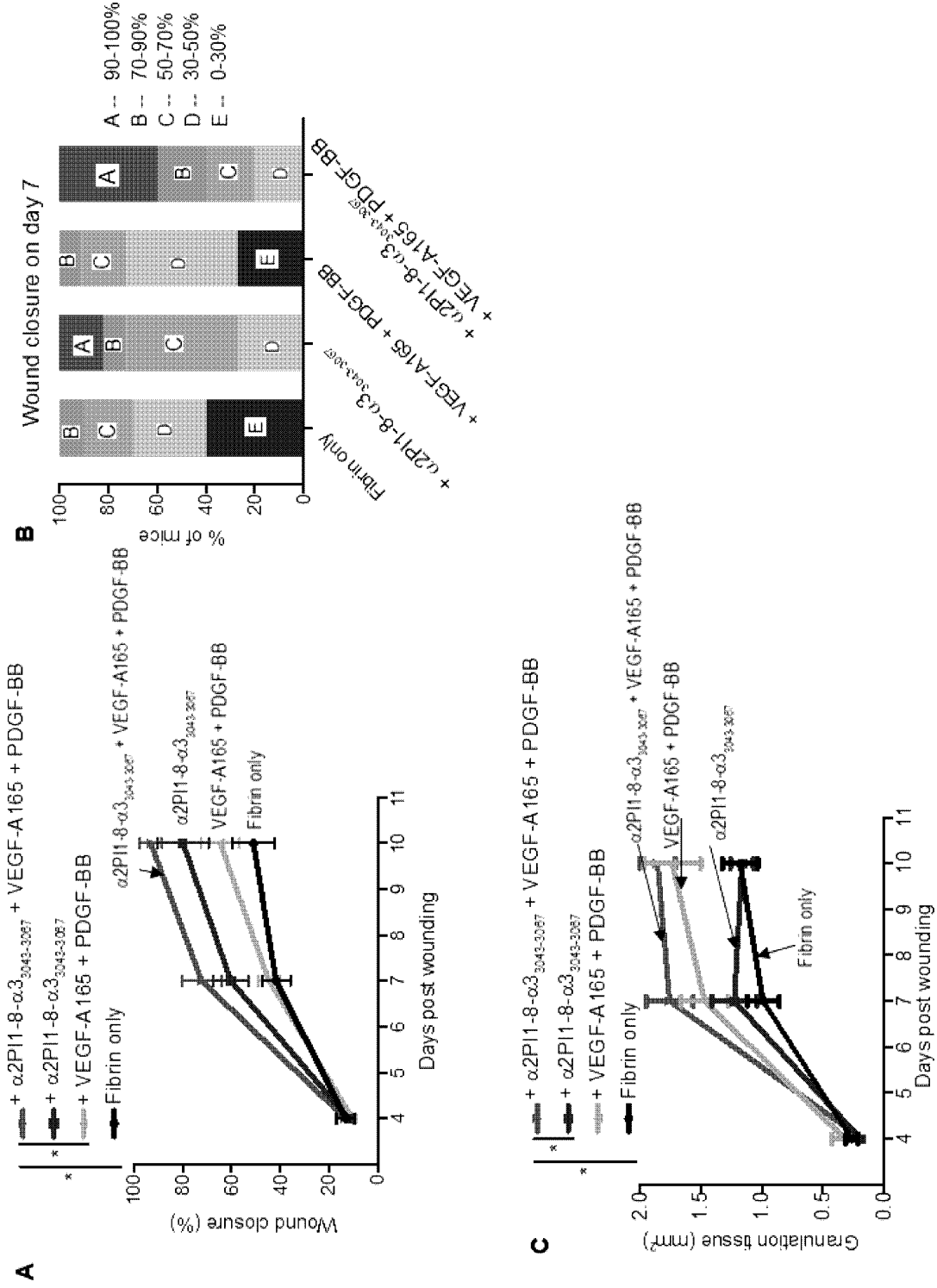


FIG. 8A-C

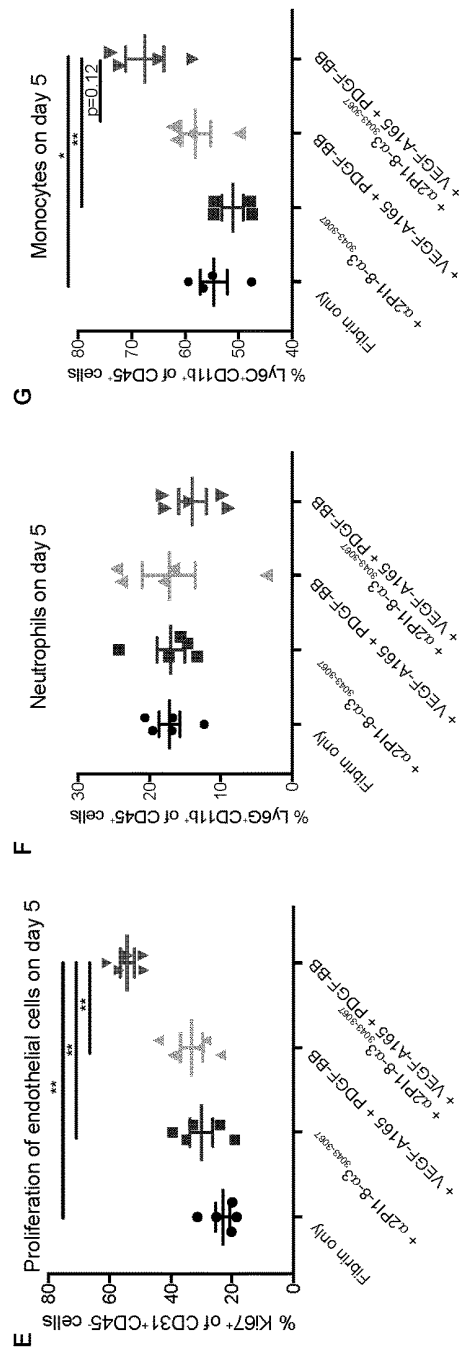
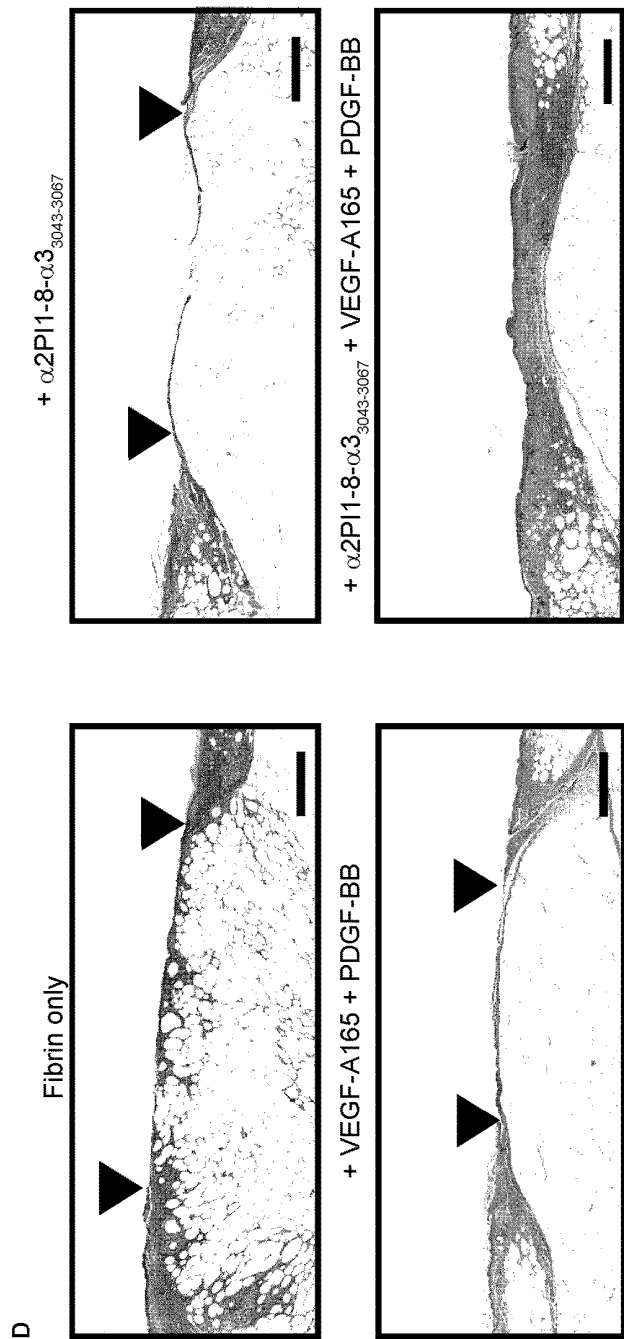


FIG. 8D-G

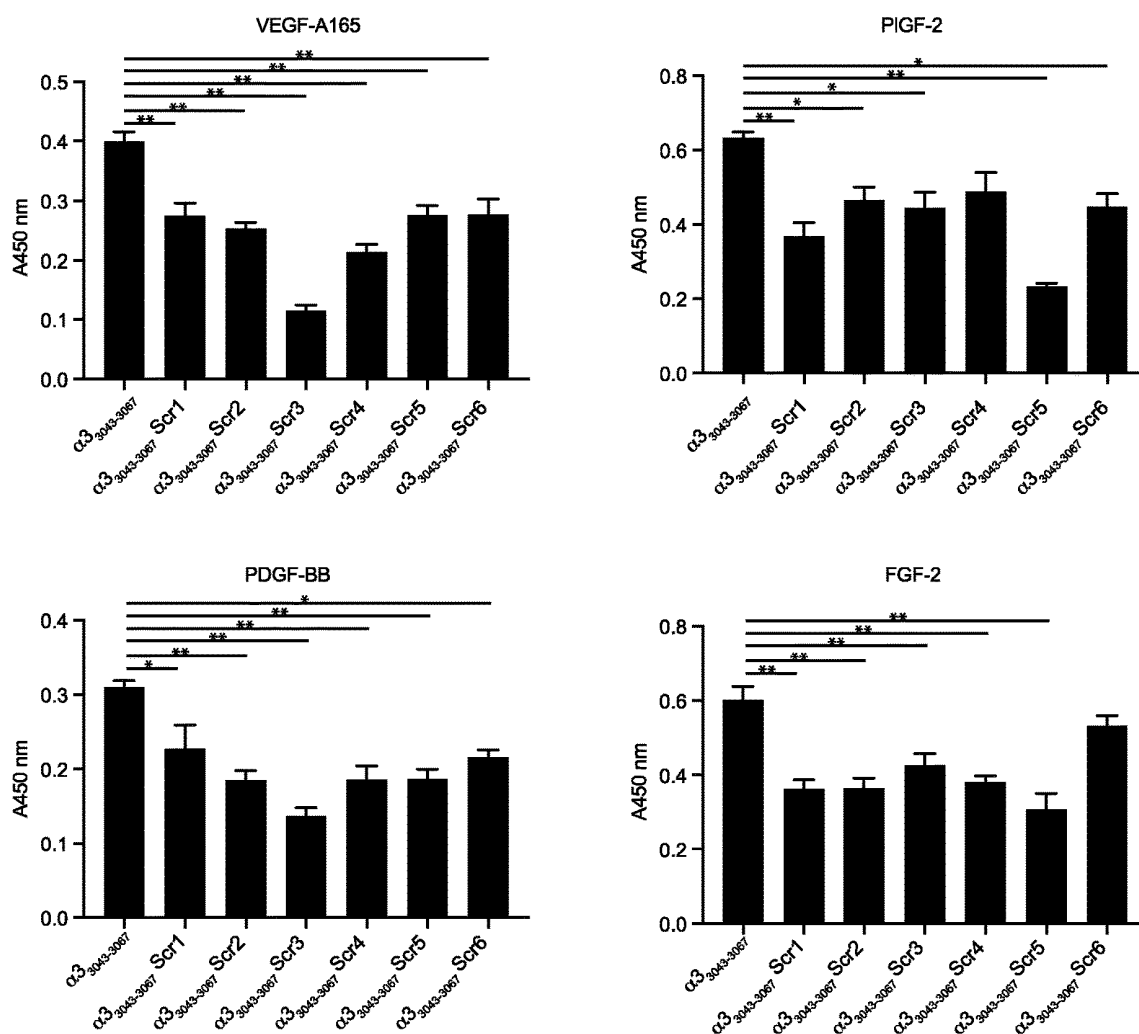


FIG. 9

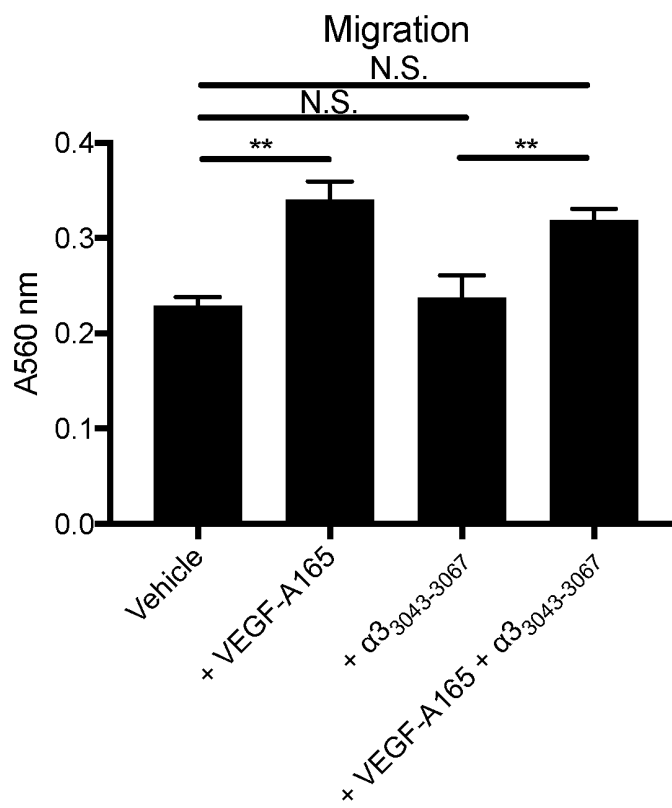
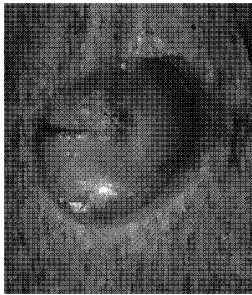


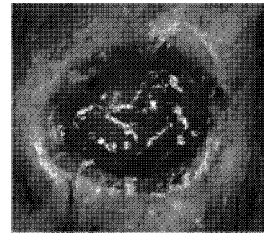
FIG. 10

Wound on day 0

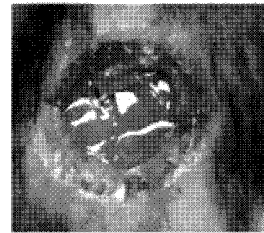


Wound on day 7

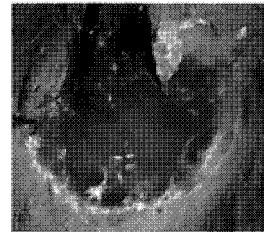
Fibrin only



+ $\alpha 2\text{PI1-8-}\alpha 3_{3043-3067}$



+ VEGF-A165 + PDGF-BB



+ $\alpha 2\text{PI1-8-}\alpha 3_{3043-3067}$
+ VEGF-A165 + PDGF-BB

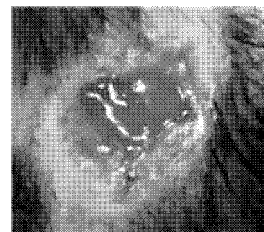


FIG. 11

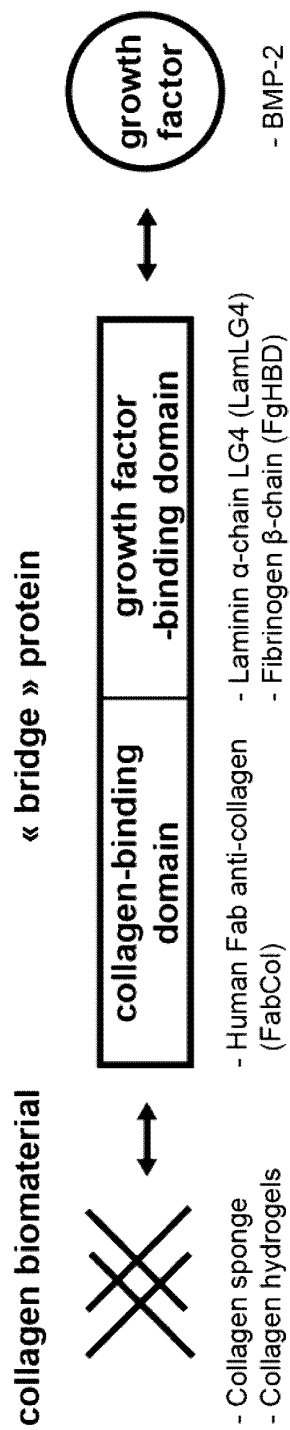


FIG. 12

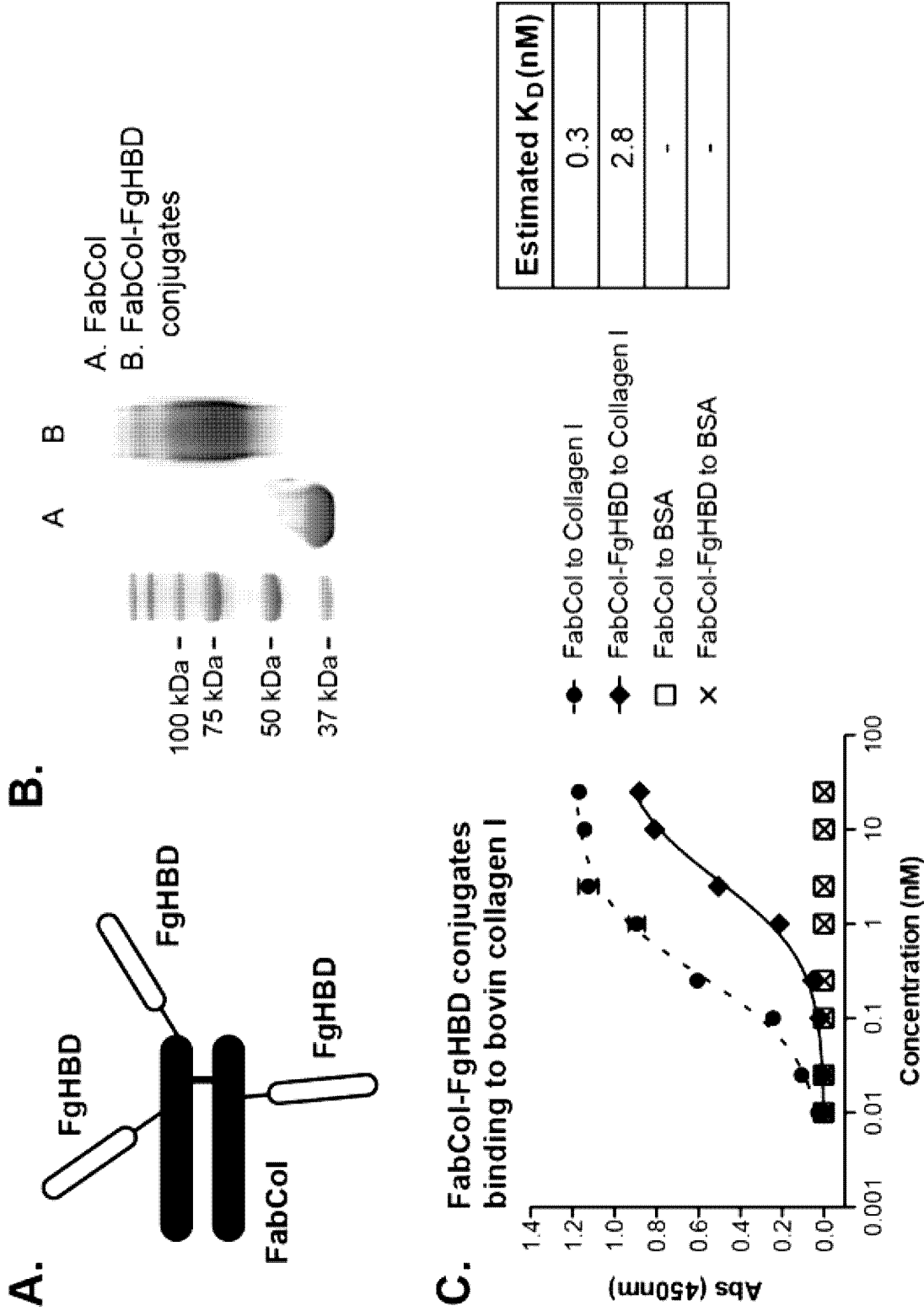


FIG. 13A-C

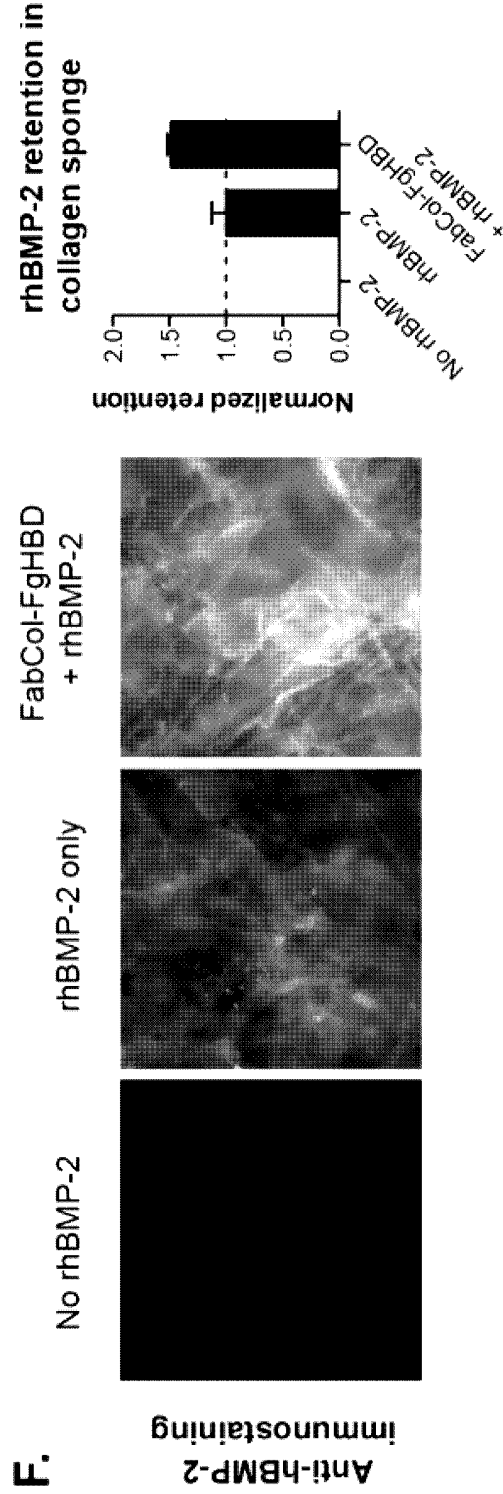
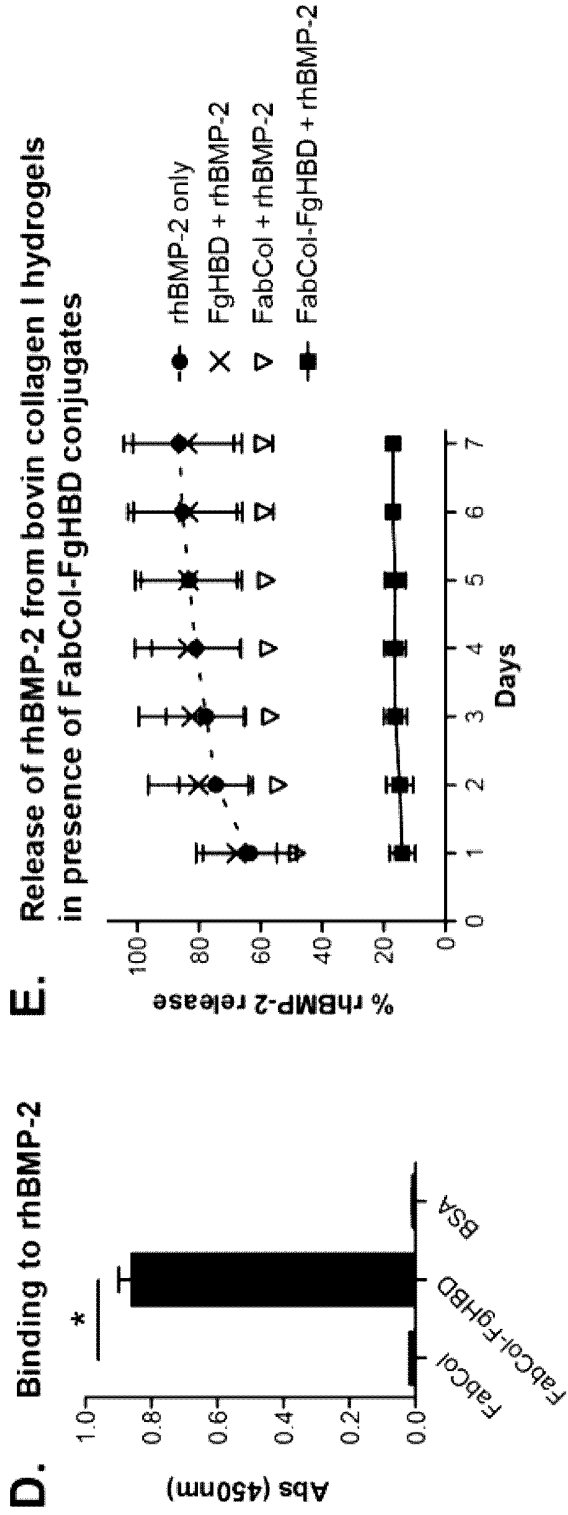


FIG. 13D-F

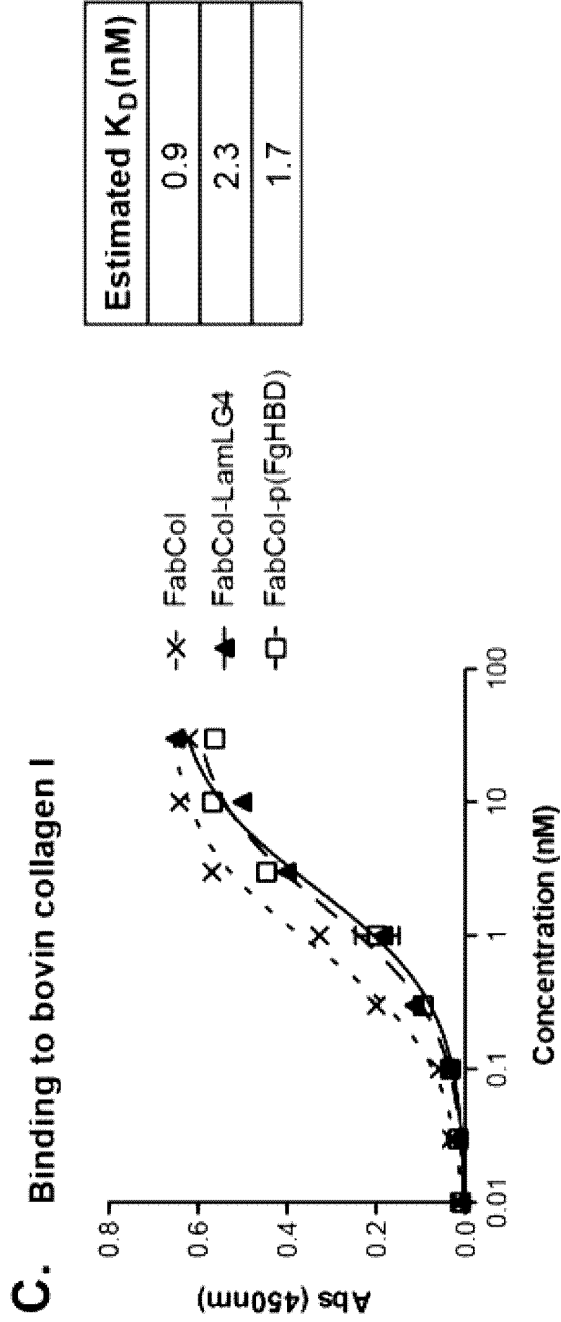
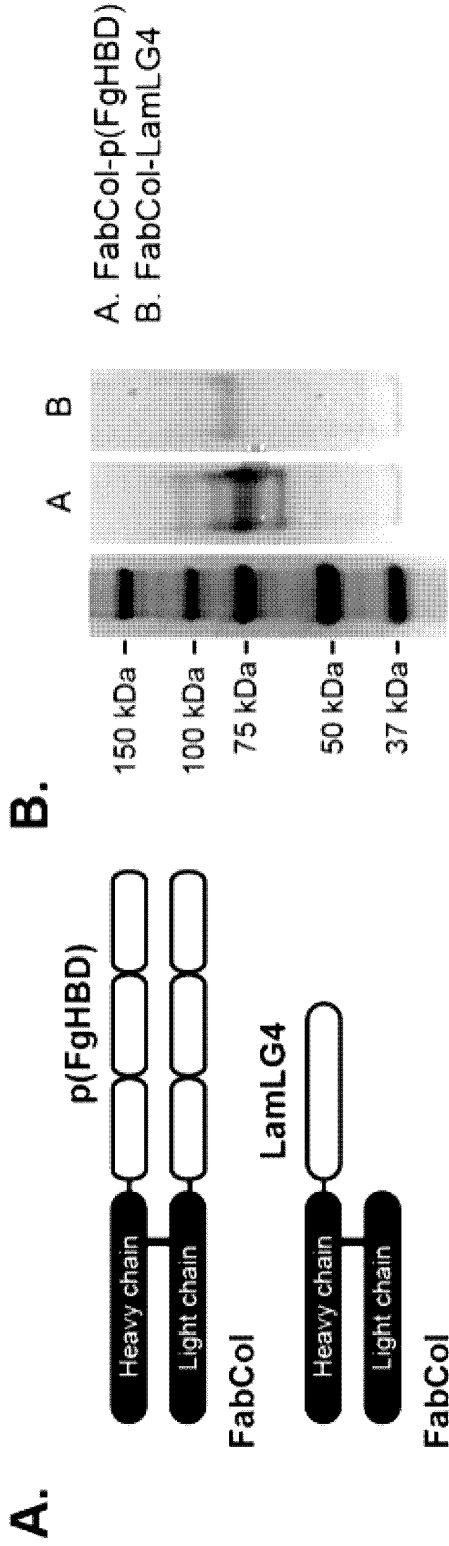
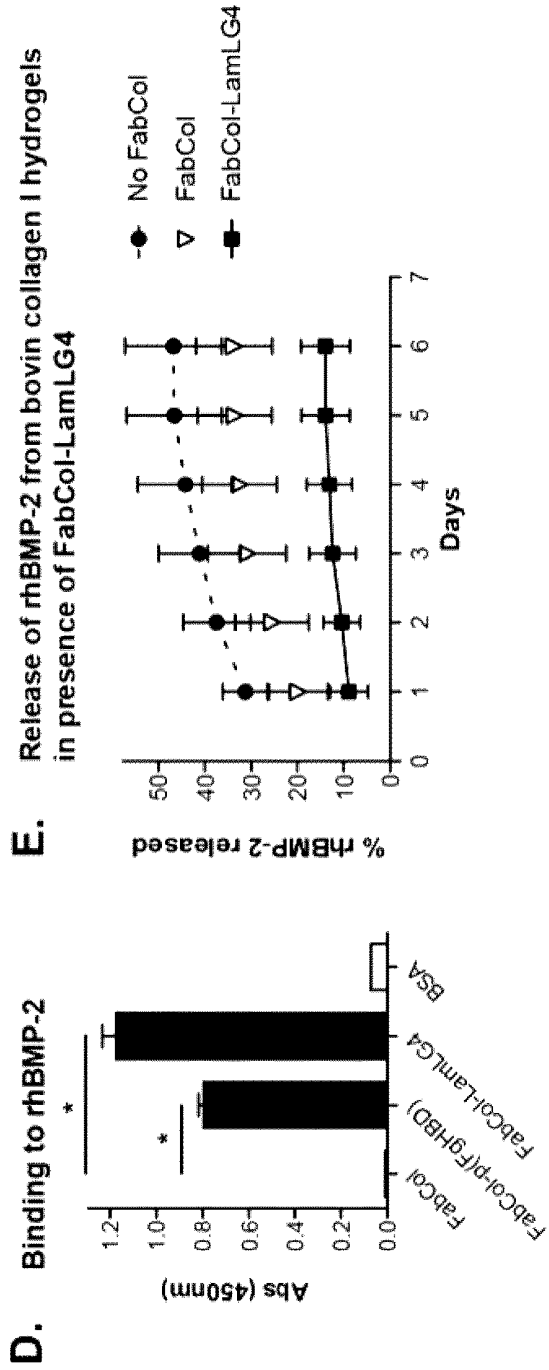


FIG. 14A-C



F. Binding to engineered super-affinity growth factors

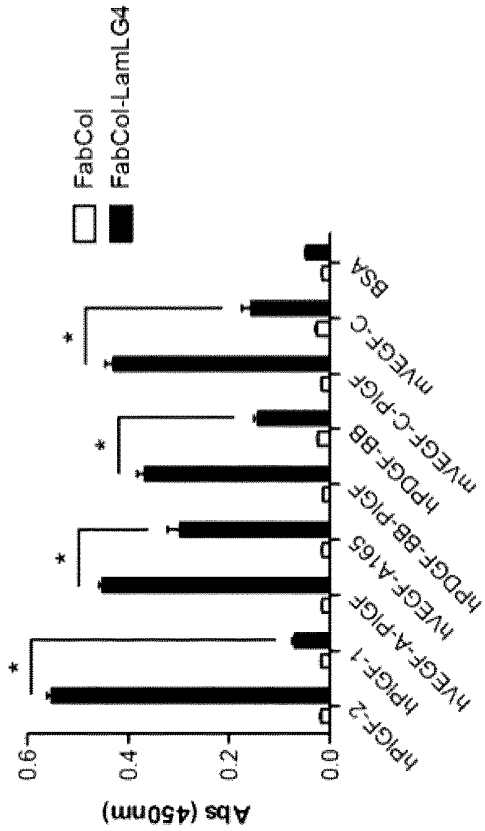


FIG. 14D-F

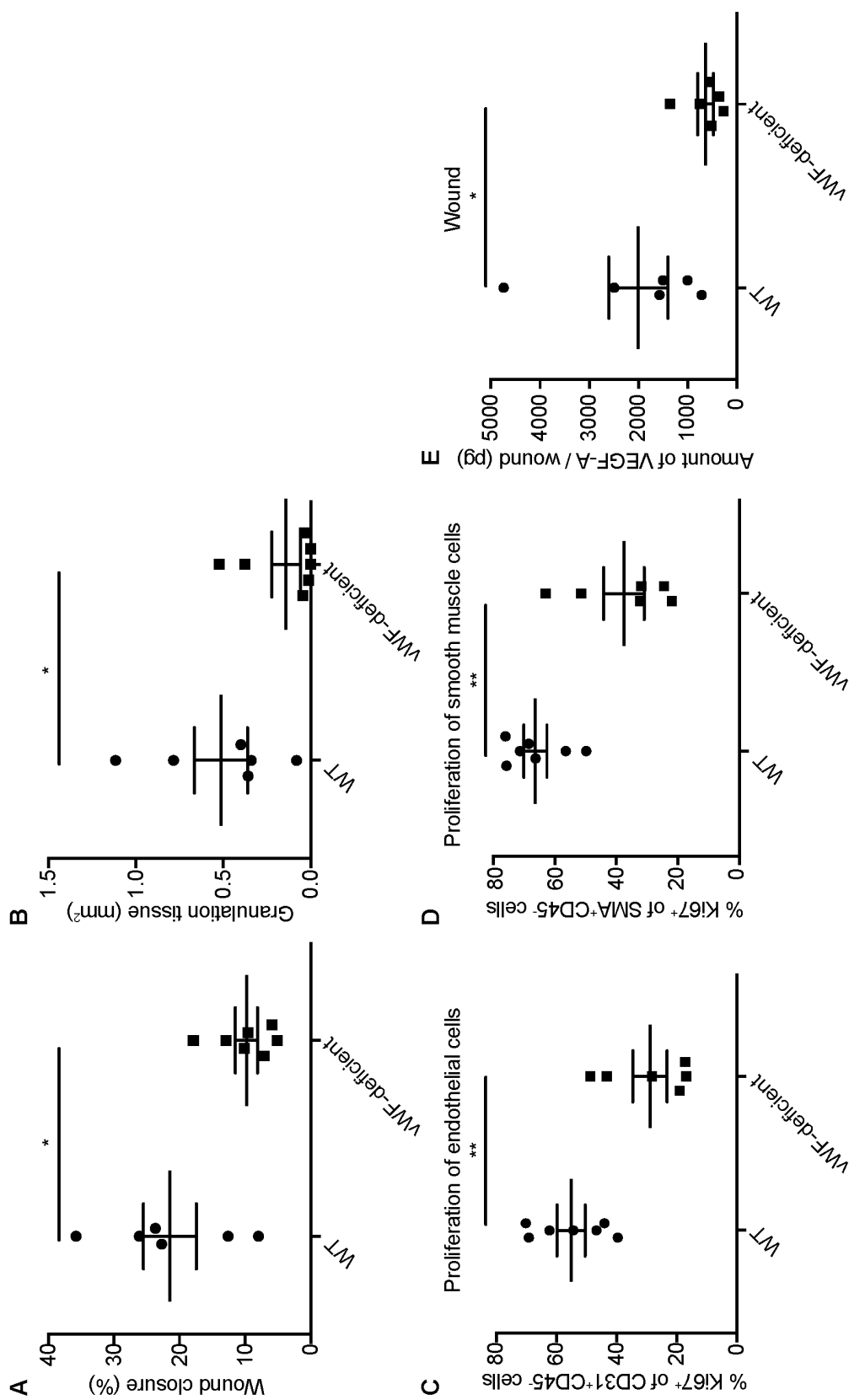


FIG. 15A-E

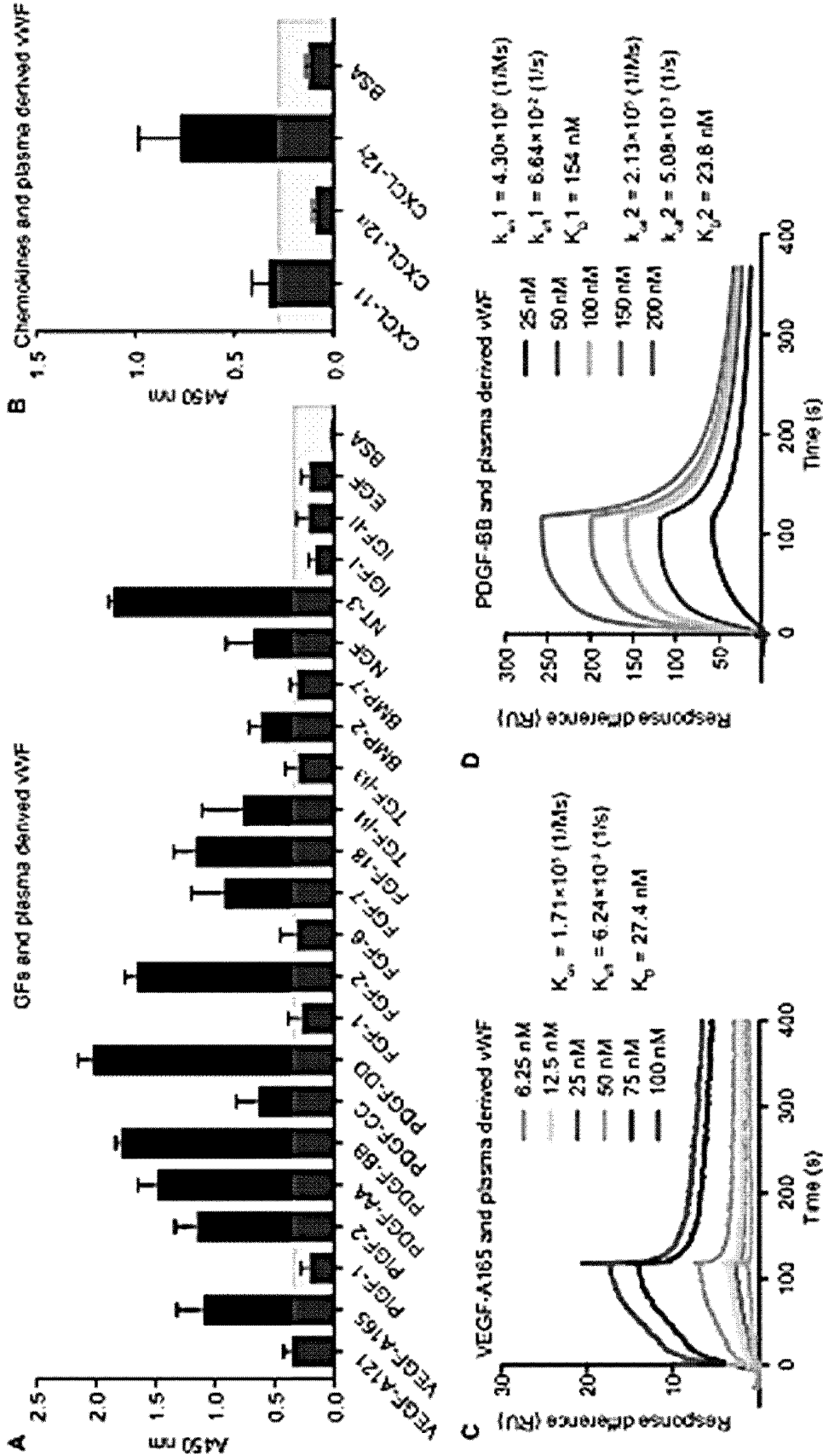


FIG. 16A-D

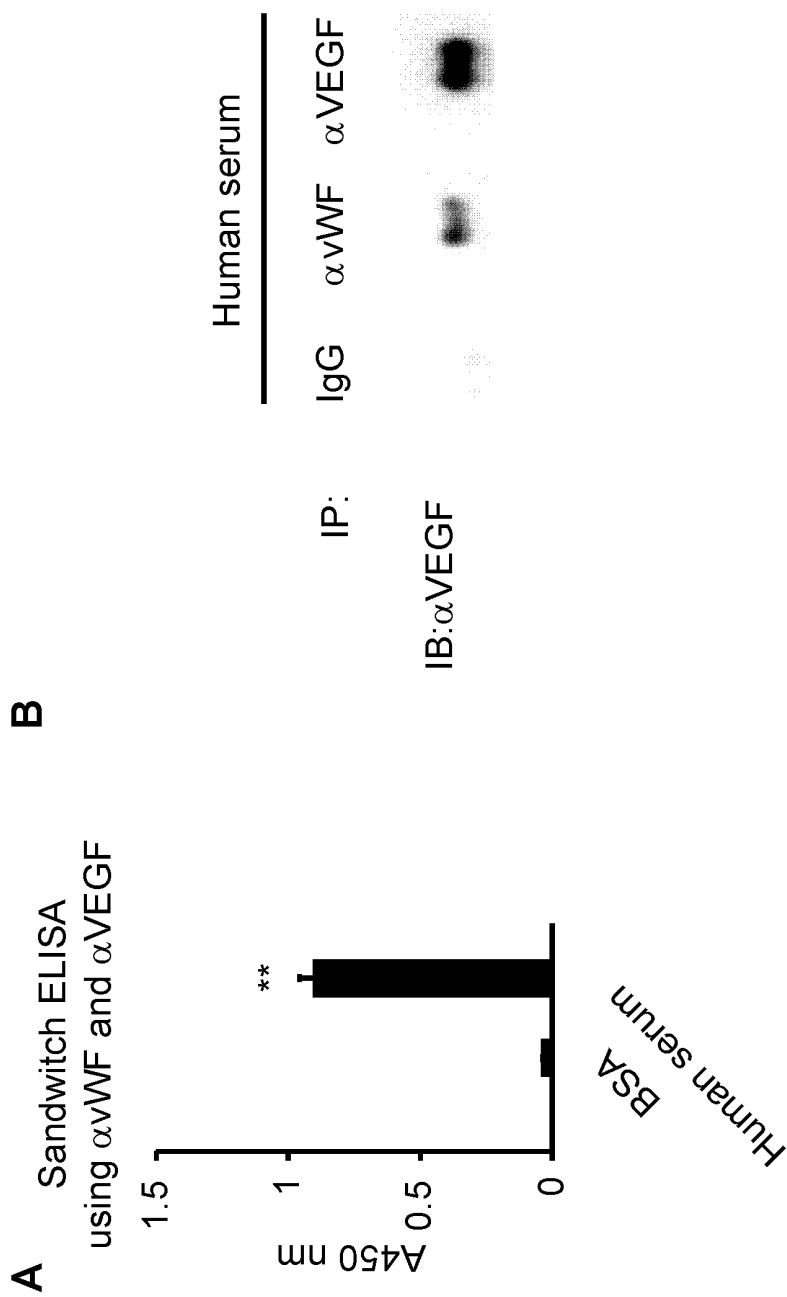


FIG. 17A-B

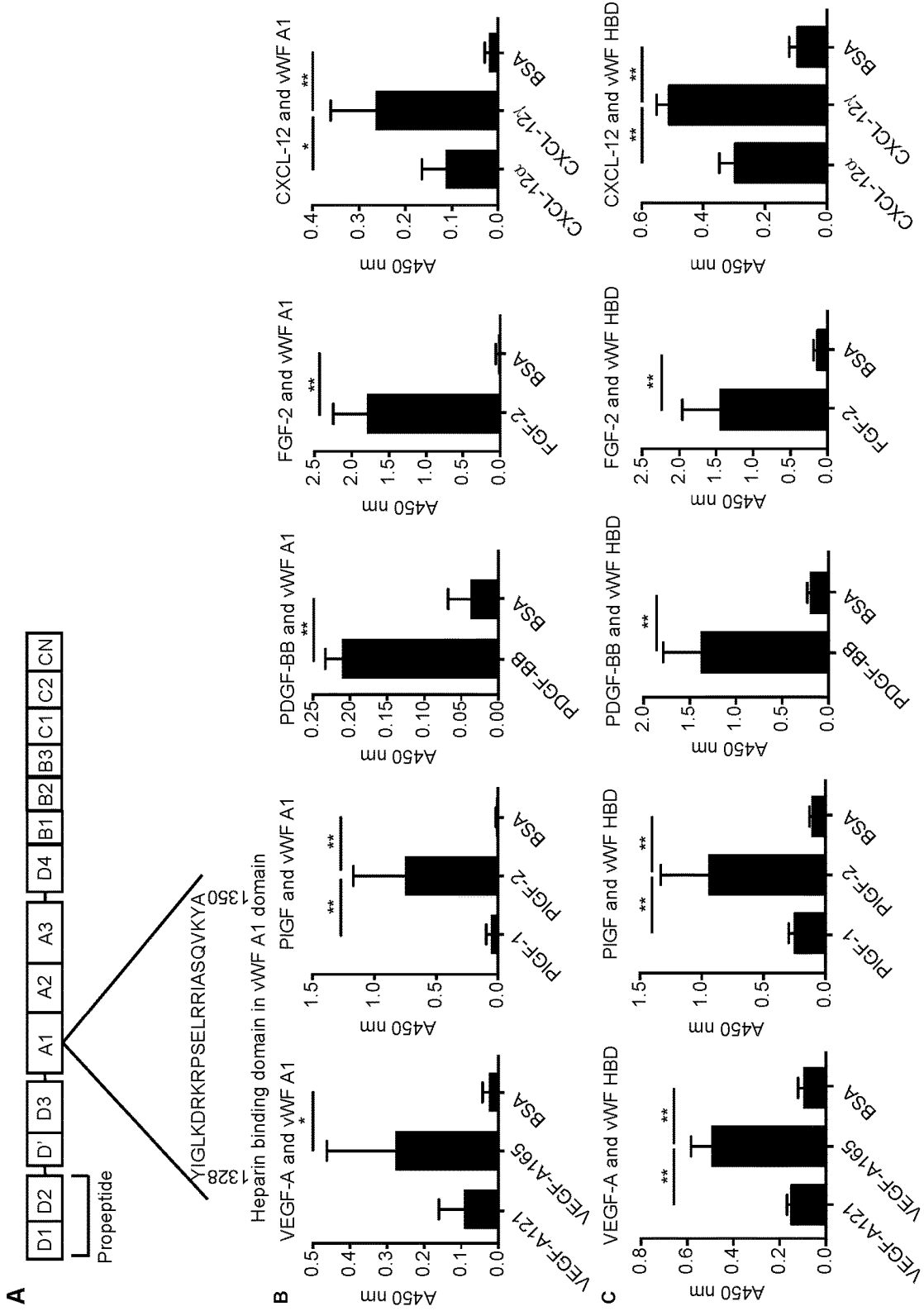


FIG. 18A-C

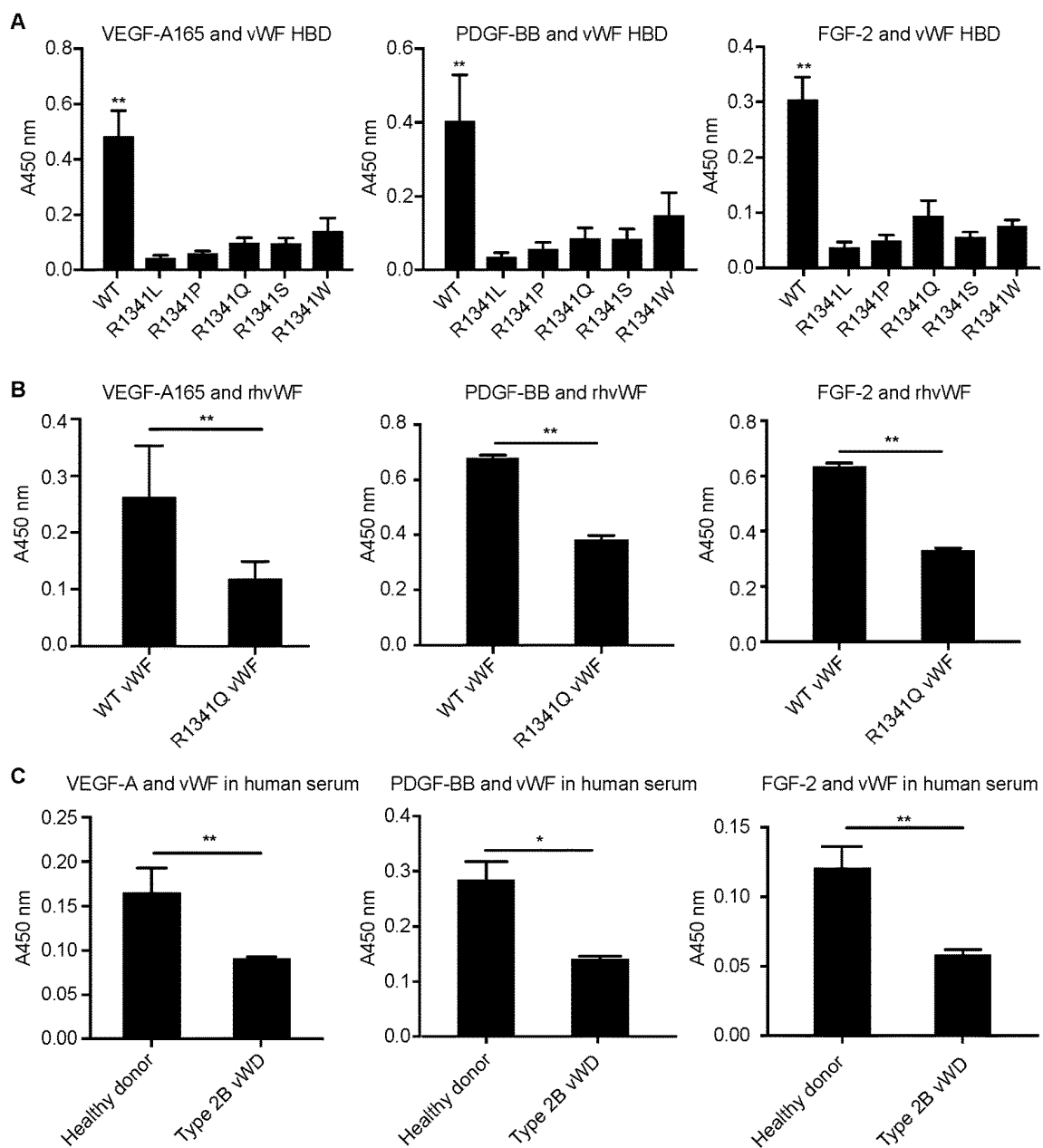


FIG. 19A-C

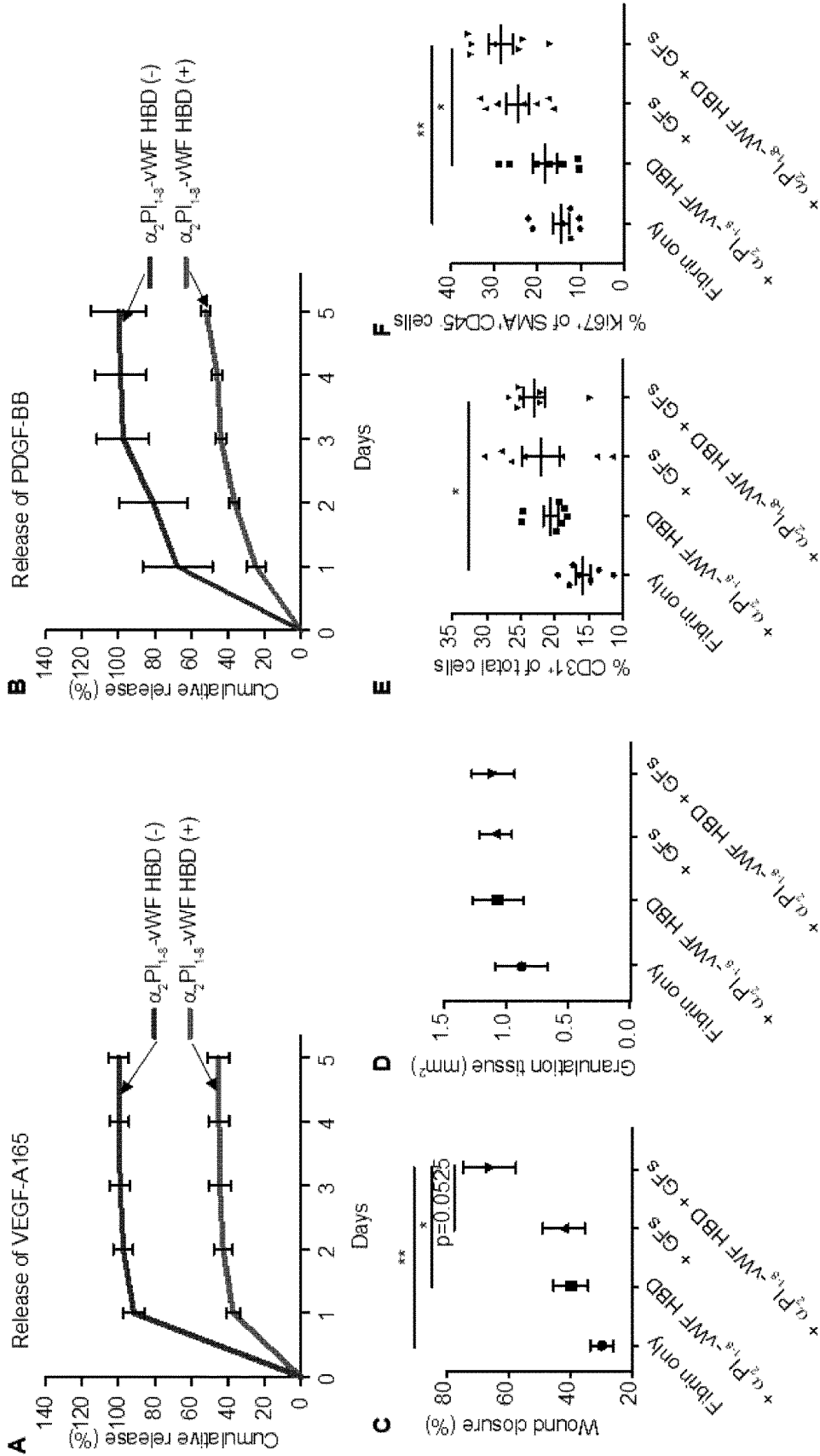


FIG 20A-F

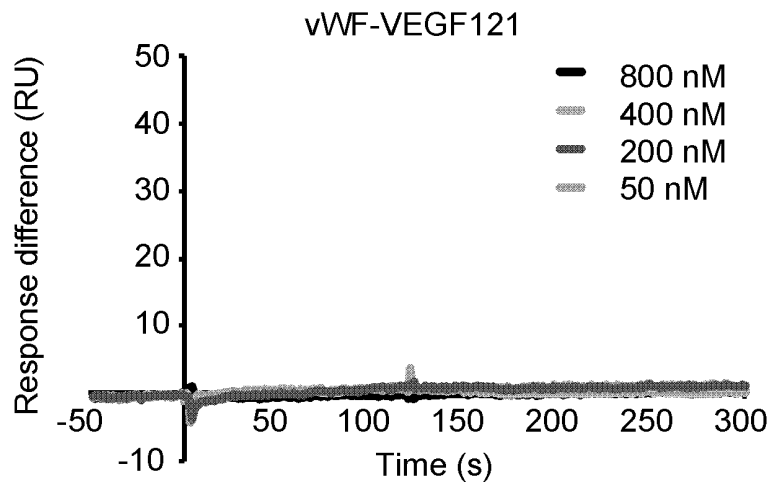


FIG. 21

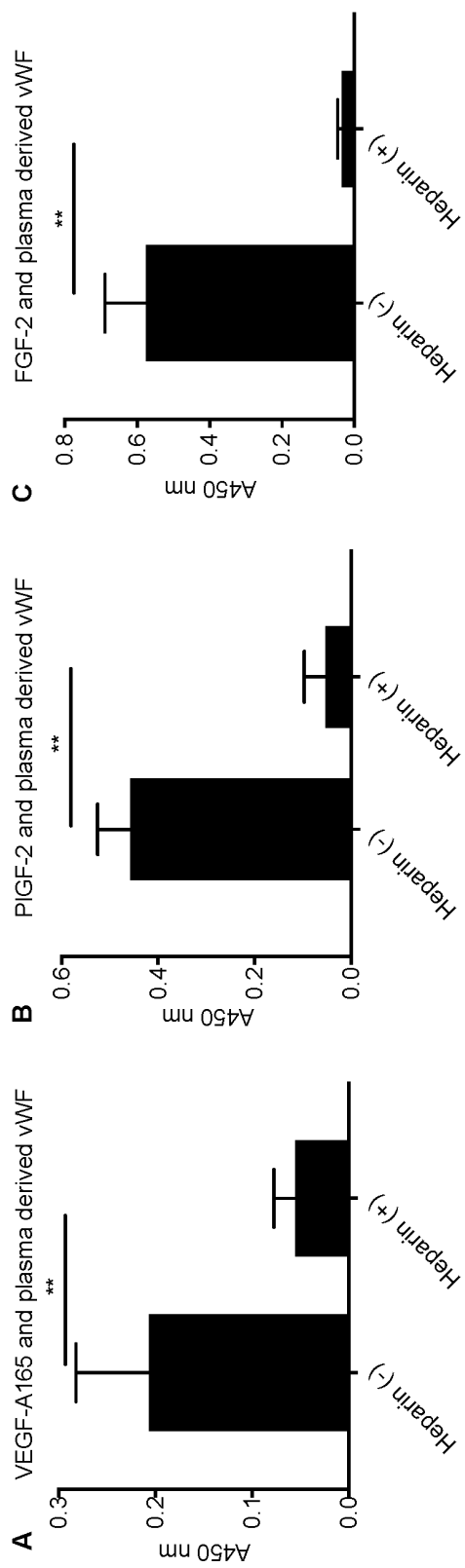


FIG. 22A-C

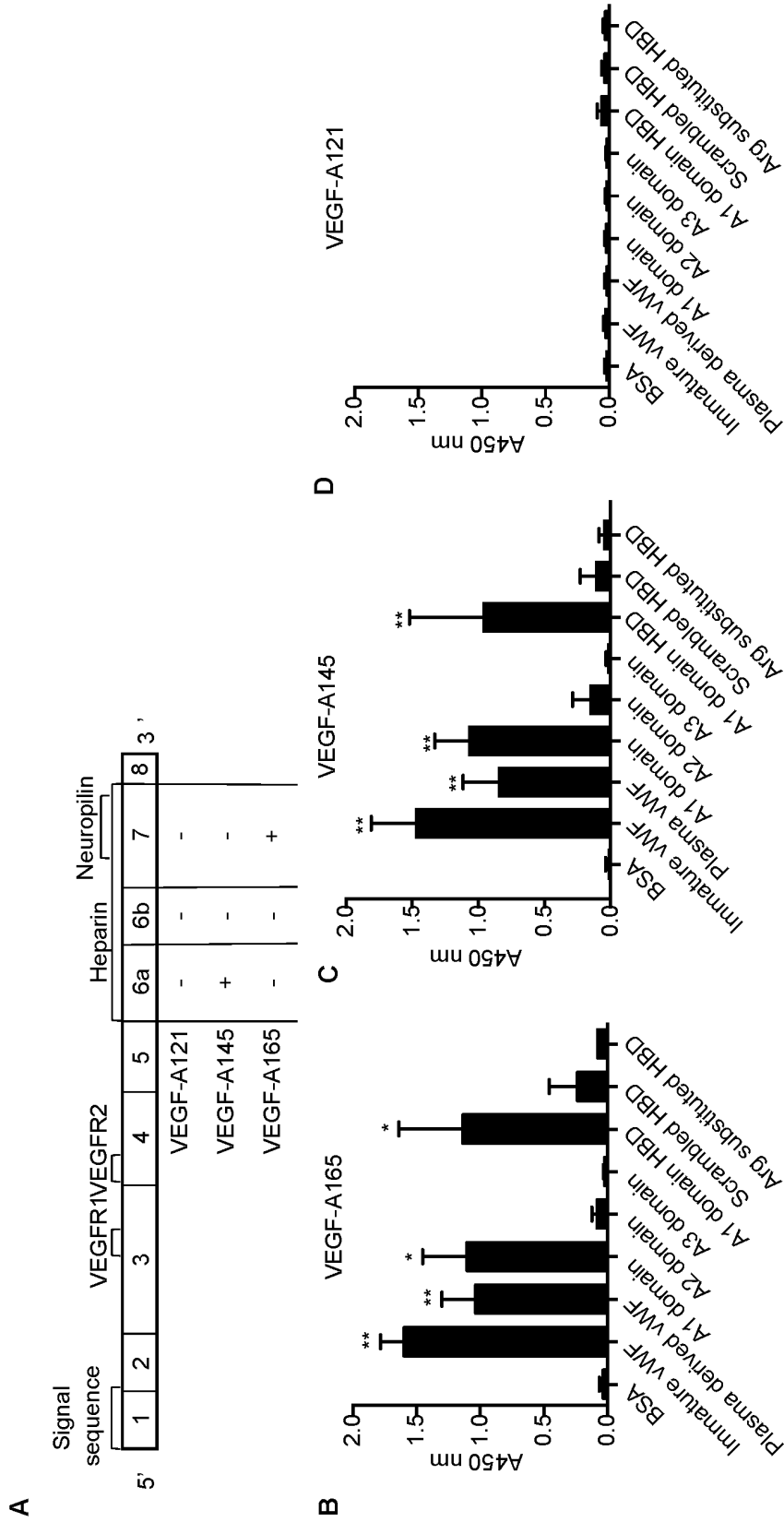


FIG. 23A-D

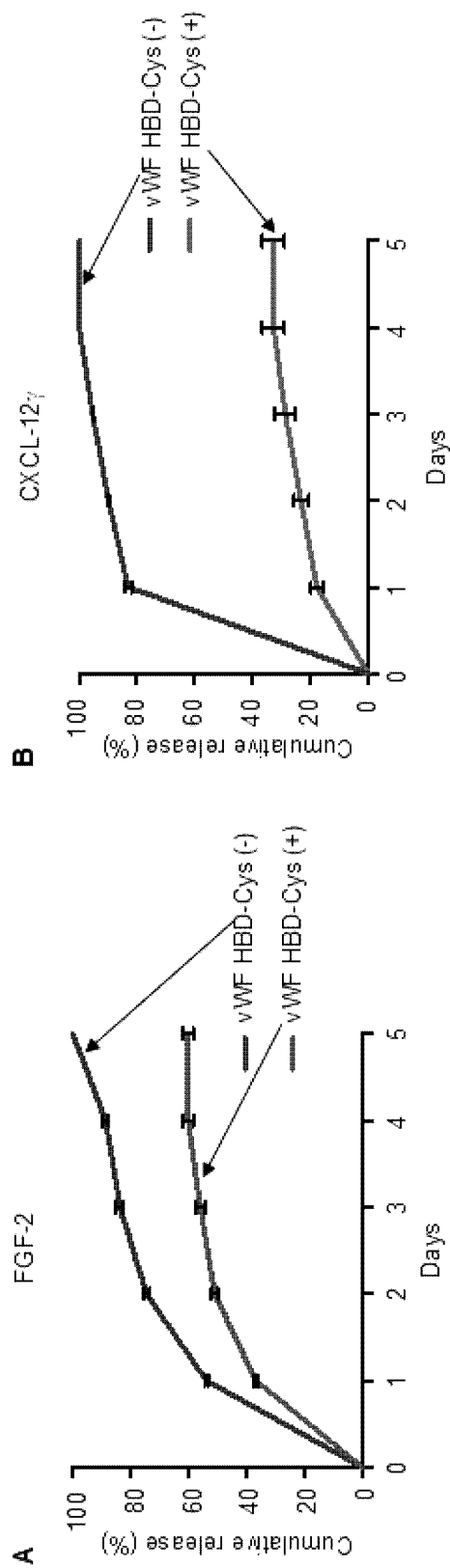


FIG. 24A-B

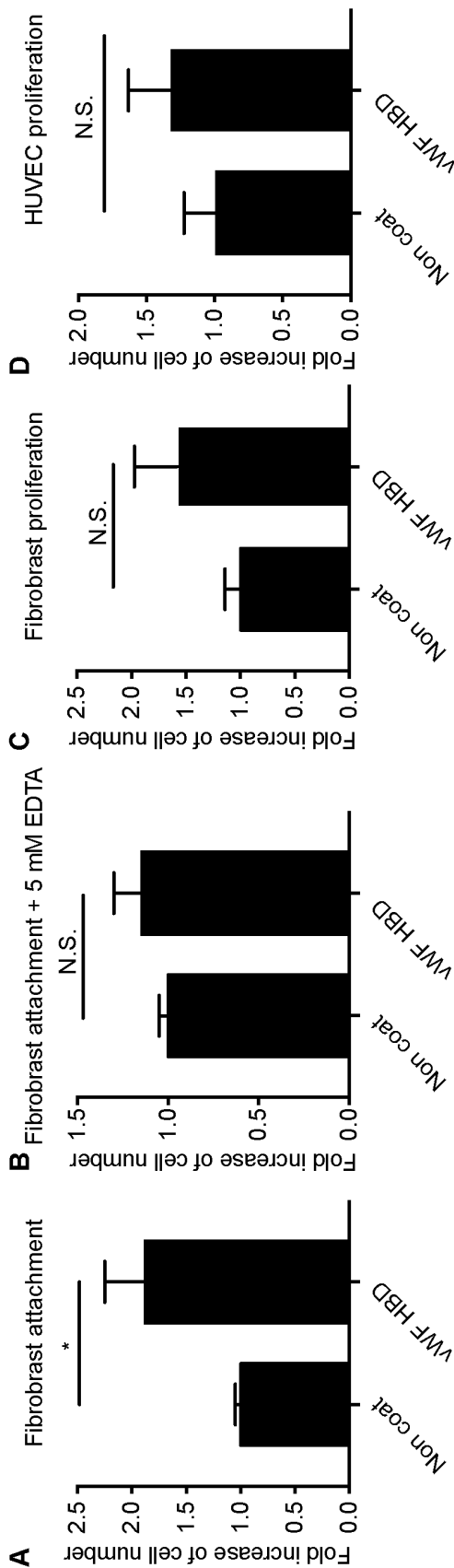


FIG. 25A-D

METHODS AND COMPOSITIONS FOR THE TREATMENT OF WOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase application under 35 U.S.C. § 371 of International Application No. PCT/US2018/060760 filed Nov. 13, 2018, which claims the benefit of priority of U.S. Provisional Patent Application No. 62/585,101 filed Nov. 13, 2017, and U.S. Provisional Patent Application No. 62/758,845 filed Nov. 12, 2018. The entire contents of each of the above-referenced disclosures are specifically incorporated herein by reference without disclaimer.

STATEMENT OF GOVERNMENT SUPPORT

The invention was made with government support under DK108215 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Field of the Invention

The invention generally relates to the field of medicine. More particularly, it concerns compositions and methods involving peptides providing for the delivery and/or in vivo recruitment of growth factors.

Background

GFs are considered as crucial molecules in regenerative medicine, including the treatment of chronic diabetic ulcers as well as the treatment of non-regenerating bone defect (chronic non-union fractures, critical bone defects). However, GFs have had only modest effects in the clinic to date (Fonder, M. A. et al. *Journal of the American Academy of Dermatology* 58, 185-206, (2008) and Falanga, V. *Lancet* (London, England) 366, 1736-1743, (2005)). For example, recombinant human VEGF-A has not been approved for clinical use by the U.S. Food and Drug Administration (FDA) due to a negative result in phase II clinical trials (Whittam, A. J. et al. *Advances in wound care* 5, 79-88 (2016)). PDGF-BB (Regranex in the clinic) has shown clinical efficacy, but safety issues such as cancer risk have been flagged, potentially due to high dosing (Marti-Carvajal, A. J. et al. The Cochrane database of systematic reviews, Cd008548, (2015) and Papanas, D. & Maltezos, E. *Drug safety* 33, 455-461 (2010)). As another example, the bone morphogenetic protein-2 (BMP-2) was delivered through collagen sponges in InFUSE® Bone Graft (Medtronic) at supraphysiological doses, and led to serious side effects as ectopic bone growth, increased cancer risk and nerve injuries. Therefore, engineering GF delivery approaches for regenerative medicine, including for wound healing and bone repair, to enhance efficacy and reduce GF doses and side effects is crucial. Due to the challenges of delivering growth factors, there is a need in the art for more advanced growth factor delivery and/or in vivo treatments.

SUMMARY OF INVENTION

The methods and compositions described herein address the need in the art by providing peptides and polypeptides comprising a growth factor binding domain that are useful in

tissue regeneration, wound healing, and the treatment of certain disorders. In some embodiments, the peptides have an amino acid sequence that is at least 80% identical to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70, or a fragment thereof wherein the peptide is less than 300 amino acids in length.

In some embodiments, the peptides have an amino acid sequence that is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70, or a fragment thereof.

In some embodiments, the peptide is less than 300, 275, 250, 225, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, or 8 amino acids in length (or any derivable range therein).

In some embodiments, the peptide is attached to a transglutaminase-reactive peptide. In some embodiments, the transglutaminase-reactive peptide is attached to the amino or carboxy end of the growth factor binding domain peptide. In some embodiments, the transglutaminase-reactive peptide is from the α 2-plasmin inhibitor. In some embodiments, the transglutaminase-reactive peptide comprises an amino acid sequence that is at least 80% identical to SEQ ID NO:12 or a fragment thereof. In some embodiments, the transglutaminase-reactive peptide comprises an amino acid sequence that is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to SEQ ID NO:12 or a fragment thereof.

In some embodiments, the peptide comprises an amino acid sequence that is at least 80% identical to SEQ ID NO:8, 16-13, or a fragment thereof. In some embodiments, the peptide comprises an amino acid sequence that is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to SEQ ID NO:8, 16-13, or a fragment thereof.

In some embodiments, the peptide comprises an amino acid sequence that is at least 80% identical to SEQ ID NO:49 or 50, or a fragment thereof. In some embodiments, the peptide comprises an amino acid sequence that is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to SEQ ID NO:49 or 50. In some embodiments, the peptide comprises a positively charged residue at position 14 of SEQ ID NO:49 or 50. In some embodiments, the positively charged residue comprises lysine, arginine, or histidine. In some embodiments, the peptide is unsubstituted at position 14 of SEQ ID NO:49 or 50. In some embodiments, the positively charged residues are unsubstituted or substituted with another positively charged residue. In some embodiments, the arginine residues are unsubstituted.

In some embodiments, the peptide is linked to one or more additional peptides, wherein each additional peptide has an amino acid sequence that is at least 80% identical to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70, or a fragment thereof. In some embodiments, at least 2, 3, 4, 5, 6, or 7 peptides are linked together, wherein each linked peptide has an amino acid sequence that is at least 80% identical to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70,

or a fragment thereof. In some embodiments, the peptides are separated by one or more linkers. In some embodiments, the linker comprises SEQ ID NO:60, wherein $x=1, 2, 3, 4, 5,$ or 6 or comprises SEQ ID NO:61. In some embodiments, the linker(s) comprises a flexible linker. In some embodiments, the flexible linker comprises glycine and serine amino acid residues.

In some embodiments, the peptide is attached to a collagen binding peptide. In some embodiments, the collagen binding peptide comprises the A3 domain of von Willebrand Factor (vWF A3) or fragment thereof, or a peptide with at least 80% identity to vWF A3 or fragment thereof. In some embodiments, the collagen binding peptide comprises a peptide having an amino acid sequence of SEQ ID NO:47 or a fragment thereof, or a peptide with at least 80% identity to SEQ ID NO:47 or fragment thereof. In some embodiments, the collagen binding peptide comprises a peptide with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% sequence identity (or any derivable range therein) to SEQ ID NO:47 or fragment thereof. In some embodiments, the collagen binding peptide comprises a decorin polypeptide or fragment thereof, or a peptide with at least 80% identity to a decorin polypeptide or fragment thereof. In some embodiments, the collagen binding peptide comprises a peptide having an amino acid sequence of SEQ ID NO:48 or a fragment thereof, or a peptide with at least 80% identity to SEQ ID NO:48 or fragment thereof. In some embodiments, the collagen binding peptide comprises a peptide with at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% sequence identity (or any derivable range therein) to SEQ ID NO:48 or fragment thereof.

In some embodiments, the collagen binding peptide comprises one or more complementarity determining regions (CDRs) from an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a CDR1, CDR2, and/or CDR3 from a light chain variable region of an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a CDR1, CDR2, and CDR3 from a light chain variable region of an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a CDR1, CDR2, and/or CDR3 from a heavy chain variable region of an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a CDR1, CDR2, and CDR3 from a heavy chain variable region of an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a heavy or light chain variable region from an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises a collagen-binding fragment from an anti-collagen antibody or a collagen-binding fragment derived from an anti-collagen antibody. In some embodiments, the collagen binding peptide comprises an anti-collagen antibody, or a Fab, scFv, nanobody, minibody, or unibody from an anti-collagen antibody or derived from an anti-collagen antibody. In some embodiments, the collagen binding peptide is humanized or chimeric. In some embodiments, the collagen binding peptide comprises human constant regions or a human framework. In some embodiments, the collagen binding peptide is chemically conjugated to the peptide. In some embodiments, there is a linker between the collagen binding peptide and the peptide comprising a growth factor binding domain. In some embodiments, the linker comprises SEQ ID NO:60, wherein $x=1, 2, 3, 4, 5,$ or 6 or comprises SEQ ID NO:61. In some

embodiments, the linker(s) comprises a flexible linker. In some embodiments, the flexible linker comprises glycine and serine amino acid residues. In some embodiments, the peptide is attached to the carboxy terminus of the collagen binding peptide. In some embodiments, the peptide is attached to the amino terminus of the collagen binding peptide.

In some embodiments, the collagen-binding domain is derived from variable regions of an anti-collagen antibody. In some embodiments, the collagen-binding domain comprises one or both of a heavy chain variable region and a light chain variable region of a collagen-binding antibody. Examples include single-chain variable fragments (scFv), antigen-binding fragments (Fab), and third-generation (3G) molecules such as nanobodies, minibodies, and unibodies.

In some embodiments, the peptide is chemically synthesized. In some embodiments, the peptide comprises a methionine as the amino-terminal amino acid. In some embodiments, the methionine is immediately adjacent to the first amino acid of one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70. In some embodiments, the amino terminal methionine is immediately adjacent to one of the peptide embodiments of the disclosure.

In some embodiments, the peptide is attached to a cell adhesion moiety. In some embodiments, the cell adhesion moiety comprises a ligand for a glycoprotein or a cell surface receptor. In some embodiments, the cell adhesion moiety comprises an integrin-binding peptide.

In some embodiments, the peptide is attached to a tag. In some embodiments, the tag comprises a purification tag, a signaling sequence, a post-translational modifier, or a targeting moiety. In some embodiments, the peptide is attached to a tag described herein. In some embodiments, the peptide is conjugated to a functional moiety. In some embodiments, the functional moiety comprises an antibody, an enzyme, a fluorescent compound, an imaging agent, or a therapeutic agent. In some embodiments, the functional moiety comprises a gadolinium chelation moiety. In some embodiments, the peptide is attached to a functional moiety described herein. In some embodiments, the tag and/or functional moiety is at the carboxy or amino terminus of the peptide.

In some embodiments, the peptide comprises two or more growth factor binding domains, wherein each growth factor binding domain has an amino acid sequence that is at least 80% identical to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70. In some embodiments, the peptide comprises two or more growth factor binding domains, wherein each growth factor binding domain has an amino acid sequence that is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to one of SEQ ID NOS:1-7, 13-15, 49-50, or 66-70.

In some embodiments, the peptide comprises one or more substitutions relative to SEQ ID NOS:1-7, 13-15, 49-50, or 66-70. For example, the peptide may comprise at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 (or any derivable range therein) substitutions at position(s) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133,

134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, and/or 200. In some embodiments, the one or more substitutions are conservative substitutions. In further embodiments, the one or more substitutions are non-conservative. In other embodiments, the one or more substitutions are a mix of conservative and non-conservative substitutions.

Further aspects of the disclosure relate to a molecular complex comprising any of the peptide embodiments described herein and one or more growth factors or cytokines are bound to the peptide. In some embodiments, the growth factors are bound by non-covalent interactions with the peptide. In some embodiments, the growth factors comprise one or more of VEGF, PIGF, PDGF, FGF, and BMP. In some embodiments, the growth factor comprises one or more of VEGF-A 165, PIGF2, PDGF-BB, PDGF-CC, FGF-2, and BMP-2. In some embodiments, the molecular complex comprises one or more growth factors or cytokines described herein. In some embodiments, the growth factor is linked to an ECM-binding domain. In some embodiments, the ECM-binding domain is from PIGF or from PIGF2. In some embodiments, the ECM-binding domain is linked to the peptide through a peptide bond. Further examples of ECM binding domains are described in WO2014006082A1.

Further aspects of the disclosure relate to a composition comprising any of the peptide or molecular complex embodiments described herein. In some embodiments, the composition further comprises one or more growth factors. In some embodiments, the growth factors comprise one or more of VEGF, PIGF, PDGF, FGF and BMP. In some embodiments, the growth factor comprises one or more of VEGF-A 165, PIGF2, PDGF-BB, FGF-2 and BMP-2. In some embodiments, the composition comprises one or more growth factors or cytokines described herein.

Further aspects of the disclosure relate to a biomaterial scaffold comprising any of the peptide or molecular complex embodiments described herein. In some embodiments, the scaffold comprises fibrin. In some embodiments, the peptide is covalently linked to the fibrin. In some embodiments, the covalent linkage is through the α 2 plasmin inhibitor peptide (α 2PI₁₋₈). In some embodiments, the scaffold comprises one or more of collagen, heparin, ceramic, a synthetic polymer, proteoglycans alginate-based substrates, chitosan, hyaluronic acid and/or methylcellulose substrates. In some embodiments, the biomaterial comprises less than 50 mg of exogenous growth factors. The term exogenous refers to materials, such as growth factors, that are added outside the body and do not include any of those materials that may be present in the body and associate with the scaffold or peptide in vivo. The exogenous components may be polypeptides and proteins that have been recombinantly or chemically produced.

In some embodiments, the dose of a growth factor is administered according to a dosage amount and schedule described herein.

In some embodiments, with respect to PDGF or specifically PDGF-BB or PDGF-CC, the dosage may be at most, at least, or exactly 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 (or any derivable range therein) μ g/kg body weight. In some embodiments, with respect to PDGF or specifically PDGF-BB, the dosage may

be at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg, μ g, or ng/dose (or any derivable range therein). In some embodiments, with respect to PDGF or specifically PDGF-BB, the dosage may be at most, at least, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 μ g/cm² wound or tissue area (or any derivable range therein). The administration may be repeated daily or every 2, 3, 4, 5, 6, or 7 days (or any derivable range therein for at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks (or any derivable range therein). In some embodiments, the dose refers to a total prescribed dose that is to be administered over a period of time.

In some embodiments, with respect to VEGF or specifically VEGF-A or VEGF-A 165, the dosage may be at most, at least, or exactly 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 52, 54, 55, 56, 58, 60, 62, 64, 66, 68, 70, 72, 75, or 100 mg, μ g, or ng/dose (or any derivable range therein). In some embodiments, with respect to VEGF or specifically VEGF-A or VEGF-A 165, the dosage may be at most, at least, or exactly 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 670, 675, 700, 725, 750, 775, or 800 μ g/cm² wound or tissue area (or any derivable range therein). The administration may be repeated daily or every 2, 3, 4, 5, 6, or 7 days (or any derivable range therein for at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks (or any derivable range therein). In some embodiments, the dose refers to a total prescribed dose that is to be administered over a period of time.

In some embodiments, with respect to FGF or specifically FGF-2, the dosage may be at most, at least, or exactly 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 (or any derivable range therein) μ g/kg body weight. In some embodiments, with respect to FGF or specifically FGF-2, the dosage may be at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg, μ g, or ng/dose (or any derivable range therein). In some embodiments, with respect to FGF or specifically FGF-2, the dosage may be at most, at least, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 μ g/cm² wound or tissue area (or any

derivable range therein). The administration may be repeated daily or every 2, 3, 4, 5, 6, or 7 days (or any derivable range therein for at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks (or any derivable range therein). In some embodiments, the dose refers to a total prescribed dose that is to be administered over a period of time.

In some embodiments, with respect to PIGF or specifically PIGF2, the dosage may be at most, at least, or exactly 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 (or any derivable range therein) $\mu\text{g}/\text{kg}$ body weight. In some embodiments, with respect to PIGF or specifically PIGF2, the dosage may be at least, at most, or exactly 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg, μg , or ng/dose (or any derivable range therein). In some embodiments, with respect to PIGF or specifically PIGF2, the dosage may be at most, at least, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 $\mu\text{g}/\text{cm}^2$ wound or tissue area (or any derivable range therein). The administration may be repeated daily or every 2, 3, 4, 5, 6, or 7 days (or any derivable range therein for at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks (or any derivable range therein). In some embodiments, the dose refers to a total prescribed dose that is to be administered over a period of time.

In some embodiments, with respect to BMP or specifically BMP-2, the dosage may be at most, at least, or exactly 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 (or any derivable range therein) $\mu\text{g}/\text{kg}$ body weight. In some embodiments, with respect to BMP or specifically BMP-2, the dosage may be at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg, μg , or ng/dose (or any derivable range therein). In some embodiments, with respect to BMP or specifically BMP-2, the dosage may be at most, at least, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 $\mu\text{g}/\text{cm}^2$ wound or tissue area (or any derivable range therein). The administration may be repeated daily or every 2, 3, 4, 5, 6, or 7 days (or any derivable range therein for at least, at most, or exactly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks (or any derivable range therein). In

some embodiments, the dose refers to a total prescribed dose that is to be administered over a period of time.

In some embodiments, externally added VEGF-A165 is in an amount of less than 20 μg , less than 10 μg , less than 1 μg , less than 500 ng, less than 400 ng, less than 300 ng, less than 200 ng, less than 100 ng, or less than 1 ng. In some embodiments, externally added PDGF-BB is in an amount of less than 10 μg , less than 1 μg , less than 500 ng, less than 400 ng, less than 300 ng, less than 200 ng, less than 100 ng, or less than 1 ng.

In some embodiments, the biomaterial scaffold or implant is one that retains at least 80% of exogenously added growth factors for at least 3 days. In some embodiments, the biomaterial scaffold or implant is one that retains at least 50, 60, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% (or any derivable range therein) of exogenously added growth factors for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days (or any derivable range therein).

Further aspects of the disclosure relate to an implant comprising any one of the peptide, molecular complex, composition, or biomaterial embodiments described herein. In some embodiment, the implant comprises a medical device, a stent, or a vascular graft.

Further aspects relate to a method for regenerating tissue in a subject, the method comprising administering a peptide, molecular complex, composition, biomaterial scaffold, or implant embodiment of the disclosure to the subject.

Further aspects relate to a method for facilitating wound or tissue healing in a subject, the method comprising administering a peptide, molecular complex, composition, biomaterial scaffold, or implant embodiment of the disclosure to the subject.

Yet further aspects relate to a method for treating angiodyspasia and/or von mucosal/cutaneous bleeding in a subject, the method comprising administering a biomaterial scaffold, composition, or implant of the disclosure to the subject. Yet further aspects relate to a method for treating von Willebrand disease (VWD) in a subject, the method comprising administering a biomaterial scaffold, composition, or implant of the disclosure to the subject. In some embodiments, von Willebrand disease comprises acquired von Willebrand disease (AVWD). In some embodiments, von Willebrand disease comprises congenital von Willebrand disease (AVWD). In some embodiments, VWD comprises type 1 VWD. In some embodiments, VWD comprises type 2 VWD. In some embodiments, VWD comprises type 3 VWD. In some embodiments, VWD comprises type 2A VWD. In some embodiments, VWD comprises type 2B VWD. In some embodiments, the method is for treating GI bleeding associated with angiodyspasia. In some embodiments, the subject is one that has reduced high molecular weight multimers (HMWM) of the vWF protein.

Yet further aspects of the disclosure relate to the treatment of diabetic ulcers in a subject, the method comprising administering a biomaterial scaffold, composition, or implant of the disclosure to the subject.

In some embodiments, the peptide, molecular complex, composition, biomaterial scaffold, or implant is administered locally to a specific tissue or wound. In some embodiments, the subject has or has been diagnosed with a deficiency in wound healing. In some embodiments, the subject has diabetes. In some embodiments, the wound comprises a diabetic ulcer. In some embodiments, the tissue comprises bone. In some embodiments, the tissue is one disclosed herein. In some embodiments, the biomaterial scaffold or implant is administered locally to bone or a location adjacent thereto. In some embodiments, the percentage of wound

closure after seven days of administration is at least 60%. In some embodiments, the percentage of wound closure after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 days (or any derivable range therein) of administration is at least 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99%, or any derivable range therein. In some embodiments, the amount of granulation of the tissue after seven days of administration is at least 1 mm². In some embodiments, the amount of granulation of the tissue after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 days (or any derivable range therein) of administration is at least 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.8, 1.9, or 2 mm², or any derivable range therein.

In some embodiments, the subject has and/or has been diagnosed with von Willebrand disease (VWD). In some embodiments, VWD comprises type 1 VWD. In some embodiments, VWD comprises severe type 1 VWD. In some embodiments, VWD comprises type 2 VWD. In some embodiments, VWD comprises type 3 VWD. In some embodiments, VWD comprises type 2A VWD. In some embodiments, VWD comprises type 2B VWD. In some embodiments, the subject has and/or has been diagnosed with acquired von Willebrand disease (AVWD). In some embodiments, the subject has and/or has been diagnosed with congenital von Willebrand disease. In some embodiments, the subject is deficient for the vWF protein. In some embodiments, the subject has been determined to be deficient for the vWF protein. In some embodiments, the subject has and/or has been determined to have a mutant vWF protein. In some embodiments, the subject has been identified with having blood vessel abnormalities. In some embodiments, the subject has and/or has been determined to have a mutation in the A1 domain of vWF. In some embodiments, the subject has a mutant vWF with increased affinity for GPIIb/IIIa. In some embodiments, the subject has been shown to have one or more of spontaneous platelet aggregation, loss of active high molecular weight vWF multimers, thrombocytopenia and/or bleeding. In some embodiments, the subject has been determined to have mutations in exon 28 of the vWF gene. In some embodiments, the subject has been determined to have a R1341 substitution or deletion in the vWF protein, or a mutation in the vWF gene which results in a R1341 substitution or deletion in the vWF protein. In some embodiments, the subject is determined to have a R1341 substitution, wherein the arginine is substituted with Leu, Pro, Gln, Trp, or Ser. In some embodiments, the subject has been diagnosed with angiodysplasia. In some embodiments, the subject has been determined to have GI bleeding. In some embodiments, the subject is one that has reduced high molecular weight multimers (HMWM) of the vWF protein.

In some embodiments, the patient has been previously treated for a condition or indication described herein. In some embodiments, the subject was resistant to the previous treatment. In some embodiments, the patient has been diagnosed with and/or is susceptible to a condition or indication described herein. In some embodiments, the method further comprises administration of an additional therapy, such as, for example, additional therapies described herein.

The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product or synthetic amino acid polymer.

The terms "subject," "mammal," and "patient" are used interchangeably. In some embodiments, the subject being treated is a mammal. In some embodiments, the subject is a human. In some embodiments, the subject is a mouse, rat,

rabbit, dog, donkey, sheep, goat, pig, or a laboratory test animal such as fruit fly, zebrafish, etc.

It is contemplated that the methods and compositions include exclusion of any of the embodiments described herein.

The terms "a" and "an" are defined as one or more unless this disclosure explicitly requires otherwise.

The term "substantially" is defined as being largely but not necessarily wholly what is specified (and include wholly what is specified) as understood by one of ordinary skill in the art. In any disclosed embodiment, the term "substantially" may be substituted with "within [a percentage] of" what is specified, where the percentage includes 0.1, 1, 5, and 10 percent.

The terms "comprise" (and any form of comprise, such as "comprises" and "comprising"), "have" (and any form of have, such as "has" and "having"), "include" (and any form of include, such as "includes" and "including") and "contain" (and any form of contain, such as "contains" and "containing") are open-ended linking verbs. As a result, the methods and systems of the present invention that "comprises," "has," "includes" or "contains" one or more elements possesses those one or more elements, but is not limited to possessing only those one or more elements. Likewise, an element of a method or system of the present invention that "comprises," "has," "includes" or "contains" one or more features possesses those one or more features, but is not limited to possessing only those one or more features.

The feature or features of one embodiment may be applied to other embodiments, even though not described or illustrated, unless expressly prohibited by this disclosure or the nature of the embodiments.

Any method or system of the present invention can consist of or consist essentially of—rather than comprise/include/contain/have—any of the described elements and/or features and/or steps. Thus, in any of the claims, the term "consisting of" or "consisting essentially of" can be substituted for any of the open-ended linking verbs recited above, in order to change the scope of a given claim from what it would otherwise be using the open-ended linking verb. A composition "consisting essentially of" the recited elements excludes any further active ingredients but does not exclude pharmaceutical excipients, buffers, structural components, etc.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-B. Multiple isoforms of laminin bind promiscuously to GFs and chemokines with high affinities. (A) Binding of multiple isoforms of full-length laminin (-111, -211, -332, -411, -421, -511, and -521) to GFs and CXCL chemokines were measured by ELISA. A450 nm represents absorbance at 450 nm. BSA-coated wells served as negative controls (n=4, mean±SEM). Signals greater than 0.1 (grey box) are considered to be significant. (B) Affinities (K_D values are shown) of full-length laminin against VEGF-A165, PlGF-2 and PDGF-BB were measured by SPR. A SPR chip was functionalized with laminin-521 (~2000 RU), and each GF was flowed over the chip at indicated concentrations. Curves represent the specific responses (in RU) to

laminin obtained. Experimental curves were fitted with Langmuir binding kinetics. Binding kinetics values [dissociation constants (K_D) and rate constants (K_{on} and K_{off})] determined from the fitted curves are shown.

FIGS. 2A-C. Excess heparin inhibits GF-laminin binding. Inhibition of GF-binding to laminin (-111, -211, -221, -411, -421, -511, and -521) by excess heparin. ELISA plates were coated with 10 μ g/mL laminin and further incubated with a 1 μ g/mL (A) VEGF-A165, (B) PIGF-2, or (C) FGF-2 solution in the absence or presence of excess (10 μ M) heparin. Bound GFs were detected using a specific antibody for each GF (n=4, mean \pm SEM). Statistical analyses were done using the Mann-Whitney U test by comparing the signals with and without heparin. *p<0.05, **p<0.01.

FIGS. 3A-D. GFs bind to recombinant LG domain protein derived from laminin α 3, α 4 and α 5 chains. Affinity of GFs against recombinant laminin LG domains. ELISA plates were coated with 1 μ g/mL (A) α 3₂₉₂₈₋₃₁₅₀, (B) α 4₈₂₆₋₁₈₁₆, or (C) α 5₃₀₂₆₋₃₄₈₂ and further incubated with 1 μ g/mL of VEGF-A165, VEGF-A121, PIGF-2, PIGF-1, PDGF-BB, or FGF-2 solution. Bound GFs were detected using a specific antibody for each GF (n=4, mean \pm SEM). Statistical analyses were done using the Mann-Whitney U test by comparing the signals obtained from the laminin domain- and the BSA-coated wells. *p<0.05, **p<0.01. (D) Affinities (K_D values are shown) of laminin α 3₂₉₂₈₋₃₁₅₀ against VEGF-A165 and PDGF-BB were measured by SPR. A SPR chip was functionalized with the laminin α 3₂₉₂₈₋₃₁₅₀ recombinant protein (~1000 RU), and each GF was flowed over the chip at indicated concentrations. Curves represent the specific responses (in RU) to laminin. Experimental curves were fitted with Langmuir binding kinetics. Binding kinetics values [dissociation constants (K_D) and rate constants (K_{on} and K_{off})] determined from the fitted curves are shown.

FIGS. 4A-F. GFs bind to chemically synthesized laminin HBD peptides derived from the LG domain of laminin α 3, α 4, and α 5 chains. (A) The location of laminin-derived peptides in the LG domain of laminin α 3, α 4, and α 5 chains. (B-F) Affinity of heparin and GFs against chemically synthesized peptides derived from the LG domain of laminin α 3, α 4, and α 5 chains. ELISA plates were coated with 10 μ g/mL laminin peptide and further incubated with (B) biotinylated heparin, (C) VEGF-A165 and VEGF-A121, (D) PIGF-2 and PIGF-1, (E) PDGF-BB, or (F) FGF-2. Concentrations were 1 μ g/mL for GFs and 10 μ g/mL for heparin. Bound heparin was detected with streptavidin, and bound GFs with a specific antibody for each GF (n=4, mean \pm SEM). Statistical analyses were done using the Mann-Whitney U test by comparing the signals obtained from the laminin peptide- and the BSA-coated wells. *p<0.05, **p<0.01.

FIGS. 5A-D. Chemically synthesized peptides derived from the LG domain of laminin α 3, α 4 and α 5 chains bind to syndecans. Affinity of syndecans to chemically synthesized peptides derived from the laminin α 3, α 4 and α 5 LG domains. ELISA plates were coated with 10 μ g/mL laminin peptide and further incubated with 1 μ g/mL of (A) syndecan-1, (B) syndecan-2, (C) syndecan-3, or (D) syndecan-4. Bound syndecans were detected using an antibody against histidine-tag on the recombinant syndecans (n=8, mean \pm SEM). Statistical analyses were done using the Mann-Whitney U test by comparing the signals obtained from the laminin peptide- and the BSA-coated wells. *p<0.05, **p<0.01.

FIGS. 6A-D. Laminin HBD peptides promote fibroblast and endothelial cell adhesion in vitro. (A, B) 3000 cells/well human lung fibroblasts were cultured (A) without or (B)

with 5 mM EDTA in FGM-2 culture media containing 1% FBS. (C, D) 3000 cells/well HUVEC were cultured (C) without or (D) with 5 mM EDTA in EBM-2 culture media containing 100 ng/ml VEGF-A165 and 1% FBS. Cells were plated on 1 μ g/mL laminin peptide pre-coated non-tissue culture treated plates and incubated for 30 min at 37° C. After plate washes, cell numbers were quantified using a CyQUANT assay (n=10, mean \pm SEM). The signals obtained from BSA-coated wells are normalized to 1, and relative fold increases of cell numbers were calculated. Statistical analyses were done using ANOVA with Tukey's test. Kruskal-Wallis test followed by Dunn's multiple comparison was used in (B, C). *p<0.05, **p<0.01.

FIGS. 7A-C. GF retention in fibrin matrices is enhanced by incorporating laminin HBD peptide. (A,B) GF retention in fibrin matrix. α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ or α 2PI₁₋₈- α 5₃₄₁₇₋₃₄₃₆ peptide-functionalized fibrin matrices were made in the presence of VEGF-A165 or PDGF-BB, and incubated in 8 volumes of physiological buffer for 5 days. The buffer was changed each day, and released GFs were quantified daily. Graphs show the cumulative release of (A) VEGF-A165 or (B) PDGF-BB over 5 days (n=4; mean \pm SEM). All data points for laminin HBD peptides were statistically significant compared to controls without laminin HBD peptide (p<0.01, Mann-Whitney U test). (C) Fibrin matrices containing VEGF-A165 (200 ng/wound) with or without α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide were placed on the full-thickness back-skin wounds in db/db diabetic mice. After 3 and 6 days, retention of VEGF-A165 after 3 and 6 days in the fibrin matrix and the tissue surrounding the wound (2 mm beyond the wound margin) were quantified. n \geq 4 per time point, mean \pm SEM. Student's t-test; **p<0.01.

FIGS. 8A-G. Delivering GFs within laminin HBD peptide-functionalized fibrin matrices enhances skin wound healing in db/db diabetic mice. Full-thickness back-skin wounds were treated with combined VEGF-A165 (100 ng/wound) and PDGF-BB (50 ng/wound). Four groups were tested: fibrin only, fibrin functionalized with α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide, fibrin containing admixed GFs, and fibrin functionalized with α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide containing GFs. After 4, 7, and 10 days, (A-B) wound closure and (C) granulation tissue area were evaluated by histology (means \pm SEM, day 4: n=6, day 7: fibrin only and α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide+GFs, n=10; other treatment groups, n=11, day 10: α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide, n=8, α 2PI₁₋₈- α 3₃₀₄₃₋₃₀₆₇ peptide+GFs, n=9, other treatment groups, n=7). (B) The proportions of the mice were categorized by the degree of healing after day 7 of wound treatment. (D) Wound histology (hematoxylin and eosin staining) at day 7. Red arrows indicate tips of the epithelium tongue. The granulation tissue (pink-violet) is characterized by a large number of granulocytes with nuclei that stain in dark-violet or black. Muscle under the wounds is stained in red. Fat tissue appears as transparent bubbles. Scale bar=800 μ m. (E-G) 5 days after the wound treatment, (E) proliferation of CD31⁺CD45⁺ endothelial cells is assessed by Ki67⁺ marker, and (F) the frequency of Ly6G⁺CD11b⁺ neutrophils within CD45⁺ cells and (G) the frequency of Ly6C⁺CD11b⁺ monocytes within CD45⁺ cells were determined using flow cytometry (means \pm SEM). *P<0.05, **P<0.01, ANOVA with Tukey's test.

FIG. 9. Scrambling the sequence of laminin HBD peptide decreases the GF binding capacity. Affinity of GFs against chemically synthesized peptides that are scrambled (Scr) the sequence of α 3₃₀₄₃₋₃₀₆₂. ELISA plates were coated with 10 μ g/mL laminin peptide and further incubated with VEGF-A165, PIGF-2, PDGF-BB, or FGF-2. Concentrations were 1

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$\mu\text{g/mL}$ for GFs. Bound GF was detected with a specific antibody for each GF ($n=4$, $\text{mean}\pm\text{SEM}$). Statistical analyses were done using one-way ANOVA. $*p<0.05$, $**p<0.01$. Sequence of the peptides are described in Table 2.

FIG. 10. Laminin HBD peptide did not enhance the migration of endothelial cells in vitro. 4×10^4 HUVEC cells were added to the transwell upper parts. Solutions containing 30 ng/mL of VEGF-A165 preincubated with or without $0.1\text{ }\mu\text{M}$ of $\alpha_{3_{3043-3067}}$ peptide were added to the bottom side of the transwell. The signals of the cells that passed through a migration transwell after 6 hr of incubation were measured. ($\text{means}\pm\text{SEM}$, $n=4$). Statistical analyses were done using one-way ANOVA. $**p<0.01$

FIG. 11. Photos of the wounds. Full-thickness back-skin wounds were treated with combined VEGF-A165 (100 ng/wound) and PDGF-BB (50 ng/wound). Four groups were tested: fibrin only, fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ - $\alpha_{3_{3043-3067}}$ peptide, fibrin containing admixed GFs, and fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ - $\alpha_{3_{3043-3067}}$ peptide containing GFs. Representative pictures of wounds after 0 and 7 days are presented.

FIG. 12. Bipartite «bridge» proteins composed of a growth factor-binding domain linked to a collagen I-binding domain.

FIGS. 13A-F. Conjugation of a collagen-binding domain FabCol to a growth factor-binding domain FgHBD.

FIGS. 14A-F. Engineering recombinant fusion protein linking a collagen-binding domain FabCol to LamLG4 or FgHBD growth factor-binding domains to sequester rhBMP-2 into collagen biomaterials.

FIGS. 15A-E. vWF-deficient mouse shows impaired wound healing through poor angiogenesis. Full-thickness back-skin wounds were made in wild-type (WT) and vWF-deficient mice. After 5 d, (A) wound closure and (B) granulation tissue area were evaluated by histomorphometry. ($\text{means}\pm\text{SEM}$). Proliferation of (C) CD31+CD45- endothelial cells and (D) SMA+CD45- SMCs assessed by Ki67+ marker determined using flow cytometry ($\text{means}\pm\text{SEM}$). (E) The amounts of VEGF-A in the wounds were quantified by ELISA. $*p<0.05$, $**p<0.01$, ANOVA with Tukey's test.

FIGS. 16A-D. Human plasma-derived vWF binds promiscuously to GFs with high affinity. vWF binding to (A) GFs and (B) chemokines were measured by ELISA. A450 nm represents absorbance at 450 nm. Signals from VEGF-A121 served as a baseline, and bovine serum albumin (BSA) served as a negative control ($n=4$, $\text{mean}\pm\text{SD}$). Affinity (KD values are shown) of vWF against (C) VEGF-A165 and (D) PDGF-BB was measured by SPR. SPR chips were functionalized with vWF ($\sim 2000\text{ RU}$), and VEGF-A165 or PDGF-BB was flowed over the chips at indicated concentrations. Curves represent the specific responses (in resonance units (RU)) to vWF obtained. Experimental curves were fitted with (C) 1:1 Langmuir fit model and (D) heterogeneous ligand-parallel reactions binding. Binding kinetics values [dissociation constants (KD) and rate constants (kon and koff)] determined from the fitted curves are shown.

FIGS. 17A-B. vWF binds to VEGF-A in human serum. (A) ELISA plates were coated with $10\text{ }\mu\text{g/mL}$ anti-human vWF monoclonal antibody and further incubated with human serum. Bound VEGF-A was detected using a specific antibody for VEGF-A ($n=3$, $\text{mean}\pm\text{SD}$). (B) Human serum was subjected to immunoprecipitation with anti-human vWF monoclonal antibody or anti-human VEGF-A monoclonal antibody. Western blotting was performed with collected proteins using anti-human VEGF-A antibody. Repre-

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sentative image of 3 human serum. Statistical analyses were done using Student's t-test. $**p<0.01$.

FIGS. 18A-C. The HBD within the A1 domain of vWF mediates GF binding. (A) The location of the A1 domain and HBD within vWF. FIG. 18A discloses SEQ ID NO: 50. (B-C) Affinity of VEGF-A, PIGF, PDGF-BB, FGF-2, or CXCL-12 against (B) recombinant vWF A1 domain protein or (C) vWF A1 HBD peptide. ELISA plates were coated with $10\text{ }\mu\text{g/mL}$ recombinant vWF A1 domain protein or $10\text{ }\mu\text{g/mL}$ vWF A1 HBD peptide and further incubated with a $1\text{ }\mu\text{g/mL}$ VEGF-A, PIGF, PDGF-BB, FGF-2, or CXCL-12 solution. Bound GFs were detected using a specific antibody for each GF ($n=4$, $\text{mean}\pm\text{SD}$). Statistical analyses were done using ANOVA with Tukey's test or Student's t-test. $*p<0.05$, $**p<0.01$.

FIGS. 19A-C. R1341 mutations observed in vWD type 2B patients impaired vWF-GF binding. (A) Binding of VEGF-A165, PDGF-BB, and FGF-2 to vWF A1 HBDs with R1341 substitutions. ($n=4$, $\text{mean}\pm\text{SD}$). (B) Binding of VEGF-A165, PDGF-BB, and FGF-2 to recombinant human (rh)vWF with R1341Q substitution. ($n=4$, $\text{mean}\pm\text{SD}$). (C) Binding of VEGF-A165, PDGF-BB, and FGF-2 to vWF in healthy donor or type 2B vWD patient serum ($n=3$, $\text{mean}\pm\text{SD}$). Statistical comparisons were carried out using (A) ANOVA with Tukey's test compared with BSA control and (B-C) Student's t-test $**p<0.01$.

FIGS. 20A-F. Delivering GFs within vWF HBD-functionalized fibrin matrices enhance skin wound healing in diabetic mice. (A-B) GF retention in fibrin matrix. Graph showing the cumulative release of (A) VEGF-A165 or (B) PDGF-BB over 5 d ($n=4$; $\text{mean}\pm\text{SEM}$). Full-thickness back-skin wounds were treated with combined 100 ng of VEGF-A165 and 50 ng of PDGF-BB. Four groups were tested: fibrin only, fibrin functionalized with $\square_2\text{PI}_{1-8}$ -vWF HBD only, fibrin containing GFs only, and fibrin functionalized with $\square_2\text{PI}_{1-8}$ -vWF HBD containing GFs. (C) After 7 d, wound closure and (D) granulation tissue area were evaluated by histomorphometry. ($\text{means}\pm\text{SEM}$, $n=11-13$ per treatment group). (E-F) 5 d after the wound treatment, (E) the frequency of CD31+CD45- endothelial cells within total alive cells and (F) proliferation of SMA+CD45- SMC assessed by Ki67+ marker were determined using flow cytometry ($\text{means}\pm\text{SEM}$). $*p<0.05$, $**p<0.01$, ANOVA with Tukey's test.

FIG. 21. No binding was observed between VEGF-A121 and vWF. Affinity of VEGF-A121 for vWF, estimated by SPR. SPR chips were functionalized with plasma derived vWF, and VEGF-A121 was flowed over the chips at various concentrations ($50-800\text{ nM}$). Curves represent the responses (in RU) to vWF obtained.

FIGS. 22A-C. Excess heparin inhibits GF binding to vWF. Inhibition of GF binding to vWF by excess heparin. ELISA plates were coated with $10\text{ }\mu\text{g/mL}$ vWF and further incubated with a $1\text{ }\mu\text{g/mL}$ (A) VEGF-A165, (B) PIGF-2, or (C) FGF-2 solution containing $10\text{ }\mu\text{M}$ heparin. Bound GFs were detected using a specific antibody for each GF ($n=4$, $\text{mean}\pm\text{SD}$).

FIGS. 23A-D. vWF A1 HBD binds to VEGF-A145 and VEGF-A165. (A) Diagram of exon sequence of VEGF-A showing inclusion (+) or exclusion (-) of heparin binding domain exons for the different VEGF-A isoforms. (B-D) Binding of (B) VEGF-A165, (C) VEGF-A145, or (D) VEGF-A121 to vWF domains. ELISA plates were coated with 50 nM vWF domains and further incubated with recombinant human VEGF-A121, VEGF-A145 or VEGF-A165 ($1\text{ }\mu\text{g/mL}$, each). Bound VEGF-A was detected using a specific antibody for VEGF-A ($n=4$, $\text{mean}\pm\text{SD}$). Statistical

comparisons were done using ANOVA with Tukey's test compared with BSA control. ** $p < 0.01$.

FIGS. 24A-B. The vWF A1 HBD retains GFs when incorporated into synthetic matrices. Retention of GFs in PEG-based synthetic matrix functionalized with C-terminus Cys added vWF HBD peptide using a Michael addition reaction. The graph shows the cumulative release of (A) FGF-2 or (B) CXCL-12 γ over 5 d. (n=3; mean \pm SEM). All data points for vWF HBD were statistically significant compared to controls without vWF HBD ($p < 0.01$, Student's t-test)

FIGS. 25A-D. Fibroblast attachment and proliferation on the vWF HBD peptide coated plate in vitro. Cell adhesion assays. 3000 cells/well human lung fibroblasts were cultured (A) without or (B) with 5 mM EDTA in FGM-2 culture media. Cells were plated on 1 μ g/mL vWF HBD pre-coated non-tissue culture treated plates and incubated for 30 min at 37° C. After plate washes, cell numbers were quantified using a CyQUANT assay (n=4, mean \pm SD). (C) 1000 cells/well human lung fibroblasts or (D) 1000 cells/well human umbilical vein endothelial cells (HUVEC) were cultured on 1 μ g/mL vWF HBD pre-coated 96-well tissue culture plates. Cell numbers were quantified after 72 hrs using a CyQUANT assay (n=4, mean \pm SD). The signals obtained from non-coated wells are normalized to 1, and relative fold increase of cell numbers were calculated. Statistical comparisons were carried out by Student's t-test. * $p < 0.05$, N.S.=not significant.

DETAILED DESCRIPTION

Lamin and von Willebrand (vWF) peptides that bind certain growth factors are useful in wound healing and tissue repair.

Laminins have been reported as crucial molecules for adhesion of various cell types, both in vitro and in vivo, thus serving as a cell scaffold protein. The inventors found that multiple isoforms of laminin promiscuously bind several growth factors (GFs) from the VEGF/PDGF, FGF, BMP, and NT families, in addition to HB-EGF and CXCL12 γ , through their heparin binding domains (HBDs). By engineering a fibrin matrix displaying the laminin peptide, the inventors have demonstrated that the laminin peptide linked to fibrin matrix promotes wound closure when applied to skin wounds in the db/db mouse, as a model of delayed wound healing, when applied with VEGF-A165 and PDGF-BB. In addition to showing a GF-modulating function for laminin, an important tissue repair protein, the examples also show that both GF- and cell-binding character promotes tissue repair when incorporated within fibrin matrix, which may be clinically useful. In addition, the inventors have demonstrated that the laminin HBD peptide can be fused or conjugated to collagen-binding domain to allow retention of GFs into collagen-based biomaterials. The inventors showed this art focusing on the sequestration of BMP-2 into collagen hydrogels and sponges for application in bone regeneration.

von Willebrand factor is a large plasma glycoprotein synthesized by endothelial cells and megakaryocytes. It is best known for its role in hemostasis, where it mediates platelet adhesion to the subendothelium at sites of endothelial damage and acts as a carrier to coagulation factor VIII. In patients with von Willebrand disease (vWD), the most common inherited bleeding disorder caused by defects in or deficiency of vWF, blood vessel abnormalities have been identified. In a subset of patients, vascular malformations in the gastrointestinal tract (i.e. angiodysplasia) can cause severe, intractable bleeding. vWF is comprised of a number

of subunits, made up of conserved modular domains in the order D1-D2-D'-D3-A1-A2-A3-D4-B1-B2-B3-C1-C2. Mature vWF is formed after proteolysis of the vWF pro-peptide, i.e. the D1 and D2 domains. The A1 domain contains the binding site for platelet glycoprotein glycoprotein Iba (GPIIb α and also binds heparin and types I and III collagen. This disclosure describes the use of vWF as a growth factor reservoir for the enhancement of angiogenesis and wound healing.

I. GROWTH FACTOR BINDING PEPTIDES AND POLYPEPTIDES

Embodiments of the disclosure relate to laminin peptides and von Willebrand factor peptides that bind to growth factors.

Laminins are major basement membrane extracellular matrix (ECM) proteins for which at least 16 isoforms exist. Five α (LAMA1-5), three β (LAMB1-3), and three γ (LAMC1-3) chains have been identified. Laminin's structure is a heterotrimer comprising an α , a β , and a γ chain that assemble into a cross shape.

A common hallmark of the laminin α chain structure is the presence of five laminin-type G domain (LG) modules arranged at the C-terminus in a tandem array. LG modules consist of 180-200 amino acids, and all the laminin α chains contain five LG domains (LG1-5). The laminin LG modules bind to heparin sulfate, perlecan and fibulin-1, as well as cellular receptors including α 6 β 1, α 7 β 1 and α 6 β 4 integrins and syndecan. The laminin α 3, α 4, and α 5 chains are processed in vivo in tissue through cleavage by proteases such as plasmin and elastase at the linker between the LG3 and LG4 domains.

A. Exemplary Growth Factor Binding Peptides and Polypeptides

In some embodiments, the growth factor binding domain comprises a heparin binding domain (HBD). In some embodiments, the growth factor binding domain is from a laminin polypeptide. In some embodiments, the growth factor binding domain is from a vWF polypeptide. In some embodiments, the growth factor binding domain is not a heparin binding domain and/or does not bind to heparin. In some embodiments, the growth factor binding domain comprises a peptide from LAMA1. In some embodiments, the growth factor binding domain comprises a peptide from LAMA2. In some embodiments, the growth factor binding domain comprises a peptide from LAMA3. In some embodiments, the growth factor binding domain comprises a peptide from LAMA4. In some embodiments, the growth factor binding domain comprises a peptide from LAMA5. In some embodiments, the growth factor binding domain comprises a peptide from LAMB1. In some embodiments, the growth factor binding domain comprises a peptide from LAMB2. In some embodiments, the growth factor binding domain comprises a peptide from LAMB3. In some embodiments, the growth factor binding domain comprises a peptide from LAMB4. In some embodiments, the growth factor binding domain comprises a peptide from LAMC1. In some embodiments, the growth factor binding domain comprises a peptide from LAMC2. In some embodiments, the growth factor binding domain comprises a peptide from LAMC3. Exemplary laminin polypeptides are shown below:

Human Laminin	Sequence
Laminin subunit alpha-1 precursor (LAMA1); SEQ ID NO: 25	MRGGVLLVLLLCVAAQCRQRGLFPAILNLASNAHISTNATCGEKGPE MFCKLVEHVPGRPVVRNPQCRI CDGNSANPRERHPISHAIDGTNNWQ SPSIQNGREYHWVTITL DLRQVFOVAVYV I I K AANAPRPGNWILERSLDG TTFSPWQYAVVSDSECLSRYNITPRRGPPTRADDEVICTSY SRLVPL EHGEIHTSLINGRPSADDLSPKLEFTSARYIRLRLQRI RTLNADLMTLS HREPKELDPIVTRRYYYSIKDISVGGMCI CYGHASSCPWDETTKLLQC QCEHNTCGESCNRCCPGYHQQVWRPGTVSSGNTCEACNCHNKA KDC YYDESVAKQKSLNTAGQFRGGGVCINCLQNTMGINCETCIDGYRYP HKVSPYEDEPCRPNCDPVGSLSSVCIKDDLHSDLHNGKQPGQCPCKE GYTGEKCDRCQLGKYDPTCVSCGCNPGVSGASDEPCTGPCVCKENVE GKACDRCKPGFYNLKEKNRPGCS ECF CFVSDVCSLSWPVGVNSM SGWLVTDLISPRKIPSQQDALGGRHQVSI NNTAVMQR LAPKYWAAP EAYLGNKLTAFGGFLKYTVSYDIPVETVDSNLMSHADVI I KGNGLTLS TQAEGLSLQPYEEYLVNVRVLPENFQDFHSKRQLDRDQLMTVLAVNT HLLIRANYS AKMALYRLESVSLDIASSNAIDLVAADV EHC ECPQGY TGTSCECLSGYRVDGILFGGI CQPCECHGAAECNVHGVCIACAHN TTGVHCEQLPGFYGEP SRGTPGDCQPCACPLTIASNNFSP TCHLNDGD EVCDCWCAPGYS GAWCERCADGYGNPTVPGESCVPDCDCSGNWDPS EAGHCDSVTGECLKLGNTDGAHCERCADGFYGDVTAKNCRACEC HVKGSHS AVCHLETGLCDCKPNVTGQQCQCLHGYGLDSGHGCRP CNC SVAGSVSDGCTDEGQCHCVPGVAGKRCRCAHGFYAYQDGSCT PCDCPHTQNTCDPETGECVCPHTQGVKCECEDGHWGYDAEVGCQ ACNCSLVGSTHHRCDVVTHGCQCKSKFGGRACDQCSLGYRDFPDCVP CDDLRGTSGDACLNEQGLCGCV EETGACPCKENVFGPQCNECREGT FALRADNPLGCSPCFC SGLSHLCS ELEDYVRTPVTLGSDQPLLRVVSQS NLRGTTEGVYQAPDFLLDAATVRQHIRAEFFYWRLPQQFQGDQLMA YGGKLYSVAFYSLDGVGT SNFEPQVLI KGGIRKQVI YMDAPAPENG VRQEQEVAMRENFWKYPNSVSEKPVTR EDFMSVLSDI EYILIKASYGQ GLQQSRISDI SMEVGRKA EKLHP EEEVASLLENCVCPGTVGFSCQDC APGYHRGKLPAGSDRGPRLVAPCVPCS CNHSDTCDPNTGKCLNCG DNTAGDHCDVCTS GYGVKVTGSASDCALCAPHSPASPTCVLEB DHDFRCDACLGLGYEGKHCERCSSSYGNPQTPGGS CQKDCNPHGVS HGDCDRTSGQCVCRLGASGLRCECEPRHILMETDCVSCDDECVGL LMDLDEIGDAVLSLNLGTGIPVPYGLLSNLENTTKYLQESLLKENMQKD LGKIKLEGVAEETDNLQKLT RMLASTQKVN RATERIFKESQDLAIAIE RLQMSIT EIMEKTTLNQTLDEDFLLPNS TLQNMQQNGTSLLEIMQIRDF TQLHQ NATLELKA AEDLLS QIQENYQKPLEEVLKEAASHVLSKHNN ELKAAEALVREAEAKMQESNHL LLMVNANLREFSDKLLHVQEEQNL TSELIVQGRGLIDAAAQTD AVQDALEHLEDHQDKLLLSAKIRHHID DLVMHMSQRNAV D LVYRAEDHAAEFQRLADVLYSGLENIRNVS LNA TSAAYVHYNI QSLIEESEELARDAHR TVTETSLLSESLVSNKAAVQRS SRFLKEGNL SRKLPGLI ALESELRNKTNRFQENAVEITRQTNESLLILR AIPKGI RDKGAKTKELATSASQS AVS TLRDVA GLSQE LLNTSASLSRVN TTLRETHQLLQDSTMATLLAGRKVKDVEIQANLLFDRLKPLKMLEEN LSRNLSEIKLLISQARKQAASIKVAVSADRDCIRAYQPQISSNTNYNTLTL NVKTPQEPDNL L FYLGSS T ASDFLAVEMRRGRVAF LWDLGSGSTRLEFP DEPIDDNRWHSIHVAREGNI GLSLVKEMSSNQKSP TKTSKSPGTANVLD VNNSTLMPVGGGLGQIKKSPAVKVT HFKGLG EAPLNGKSI GLWNYIE REGKCRGCFGSSQNE D PSEHFDGSGYSVVEKSLPATV TQIIMLENTESP NGLLLYLGSYGTDFLSIELFRGRVVM TDLGSGPI TLLTDRRYNNGT WYKIAFQRNRKQGLAV IDAYNTSNKETKQGETPGASSDLNRLDKDPI YVGG LPRSRVRRGVTTKSPVGC IKNLEISRS TFDLLRNSYGVKGC LL EPIRSV SFLKGGYIELPPKSLSP ESENLVTFATN SSGI I LAALGGDV EKR GDREEAHV PPFV MLI GGNIEVHVNP GDGTGLRKALLHAPTGTCS DQG AHSISLVRNRR IITVQLDENNPVEMKLGTLV ESR TINVSNLVYGGIPEGE GTSLLTMRRESHGCIKNL IENLELLEDENS AVGHEQV DLDTCWLSERP K LAPDAEDSKLLPEPRAPPEQC VVDAALEYVPGAHQEGLTQNSHEI LPEN QS AVRKKLSVELSIRTFASGLIYYMAHQNQADYAVLQLHGGR LHF FDLGKGRTKVSHPALSDGKWHVTVDYV KRKGFITVDGRES PMVTV VGDGTM L DVEGLFYL GGLPSQYQARKIGNI THSIPACIGDVTVNSKQL DKDSPVSAFTVNR CYAVAQEGTYPDGSGY AALVKEGYKQSDVNI TL EFRTSSQNGVLLGIS TAKVDAIGLELVDGKVL FHVNNAGRITAA YEP KTATVLC DGKWH TLQANKS KHRI TLI V DGN AVGAES PHTQSTSVD TN NP IYVGGYPA GVKQKCLRSQTSFRGCLRKLALIKSPQVQSEDESRAP EL HGVFLHSCPGTES
laminin subunit alpha-2 isoform a precursor (LAMA2-isoform a); SEQ ID NO: 26	MPGAAGVLLLLLLSGGLGGVQAQRPOQQRQSAHQQRGLFPVAVNL ASNALITTNATCGEKGPEMYCKLVEHVGQPVVRNPQCRI CNQSSNPN QRHPITNAIDGKNTWWQSPSINKGIEHYHYVTITL DLRQVFOIAYVIVKA ANSRPRGNWILERSLD DVEYKPKWQYHAVTDTECLTYNYIYPRTPGPSY AKDDEVICTSYSKIHPLENGEIHISLINGRPSADDPSPELLEF TSARYIRL RFQRI RTLNADLMMFAHKDPREIDPIVTRRYYYSVKDISVGGMCI CYG HARACPLDPA TNKSRCEHNTCGDS CDQCCPFH GKPWRA GTFLTK TECEACNCHGKAEECYDENVARRNLSLNI RGYIGGGVCINCTQNT AGINCETCTDGFPRKGVSPNYPRPCQPCHCDPIGSLNEVCVKDEKHA RRGLAPGSC HCKTGF GGVS CDRCARGTYGPDCKACNCSGLGSKNED PCFGPCI CKENVEGGDCSRCKSGFFNLQEDNWKGCDECFCSGVSNRCQ SSYWTYGIQDMSGWYLTDLPGRIRVAPQDDLDLSPQQI S ISNAEARQ

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Human Laminin	Sequence
	ALPHSYYSAPAPYLGNKLPVGGQLTFTI SYDLEEEEEEDTERVLQLM IILEGNDLSI STAQDEVYVLPSEHTNVLLKKEESPTIHGTHFPVRRKEF MTVLANLKRVLQITYSFGMDAIFRLSSVNLSEAVSYPTDGSIAAAVE VCQCPGGYTGSSCESCWPRHRRVNGTIFGGICEPCQCFGHAESDDVT GECNLCKDHTGGPYCDKCLPGFYGEPKGTSEDCQPCACPLNIPSNNF SPTCHLDRSLGLICDGCVPVGTGPRCERCAEGYFGQPSVPGGSCQPCQ CNDNLDFSIPGSCDSLGSCLICKPGTTGRYCELCADGYFGDAVDAKN CQPCRCNAGGSFSEVCHSQTGQCECRANVQGRCDKCKAGTFGLQSA RGCVPNCNSFGSKSFDCEESGQCWCQPGVTGKKCDRCAHGYNFQOE GGCTACECSHLGNNDPKTGRICPPNTIGEKSKCAPNTWGHSI TTG CKACNCSTVGSLDQCINVTGQCNCNPKFSGAKTECSRGHWNYPRC NLCDCLPGLTATTCDSETKKCSQDQTGQCTCKVNVGEGIHCDRCRPG KFGLDAKNPLGSSCYCFGTTTQCEAKGLIRTWVTLKAEQITLPLVD EALQHTTTKGI VFOHPEIVAHMDLMREDLHLEPFYWKLEPQFEGKKL MAYGGKLYAYFEAREETGFSTYNPQVIIRGGTPTHARIIVRHMAAPL IGQLTRHEIEMTEKEWKYVGDPRVHRTVTREDFLDILYDIHYILIKAT YGNFMRQSRISSEI SMEVAEQGRGTTMTPPADLIEKDCPLGYSGLSCEA CLPGFYRLRSQPGGRTPGPTLGT CVPCCNGHSSLCDPETSICQNCQHH TAGDFCERCALGYGIVKGLPNDCCQACPLISSNNFSPSCVAEGLD DYRCTACPRGYEGQYCERCAPGYTSGPNPGGSCQCECDPYGSLPVP CDPVTFCTCRPGATGRKCDGCKHWHAREGWECVFCGDECTGLLLG DLARLEQVMMSINLTGPLPAPYKMLYGLNIVITQELKHLSPQRAPER LIQLAEGNLNLTVMNELLTRATKV TADGEGTQDAERTNTRAKSL GEFIKELARDAEAVNEKAIKLNELTGRDEAFERNLEGLQKEIDQMIKE LRRKNLETQKEIAEDELVAEALKKVKLFGESRGENEEMEKDLRE KLADYKNKVDADWLREATDKIREANRFLAVNQKNMTALEKKKEA VESGKRQIEN TLKEGNDILDEANRLADEINSI IDYVEDIQTCLPMSSEEL NDKIDDLSEIKDRKLAEKVSAESHAAQLNDSSAVLDGILDEAKNISF NATAAFKAYSNIKDYIDEAEKVAKEAKDLAHEATKLATGPRGLLKEED AKGCLQKSRILNEAKLANDVKENEDHLNGLKTRINADARNGLDL RTLNDTLGKLSAIPNDTAAKLQAVKDKARQANDTAKDVLAQITELHQ NLDGLKKNYNKLADSVAKTNAVVKDP SKNKI IADADATVKNLEQEA DRLIDKLPKIELEDNLKKNISEIKELINQARKQANSIKVSVSSGDCIR TYKPEIKKGSYNNIVVNVKTAVDNLLFYLGS AKFIDFLAEMRKGK SFLVDVSGVGRVEYVVDLTDIDSYWYRIVASRTGRNGTISVRALDGP ASIVPSTHHS TSPPGYTLDDVANAMLFVGGTLGKLLKADAVRVI TFT CGMGETYFDNPKI GLWVFRKEKGDCKGCTVSPQVEDSEGTIQFDGEG YALVSRPIRWYPNISTVMFKFRTPSSALLMYLATRDLRDFMSVELTD GHIKVSYDLGSGMASVSNQNHNDGKWSFTLSRIQKQANISIVDIDT NQEENIATSSSGNDFGLDKADDKIYFGGLPTLRNLSMKARPEVNLKK YSGCLKDIEISRTPYNILSPDYVGVTKGCSLENVYTVSFPKPGFVELSP VFIDVGTENLSTKNESEGI LLGSGGTPAPPRKRRRTGQAYYVILLN RGRLEVHLSTGARTMRKIVIRPEPNLPHDGREHVSVHVERTRGI FTVQV DENRRYMQNLTVQPIEVKLVFGGAPPEFQPSPLRNIPPFEGCINWLV INSVPMDFARPVSFKNADIGRCAHQKLEDEDEGAAPAEI VIQPEPVPTP AFPTPTVLTGHCAAESEPALLIGSKQFGLSRNSHIAIAFDTKVKNRL TIELEVRTEAESGLLFYMARINHADPATVQLRNGLPYFSYDLGSGDTH TMIPTKINDQWHKIKIMRSKQEGILYVDGASNRTI SPKADILDVVG MLYVGGLPIN YTTTRRIGPVYTSIDGCVRNLMHMAEAPADLEQPTSSFHV GTCFANAQRGTYPDGTGFAKAVGGFKVGLDILLVEFEFRTTTTGVLG GISSQKMDMGIEMI DEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQ WHKV TANKIKHRIELTV DGNQVEAQSPNPASTSADTNDPVFVGGFPD DLKQFGLTTSIPFRGCI RSLKLTGKTGKPLEVNF AKALELRGVQPVSCP AN
laminin subunit alpha-2 isoform b precursor (LAMA2-isoform b); SEQ ID NO: 27	MPGAAGVLLLLLLSGGLGGVQAQRPOQRQSQAHQQRGLFPVAVLN ASNALITTNATCGEKPEMYCKLVEHVPGQPVVRNPQCRICNQNSSNP QRHPITNAIDGKNTWWQSPSINKGIEYHYVTITL DLQVVFQIAYVIVKA ANSRPRGNWILERSLDDVEYKWPQYHAVTDTECLTLYNIYPRTGPPSY AKDDEVICTSFYSKIHPLENGEIHISLINGRPSADDPSELEFTSARYIRL RFQIRTLNADLMMFAHKDPREIDPIVTRRYYSVKDISVGGMCI CYG HARACPLDPATNKSRCCEHNTCGDSCDQCPCGFHQKPRWAGTFLTK TECEACNCHGKAEECYDENVARRNLSLNI RGYIGGGVCINCTQNT AGINCETCTDGFRRPKGVS PNYPRPCQPCHCDPIGSLNEVCVKDEKHA RRGLAPGSCCHCKTGFGVSCDRARGYTGYPDCACNCNSGLGSKNED PCFGPCICKENVEGGDCSRCKSGFFNLQEDNWKGCEPCSGVSNRCQ SSYWTYGIQDMSGWYLTDL PGRIRVAPQDDLDSPQQISISNAEARQ ALPHSYYSAPAPYLGNKLPVGGQLTFTI SYDLEEEEEEDTERVLQLM IILEGNDLSI STAQDEVYVLPSEHTNVLLKKEESPTIHGTHFPVRRKEF MTVLANLKRVLQITYSFGMDAIFRLSSVNLSEAVSYPTDGSIAAAVE VCQCPGGYTGSSCESCWPRHRRVNGTIFGGICEPCQCFGHAESDDVT GECNLCKDHTGGPYCDKCLPGFYGEPKGTSEDCQPCACPLNIPSNNF SPTCHLDRSLGLICDGCVPVGTGPRCERCAEGYFGQPSVPGGSCQPCQ CNDNLDFSIPGSCDSLGSCLICKPGTTGRYCELCADGYFGDAVDAKN CQPCRCNAGGSFSEVCHSQTGQCECRANVQGRCDKCKAGTFGLQSA RGCVPNCNSFGSKSFDCEESGQCWCQPGVTGKKCDRCAHGYNFQOE

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Human Laminin	Sequence
	GGCTACECSHLGNNDPKTGRCICPPNTIGEKCSKCAPNTWGHSI TTG CKACNCSTVGLSDFQCNVNTGQCNCCHKPKFSGAKTECSRGHWNYP NLDCFLPGTDATTCDSSEKTKCSQSDQGTQCKVNVVEGICDCRCP KFGLDKPNPLGSSCYCFGTTTQCSEAKGLIRTWVTLKAEQTI LPLVD EALQHTTTKGI VFOHPEIVAHMDLMREDLHLEPFYWKLPQEFEGK MAYGGKLYAIYFEAREETGFSTYNPQVIIRGGTPTHARIIVRHMAAP IGQLTRHEIEMTEKEWKYGGDDPRVHRTVTREDFLDILYDIHYLIKAT YGNFMRQSRISSEIEMEVAEQGRGTTMTPPADLIEKDCPLGYSGLSCEA CLPGFYRLRSQPGGRTPGPTLGTGCVPCQCNHSSLCDPETSICQNCQHH TAGDFCERCALGYGIVKGLPNDCCQACPLISSNNFSPSCVAEGLD DYRCTACPRGYEQYCERCAPGYTGS PGNPGSSCQCECEDPYGSLFVP CDPVTFGCTCRPGATGRKCDGCKHWHAREGWEVFCGDECTGLLLG DLARLEQMVMSINLTGPLPAPYKMLYGLNMTQELKHLSPQRAPER LIQLAEGNLNLTVMENELLTRATKV TADGEQGTQDAERTNTRAKSL GEFIELARDABAVNEKAIKLNETLGTREAFERNLEGLQKEIDQMIKE LRRKNLETQKETAEDDELVAEALLKKVKLFGESRGENEEMEKKDLRE KLADYKNKVDDAWDLREATDKIREANRLFAVNQKNMTALEKKKEA VESGMRQIENLTKEGNDILDEANRLADEINSI IDYVEDIQTKLPPMSEEL NDKIDDLSQEIKRDLKAEKVSQAESHAAQLNDSAVLDGILDEAKNISF NATAAFKAYSNIKDYIDEAEKVAKEAKDLAHEATKLATGPRGLLKED AKGCLQKSFRI LNEAKKLANDVKENEDHLNGLKTRINENADARNGDLL RTLNDTLGKLSAIPNDTAAKLQAVKDKARQANDTAKDVLQAITELHQ NLDGLKKNYNKLADSVAKTNAVVKDP SKNKI IADADATVKNLEQEA DRLIDKLPKIELEDNLKKNISEIKELINQARKQANSIKVSVSSGGDCIR TYKPEIKKGSYNNIVNVKTAVDNLLFYLGS AKFIDFLAIEMRKGKV SFLWDVSGVGRVEY PDLTIDDSYWYRIVASRTGRNGTISVRALDGP ASIVPSTHHS TSPPGYTLIDVDANAMLFVGGTLGKLLKADAVRVI T GCMGETYFDNKPIGLWNFREKEGDKGCTVSPQVIEDSEGTIQDFGEG YALVSRP IRWYPNISTVMEKERTFSSALLMYLATRDLRDFMSVELTD GHIKVSYDLGSGMASVSNQNHNDGKWSFTLSRIQKQANISIVDIDT NQEENIATSSSGNFGDLKADDKIYFGGLPTLRNLRPEVNLKYSGC LKDIEISRTPYNILLSPDYGVTKGCSLENNVTVSFPKPGVELSFPVID EVHLEINLSFSTKNESGILLGSGGTPAPPRKRRTQQAAYVILLNRGR LSTGARTMRKIVIRPEPNLPHDGREHSHVHVERTRGI FTVQVDENR RYMQLNLTVEQPIEVKLVFVGGAPPEFQPSPLRNI PPFEGCIWNLVINSVP MDFARPVSKFNADIGRCAHQKLEDEDDGAAPAEI VIQPEPVP TPAFPT TPVLTHGPCAES EPALLIGSKQFGLSRNSHIAI AFDDTKVKNRLTILE VRTEAESGLLFYMARINHADFATVQLRNLGYPFSDYLGSDTHTMIPT KINDGQWHKIKIMRSKQEGILYVDGASNRITSPKKADILDVVGMLYV GLPINYTTTRRIGPVTYSIDGCVRNLMHMAEPADLEQPTS SFHVGT CFAN AQRGTYPDGTGFAKAVGGEKVGDLLEVEFEERTTTTGVLLG ISSQKMDGMGIEMIDEKLMFHDNGAGRFTAVYDAGVPGHLCDGQWHK VTA NKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDL KQFGL TTSIPERGCIRSLKLTGKTGKPLEVNFKALELRGVQPVSCPAN
laminin subunit alpha-3 isoform 1 precursor (LAMA3-isoform 1); SEQ ID NO: 28	MAAARPRGRALGPVLPPTPLLLLVLRLVLPACGATARDPAAAAGLSL HPTYFNLEAAARIWATATCGERGPGGRPOPELYCKLVGGPTAPGSGH TIQQGFCDYCNSEDPKRAHPVTNAIDGSEWQSPPLSSGTQYNRVNL TLDLGLQLFHVAYILIKFANSRPRDLWVLERSVDFGSTYSPWQYFAH KVDLKEFGREANMAVTRDDVLCVTEYSRIVPLENGEVVSVLNGRPG AKNFTFSHTLREFTKATNIRLRLRNTLLGHLISKAQRDPTVTRRY YYSIKDISIGGCVCNGHAEVCNINNPEKLFRCCEQHHTCGETCDRCCT GYNQRRWRPAAEQSHCEACNCHGASNCYDIPDVERQASLNTQGI YAGGGVCINCOHNTAGVNCQCAKGYRYPYGVVDPADPGCIPCS CDPEHADGCEQSGRCHCKPNFHDGDNCEKCAIGYYNPFPLRIP IFPVSTPS SEDPVAGDIKGCDCNLEGLPEICDAHGRCLCRPGVEGPR CDTCSRSGFYFPIQACWCSALGSYQMPCCSSVTGQCECRPGVTGQR CDRCLSGAYDFPHCQSSSACDPAGTINSNLGYCQCKLHVEGPTC SRCKLLYWNLDKENPSGCSECKCHKAGTVSGTGEQRQGDGCHCK SHVGGSDCTCEDGYFALEKSNYFGCQGCQCDIGGALSSMCSG SPSGVCCREHVVGVKVCQRPENNYFPDLHHMKYIEDGSTPN GRDLRFGFDPLAFPEFSWRGYAQMITSVQNDVRI TLNVGKS SGSLFRVILRYVNPSTEAVSGHITIIYPSWGAAQSKEIIFLPS KEPAFVTVPNGPADPFSITPGI WVACIKAEVLLDYLVLLPRD YYEASVLQLPVTEPCAYAGPPQENCLLYOHLVTRFPCTLACEA RHFLLDGEPRPVAVRQPTPAHPVMVDLSGREVELHLRLRIPQV GHYVVVEYSTAAQLFVVDVNVKSSGSLAGQVNIYSCNYSVLCR SAVIDHMSRIAMYELLADADILQKGHMARFLHQCIIPIEFESAE YVRPQVHCISYGRFVNQSATCVSLAHETPPTALILDVLSGRPP PHLPQSSSPSDVLPVTLKAPQNVTLRGRVPHLGRYVVIHFYQAAH PTFAQVSVDDGWRPAGSFHASFCHVLCRQVIAEGQIEFDISEPEVA ATVKVPEGKSLVLVRVLPVAENYDQILHKKSMKDSLEFINTCGK NSFYLDPQTASRFCNSARSLVAFYHKGALPCECHPTGATGPHCS PEGGQCPCQPNVIGRQCTRCATGHYGFPRCKPCSGRR LCEEMTGQCRCPRTVRPQCEVCETHSFSHPMAGCEGNC SRRTGIEAAMPEDRDSGQCRCKPRI TGRQCDRCASGFYR FPECVPCNCRDGTPEGVCDPGTAGLCKENVEGTECNV REGSPHLDPANLKGCTSCFCFGVNNQCHSSHRRRTKFDV MLGWHLET

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Human Laminin	Sequence
	<p>ADRVDI PVSNFPGNSMVADLQELPATIHSASWVAPTSYLGDKVSSYGGYLTYQAKSFLPGDMVLEKKPDVQLTGQHMMSI IYEETNTPRPDRRLHGRVHVVEGNFRHASSRAPVSRRELMTVLSRLADVRIQGLYPTETQRLTLSEVGLLEASDTGSGRIALAVEICACPPAYAGDSCQGCSPGYRDHKGGLYTGRCVPCNCGHNSQCQDGGSCVNCQHNHTAGEHCERCQEGYYGNAVHGS CRACPCPHTNSFATGCVVNGGDVRCSCKAGYGTQCERCAPGYFGNPQKFGGSCQPCSCNSNGQLGSGHPLTGDCINQEPKDS SPAE ECDDCDSCVMTLLNLDLATMGEQLRLVKSQQLGSLASAGLLEQMRHMETQAKDLRNQLLNYSRAISNHGSKI EGLERELTDLNQEFETLQEKAVQVNSRKAQTLNINNVNRTQSAKELDVKIKNVIRNVHILLKQISGTDGEGNVVPSGDFPREWAEQRMMRELNRNFKGLHREAEADKRESQLLNRI RTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRRLQEAQAQKQANGLNQENRALGAIQRQVKEINLSQDFTKYLTADSSLLQTNIALQLMEKSQKEYEKLAASLNEARQELSDKVRRELSRSAGKTSLV EEA EKHARSLQELAKQLEEEIKRNASGDELVRCAVDAATAYENILNAIKAAEDANRAASASESALQTVIKEDLPRKAKTSSNSDKLLNEAKMTQKKLKQEVSPALNNLQQT LNIVTVQKEVIDTNLTTLRDGLHG IQRGDI DAMISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDITYGRTONEDFKKALTDADNSV NKLTNKL PDLWRKIESINQQLPLGNISDNMDRIRELIQQARDAASKVA VPMRFNGKSGVEVRLPNDLEDLKGYSLSLFLQRPNSRENGGTENMFVMYLGNK DASRDYIGMAVVDGQLTCVYNLGDREAELQVDQILTKSE TKEAVMDRVKQRIYQFARLNYTKGATSSKPETPGVYDMDGRNSNTLLNLDPENVVVFYVGGYPPDFKLP S RLSFPPYKGCIELDDL NENVLSLYNFKKT FNLTTEVEPCRRRKEESDKNYFEGTGYARVPTQPHAPIPTFGQTIQT TVDRGLLFAENGDRFISLNI EDGKLMVRYKLNSELPKERGVGDAI NNGRDHSIQIKIGLQKRMWINVDVQNTIIDGEVDFSTYYLGGIPIAIRERFNI STPAFRGCMKNL KKTSGVVRLNDTVGVTKKCEDWKLVRSAFSRGGQLSFTDLGLPPTDHLQASFGPQTFQPSGILLDHQWTNRNLQVTL EDGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNGLRLLIDDQLLRNSKRLKHISSSRQSLRLLGGSNFEGCISNVFVQRLSLSPEVLDLTSNSLKR DVSLGGCSLNKPPFLMMLKGS TRFNKTKTFRINQLLQDTPVASPRSVK VWQDACSPLPKTQANHGALQFGDIPTSHLLFKLPQELKPRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTGDKKLRIKSKEKCN DGKWHTVVFGHDGKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPSGKPKSLPTNSFVGLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVVLAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHL CVYLEAKV TASMDSGAGGTSSTVTPKQSLCDGQWHSVAVTIKQHILHLELDTSSYTAGQIPFPASTQEPHLHGGAPANLTLRLIPVWKSFFGCLRNHVNHI PVPVTEALEVQGPVSLNGCPDQ</p>
laminin subunit alpha-3 isoform 2 precursor (LAMA3-isoform 2); SEQ ID NO: 29	<p>MPPAVRRSACSMGLWIFGAALGQCLGYSSQQQRPVFLQPPGQSQLQASVVEFRPSQGCSPGYRDHKGGLYTGRCVPCNCGHNSQCQDGGSCIVNCQHNHTAGEHCERCQEGYGNNAVHGS CRACPCPHTNSFATGCVVNGGDVRCSCKAGYGTQCERCAPGYFGNPQKFGGSCQPCSCNSNGQLGSGHPLTGDCINQEPKDS SPAE ECDDCDSCVMTLLNLDLATMGEQLRLVKSQQLGSLASAGLLEQMRHMETQAKDLRNQLLNYSRAISNHGSKI EGLERELTDLNQEFETLQEKAVQVNSRKAQTLNINNVNRTQSAKELDVKIKNVIRNVHILLKQISGTDGEGNVVPSGDFPREWAEQRMMRELNRNFKGLHREAEADKRESQLLNRI RTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRRLQEAQAQKQANGLNQENRALGAIQRQVKEINLSQDFTKYLTADSSLLQTNIALQLMEKSQKEYEKLAASLNEARQELSDKVRRELSRSAGKTSLV EEA EKHARSLQELAKQLEEEIKRNASGDELVRCAVDAATAYENILNAIKAAEDANRAASASESALQTVIKEDLPRKAKTSSNSDKLLNEAKMTQKKLKQEVSPALNNLQQT LNIVTVQKEVIDTNLTTLRDGLHG IQRGDI DANTISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDITYGRTONEDFKKALTDADNSV NKLTNKL PDLWRKIESINQQLPLGNISDNMDRIRELIQQARDAASKVA VPMRFNGKSGVEVRLPNDLEDLKGYSLSLFLQRPNSRENGGTENMFVMYLGNK DASRDYIGMAVVDGQLTCVYNLGDREAELQVDQILTKSE TKEAVMDRVKQRIYQFARLNYTKGATSSKPETPGVYDMDGRNSNTLLNLDPENVVVFYVGGYPPDFKLP S RLSFPPYKGCIELDDL NENVLSLYNFKKT FNLTTEVEPCRRRKEESDKNYFEGTGYARVPTQPHAPIPTFGQTIQT TVDRGLLFAENGDRFISLNI EDGKLMVRYKLNSELPKERGVGDAI NNGRDHSIQIKIGLQKRMWINVDVQNTIIDGEVDFSTYYLGGIPIAIRERFNI STPAFRGCMKNL KKTSGVVRLNDTVGVTKKCEDWKLVRSAFSRGGQLSFTDLGLPPTDHLQASFGPQTFQPSGILLDHQWTNRNLQVTL EDGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNGLRLLIDDQLLRNSKRLKHISSSRQSLRLLGGSNFEGCISNVFVQRLSLSPEVLDLTSNSLKR DVSLGGCSLNKPPFLMMLKGS TRFNKTKTFRINQLLQDTPVASPRSVK VWQDACSPLPKTQANHGALQFGDIPTSHLLFKLPQELKPRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTGDKKLRIKSKEKCN DGKWHTVVFGHDGKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPSGKPKSLPTNSFVGLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVVLAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHL CVYLEAKV TASMDSGAGGTSSTVTPKQSLCDGQWHSVAVTIKQHILHLELDTSSYTAGQIPFPASTQEPHLHGGAPANLTLRLIPVWKSFFGCLRNHVNHI PVPVTEALEVQGPVSLNGCPDQ</p>

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Human Laminin	Sequence
laminin subunit alpha-3 isoform 3 precursor (LAMA3-isoform 3); SEQ ID NO: 30	<p>MAAAARPRGRALGPVLPPTPLLLLVLRVLPACGATARDPGAAAGLSL HPTYFNLAEEARIWATATCGERGPGEGRPQPELYCKLVGGPTAPGSGH TIQQQFCDYCNSEDPRKAHPVTNAIDGSEWRWQSPPLSSGTQYNRVNL TLDLGGQLFHVAYILI K FANSRPDLWVLSRVDFGTSYSPWQYFAHSK VDCLKEFGREANMAVTRDDVLCVTEYSRI VPLENGEVVSVLNGRPG AKNFTFSHTLREFTKATNIRLRLRNTLLGHLISKAQRDPTVTRYYY SIKDISIGGCVCNGHAEVCNINNPEKLPRECEQHHTCGETCDRCCTGY NQRRWRPAAWEQSHECEACNCHGASNCYYPDPVERQQASLNTQGI YAGGGVCINCQHNTAGVNCEQCAKGYRYPYGVVDAPDGCIPCSGDP EHADGCEQSGRCHCKPNFHGDNCEKCAIGYNYFPCLRIPIFPVSTPS SEDPVAGDIKGCDCNLEGLPEICDAHGRCLCRPGVEGPRCDTCRSGF YSFPICQACWCSCALGSYQMPCCSVTGQCECRPGVTGQRCRCLSGAY DFPHCQSSSACDPAGTINSNLGYCQCKLHVEGPTCSRCKLLYWNLD KENPSSGCECKCHKAGTVSGTGECRQGDGDCHCKSHVGGSDCTCED GYFALEKSNYFGCQGCQCDIGGALSSMCSGSPVGCQCREHVVGKVCQ RPENNYFPDLHHMKYEIEDGSTPNGRDLRFGFDPLAFPEFSWRGYAQ MTSVQNDVRI TLNVGKSSGSLFRVILRYVNPGEAVSGHIT IYPSWGAA QSKELIIFLPSKEPAFVTPGNGPDPFSTITPGIWWACIKAEVLLDYLVL LPRDYEASVQLQPVTEPCAYAGPPQENCLLYOHLPVTRFPCTLACEA RHFLLDGEPRPVAVRQPTPAHPVMVDLSGREVELHLRLRIPQVGHYVV VVEYSTEAQFLVVDVNVKSSGSLVLAGQVNIYSCNYSVLCRSVIDH MSRIAMYELLADADIQLKGHMARFLHQVCI IPIEEFSAEYVRPQVHCI ASYGRFVNQSATCVSLAHETPPTALI LDVLSGRPPPHLPQQSSPSVDVL PGVTLKAPQONQVTLRGRVPHLGRYVFIHFYQAAHPTFPAQVSVDDG WFRAGSFPASFCPHVLGCRDQVIAEGQIEFDISEPEVAATVKVPEKSL VLVRVLPVPAENYDQILHKKSMDSLEFITNCGKNSFYLDPQTASRF CKNSARSLVAFYHKGALPCECHPTGATGPHCSPEGGQPCQPNVIGRQ CTRCATGHYGFPRCKPCSCGRRLCEEMTQGCRCPPRTVTRPQCEVCEH SFSFHPMAGCEGCNCSRRTIEAAMP ECDRDSGQCRCKPRI TGRQCDR CASGFYRFPCEVPCNCRDGTGPGVCDPDTGACLCKENVEGTECNVC REGSFHLDPANLKGCTSCFCFVNNQCHSSHRRRTKFDVMDLGHLEET ADRVDI PVSFNPGNSMVA DLQELPATIHSASVWAPTSLYLGDKVSSYG GYLTYQAKSFGLPDGMVLLKPKDPVQLTGQMSI IYEETNTPRPDLRH HGRVHVVEGNFRHASSRAPVSRRELMTVLSRLADVRIQGLYFTETQRL TLSEVGLLEASDTGSGRIALAVEICACPPAYAGDSCQGCSPGYRDHK GLYTGRVPCVPCNCHGNSNQCQDGSIGVNCQHNTAGEHCERCQEGY GNAVHGS CRACPCPHNTSFATGCVVNGGDVRC SCKAGYTGTCERC APGYFGNPQKFGGSCQPCSCNSNGQLGSC HPLTGDCINQEPKDS SPAE ECDDCDSVMTLLNDLATMGEQLRLVKSQQLGSLASAGLLEQMRHM ETQAKDLRNQLLNYSAI SNHGSKIEGLERELTDLNQEPETLQEKQV NSRKAQTLNNVNRRATQSAKELVDKIKNVI RNVMHLNRI RTWQKTHQ GENNGLANSIRDSLNEYEAKLSDLRLRLQEAQAQKQANGLNQENER ALGAIQRQVKEINSLQSDFTKYLTTADSLLQTNIALQLMEKSQKEYEK LAASLNEARQELSDKVRLELSRAGKTSLVEEAEKHARS LQELAKQLEE IKRNASGDELVRCVDAATAAYENILNAI KAAEDAANRAASASESALQT VIKEDLPRAKATLSSNSDKLLNEAKMTQKKLQEVSPALNNLQQT LNI VTVQKEVIDTNLTTLRDGLHGIQRGDI DAVISAKSMVRKANDITDEV LDGLNPIQTDVERIKD TYGRTONEDFKKALTDADNSVNKLTNKL PDL WRKIESINQQLLPLGNI SDNMDR IRELIQQARDAASKVAVPMRENGKS GVEVRLPNDLEDLKGYSLSLFLQRPNSRENGGTENMFVYMLGNKDA SRDYIGMAVVDGQLTCVYNLGDREAELOVDQILTKSETKEAVMDRV KFQRIYQFARLNYTKGATSSKPETPGVYDMDGRNSNTLLNDPENNVF YVGGYPPDFKLP SRLSFPYKGCIELDLNLNENVLSLYNFKTFNLNTTE VEPCRRRKEESDKNYFEGTGYARVPTQPHAPIPTFGQTIQT TVDRGLLF FAENGDRFISLNI EDGKLMVRYKLNSELPKERGVGDAINNGRDHSIQIK IGLKQKRMWINVDVQNTIIDGEVEDFSTYYLGGIPIAIRERFNISTPAFR GCMKNLKKTSGVVRLNDTVGVTKKCS EDWKLVRSAFSRGGQLSFT DLGLPPTDHLQASFGFQTFQPSGILLDHQWTRNLQVTLQVLEGGYIELSTS DSGGPIFKSPQTYMDGLLHYVSVISDNSGLRLLIDQLLRNSKRLKHIS SSRQSLRLGGSNFEGCISNVFVQRLSLSPEVLDLTSNSLKRVDVSLGGCS LNKPPFLMLLKGSTRFNKTKTRINQLLQDTPVASPRSVKVVQDACSP LPKQTQANH GALQFGDIP TSHLLFKLPQELLKPRSQFAVDMQTTSSRGL VFHTGTKNSFMALYLSKGRLVFALGTDGKKLR IKSKEKCN DGKWHTV VFGHDGEGKRLVVDGLRAREGSLPGNSTISIRAPVYLSGPPSGPKPSLP TNSFVGLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGHVV LAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHL CVYLEAGKV TASM DSGAGGTSVTPKQSLCDGQWHSVAVTIKQHILHLELDTDSSYTAGQ IPFPFPASTQEPLHLGGAPANLTLRI PVWKSFFGLRNIHVNHIPVPVTE ALEVQGPVSLNGCPDQ</p>
laminin subunit alpha-3 isoform 4 precursor	<p>MPPAVRRSACSMGLWIFGAALGQCLGYSSQQQRVFPFLQPPGQSLLQ ASYVEFRPSQGCSPGYRDHKGLYTGRCVPCNCHGNSNQCQDGSIGC VNCQHNTAGEHCERCQEGYGNVAVHGS CRACPCPHNTSFATGCVVN GGDVRC SCKAGYTGTCERCAPGYFGNPQKFGGSCQPCSCNSNGQL SCHPLTGDCINQEPKDS SPAECCDDCDSVMTLLNDLATMGEQLRLVK</p>

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Human Laminin	Sequence
(LAMA3-isoform 4); SEQ ID NO: 31	<p>SQLQGLSASAGLLEQMRHMETQAKDLRNQLLNYSASISNHGSKIEGLE RELTDLNQEFETLQEKQVNSRKAQTLLNNVNRATQSAKELDVKIKN VIRNVHMLNRIRTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRARL QEAAAQAKQANGLNQENERALGAIQRQVKEINSLQSDFTKYLTADS SLLQTNIALQLMEKSQKEYEKLAASLNEARQELSDKVRLESRASGKTS LVEEAEKHARSLQELAKQLEEIKRNASGDELVRCVDAATAAYENILNA IKAEDAANRAASASESALQTVIKEDLPRKAKTLSSNSDKLLNEAKMT QKKLKQEVSPALNNLQQTLLNIIVTVQKEVIDTNLTLLRDGLHGIQRGDI DAMISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDTYGRTONEDFK KALTDADNSVNKLTKLPDLWRKIESINQQLLPLGNISDNMDRIRELIQ QARDAASKVAVPMRFNGKSGVEVRLPNDLEDLKGYSLSLFLQRPNS RENGGTENNI FVMYLGKNDASRDYIGMAVVDGQLTCVYNLGDREAEL QVDQILTKSETKEAVMDRVKQRIYQFARLNYTKGATSSKPETPGVYD MDGRNSNTLLNLDPENVVYVGGYPPDFKLPRLSFPFYKGCIELEDDL NENVLSLNFKKTFLNLTTEVEPCRRRKEESDKNYFEGTGYARVPTQP HAPIPTFGQTIQTTVDRGLFFAENGDRFISLNI EDGKLMVRYKLSLSELP KERGVGDAINNGRDHSIQIKIGKQKRMWINVDVQNTIIDGEVDFPSTY YLGGPIAIRERFNI STPAFRGCMKLNKKTSGVVRNLDTVGVTKKCS ED WKLVRSASFRRGGQSFDTLGLPPTDHLQASFGQTFQPSGILLDHDQ WTRNLQVTLLEDGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNSGL RLLIDDQLLRNSKRLKHISSSRQSLRGGSNFEGCISNVFVQRLSLSPEV LDLTNSNLRKRVDSLGGCSLNKPPFLMLLKGSTRFNKTKTFRINQLQDT PVASPRSVKVVQDACSPKPTQANHGALQFGDIP TSHLLFKLPQELLK PRSQFAVDMQTTSSRGLVVFHTGTKNSFMALYLSKGRLVFALGTDGKK LRISKSEKCNDEKWHVTVFGHDGEGKRLVVDGLRAREGSLPGENSTIS I RAPVYLGSPSPSGKPKSLPTNSFVGCLEKFNQDLSKPLYTPSSSFGVSC GGPLEKGIYFSEEGGHVVLHSAVLLGPEFKLVFSIRPRSLTGLIHIHGSQ GKHLVYLEAGKVTASMDSGAGGTSTSVTPKQSLCDGQWHSVAVTIK QHILHLELDDTSSYTAGQIPFPASTQEPHLHLGGAPANLTLRIPVWKSF FGCLRNIFIVNHI PVPVTEALEVQGPVSLNGCPDQ</p>
laminin subunit alpha-3 isoform 5 precursor (LAMA3-isoform 5); SEQ ID NO: 32	<p>MAAARPRGRALGPVLPPTPLLLLVLRLVLPACGATARDPAAAAGLSL HPTYFNLAEEAARIWATATCGERGPGGRPOPELYCKLVGGPTAPGSGH TIQQQFCDYCNSEDPKHAHPVTNAIDGSEWRWQSPPLSSGTQYNRVNL TLDLGGQLFHVAYILIKFANSRPRDLWVLEERSVDFGSTYSFWQYFAHSK VDCLKEFGREANMAVTRDDDDVLCVTEYSRIVPLENGEVVVS LINGRPG AKNFTFSHTLREFTKATNIRLRLRNTNLLGHLISKAQRDPTVTRRYYY SIKDISIGGCVCNGHAEVCININNEKLFRCCECQHHTCGETCDRCCTGY NQRRWRPAAWEQSHECEACNCHGHASNCYDIPDVERQOASLNTQGI YAGGVGCINCOHNTAGVNCBQCAKGYRYPYGPVADPDGCI RKFHF KLVYLSLQVLPQRSHQANFGSVNNFLHALSLQSI SCARYVTSVTVTYS LNFGFIAACKWK</p>
laminin subunit alpha-4 isoform 1 precursor (LAMA4-isoform 1); SEQ ID NO: 33	<p>MALS SAWSVLPWLWLSAACSRAASGDDNAPFFDI EGSSAVGRQDP PETSEPRVALGRLPPAAEKCNAGFFHTLSGCEVPCDCNGNSNECLDGS GYCVHCQRNTTGEHCEKCLDGYIGDS IRGAPQFCQPCPLPHLANFA ESCYRKNGAVRNICNENYAGPNCERCAPGYGNPLLIGSTCKKDCSG NSDPNLI FEDCEVTVGQCRNCLRNTTGKFCERCAPGYGDARI AKNCA VCNCGGGPCDSVTGECLEEGFEPPTGMDCPTISCDKCVWDLTDDLRL AALSIEEGKSGVLSVSSGAAHRHVNEINATI YLLTKLSERENQYALR KIQINNAENTMKSLLSDVEELVEKENQASRKGQLVQKESMDTINHASQ LVEQAHDMRDKIQEINNKMLYGEHEHLSPKIESEKLVLAQKMLEEIR SRQPFPTQRELVDEEADAEYELLSQAESWQRLHNETRRTLFPVVLQQLD DYNAKLSDLQEQALDQALNYVRDAEDMNRATAARQDRDEKQOQERVR EQMEVVNMSLSTSDSLTTPRLTLESELDDI IKNASGIYAEIDGAKSELQ VKLSNLSNLSHDLVQEAIDHAQDLQEQANELSRKLSHSSDMNGLVQKA LDASNVIENI VNYVSEANETAEPALNTDDR IYDAVSGIDTQII YHKDES ENLLNQARELQAKAESSDEAVADTSRRVGGALARKSALKTRLSDAV KQLQAAERGAQQRRLGQSRLITEANRTTMEVQOATAPMANNLTNW SQNLQHPDSSAYNTAVNSARDAVRNLTVEVPQLLDQLRTVEQKRPAS NTSASIQRIRELI AQTRSVASKIQVSMMPDQSAVEVHSRTSMDDLKA FTLSLVMKPVKRPPELTETADQF ILYLGSKNAKKEYMGLAI KNDNLV VYVNLGTDKVEIPLDSKPVSSWPAYFSIVKIERVKGKGVFLTVPSLSS TAEKFIKKGEFGDSDLDDLPEDTVFYVGGVPSNFKLP TSLNLPGFV GCLELATLNDVIVSLYFNFKHI YNMDPSTSVPCARDKLAFTQSRASYSF PDGSGYAVVRDITRRKFGQVTRFDI EVRTPADNGLILLMVNGSMFFR LEMRNGYLHVFPYDFGSGGVVHLEDLTKKAQINDAKYHEISII YHNDK KMILVDDRHRVKSMDNEKMKI PFTDIYIGGAPPEILQSRALRAHLPLDI NFRGCMKGFQPKKDFNLLBQTELVGVGYGCPEDSLISRRAYFNGQSF IASIQKISFFDGFEGGPNFRTLQPNGLLFFYASGSDVFSISLDNGTVIMD VKGIVQVSDKQYNDGLSHFV I SSVSPTRYELIVDKSRVGSKNPTKGI EQTQASEKFKYFGGSPISAQYANFTGCI SNAYFTRVDRDVEVEDFQRY TEKVHTSLYECPIESSPLFLHKKGKNSKPKASQNKGGKSKDAPSW DFPALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQEFHEHLKG DFGAKSQFSIRLRTRSSHGMI FVYSDQEEENDFMTLFLAHGRLVYMFNV GHKKLKIRSQEKYNDGLWHDFIRIRSSGRLVIDGLRVLEESLPTEA</p>

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Human Laminin	Sequence
	TWKIKGPIYLGAVGKAVKQVINSIYFSFGCLSNLQNLGASITSASQ TFSVTPCFEGPMETGTYSFTEGGYVVLDESFNIGLKFETAFEVPRSSSG TLVHGHSVNGEYLVNVMKNGQVIVKVNNGIRDSTSVTPKQSLCDGR WHRITVIRDSNVVQLDVSDEVNHVVGPLNPKPIDHREPVFVGGVPESL LTPRLAPSKPFTGCIRHFVIDGHPVVSFKAALVSGAVSINSCPA
laminin subunit alpha-4 isoform 2 precursor (LAMA4-isoform 2); SEQ ID NO: 34	MALSSAWRSVLPWLWLSAACSRASGDDNAPFFDI EGSSAVGRQDP PETS EPRVALGRLPPAAEKCNAFFHTLSGECVPCDCNNSNECLDGS GYCVHCQRNTTGEHCEKCLDGYIGDSIRGAPQFCPCPCPLPHLANFA ESCVRKNGAVRCINENYAGPNCERCAPGYGNPLLIGSTCKKDCSG NSDPNLI FEFDCDEVTGQCRNCLRNTTGFKCERCAPGYGDARI AKNCA VCNCGGGPCDSVTGECLEEGFEPPTGCDKCVWDLTDDLRLAALSIEEG KSGVLSVSSGAAHRHVNEINAT IYLLKTKLSERENQYALRKIQINNAE NTMKSLSDVEELVEKENQASRKGQLVQKESMDTINHASQLVEQAH MRDKIQEINNKMLYYGEHEHLSPEKISEKLVLAQKMLEEIRSRQPFPTQ RELVDDEADEAYELLSQAESWQRLHNETR TLFVVLVQLDDYNAKLS DLQEALDQALNYVRDAEDMNRATAARQDRHEKQOQVREQMEVVN MSLSTADSLTTPRLTSELDI IKNASGIYAEIDGAKSELQVKSLSNLS LSHDLVQEAIDHAQDLQOEA NELSRKLHSSDMNGLVQKALDASNVYE NIVNVVSEANETA EFALNTDRIYDAVSGIDTQI IYHKDESENLLNQAR ELQAKAESSSDEAVADTSRRVGGALARKSALKTRLSDAVKQLQAAER GDAQQLGQSR LI TEEANRTTMEVQQA TAPMANNLTNWSQLQHPD SSAYNTAVNSARDAVRNLTEVVPQLDQLRTVEQKR PASNVASIQRI RELIAQTRSVASKIQVSMFDDGQSAVEVHSRTSMDLKAFTSLSLYM KPPVKRPELLETADQF ILYLGSKNAKKEYMGLAIKNDNLVYVYVNLGT KDVEIPLDSKPVSSWPAYFSIVKIERVGHGKVF LTVPSLSTAEKFIK KGEFSGDSDLDPEDTVFVVGVP SNFKLPTSLNLPGFVGCLELATL NNDV I SLYNFKHI YNMDPSTSVPCARDKLAFTQSRASVYFFDGGSYAV VRDI TRRGKFGQVTRFDIEVRTPADNGLILLMVNGSMFPRLEMRNGYL HVFYDFGFGSGPVHLEDTLKKAQINDAKYHEI SI IYHNDKMI LVVDR RHVKSMDNEKMKI PFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMKG PQFQKDFNLLLEQTE TLGVGYGCPEDSLISRRAYFNGQSFIASIQKISFF DGFEGGFNFR TLQPNGLLFYASGSDVFSISLDNGTVIMDVKGIKQVS VDKQYNDGLSHFV I SVSPTRYELIVDKSRVGSKNPTKGI EQTQASEK KPYFGGSP ISAQYANFTGCI SNAYFTRVDRDVEEDFQRYTEKVHTSL YECPIESSPLFLHKKGNLSKPKASQNKKGKSKDAPSVDVVALKLP ERNTPRNHCHLSNSPRAI EHAYQYGGTANSRQEFELKGDGAKSQF SIRLRTSRSHGMI FYVSDQEENDFMTLFLAHGRLVYMFNVGHKCLKIR SQEKYNDGLWHDF IFRERSSGRLVIDGLRVLEESLPPTTEATWKIKGPI YLGAVGKAVKQVINSIYFSFGCLSNLQNLGASITSASQTFSVTPCF EGPMETGTYSFTEGGYVVLDESFNIGLKFETAFEVPRSSSGTLVHGHS VNGEYLVNVMKNGQVIVKVNNGIRDSTSVTPKQSLCDGRWHRITVI RDSNVVQLDVSDEVNHVVGPLNPKPIDHREPVFVGGVPESLTPRLAP SKPFTGCIRHFVIDGHPVVSFKAALVSGAVSINSCPA
laminin subunit alpha-4 isoform 3 precursor (LAMA4-isoform 3); SEQ ID NO: 35	MALSSAWRSVLPWLWLSAACSRASGDDNAPFFDI EGSSAVGRQDP PETS EPRVALGRLPPAAEVQCPCCHPAGAPAPPRVPHSSFSLSPLSS PQCLESTWARSVRKLEIKSFPL
laminin subunit alpha-5 precursor (LAMA5); SEQ ID NO: 36	MAKRLCAGSALCVRGRGPAPLLLVGLLALLGAARAREEAGGFSLHP PYFNLAEGARIAASATCGEEAPARGSPRPTEDLYCKLVGGPVAGGDPN QTRGQYCDICTAANSNKAHPASNAIDGTERWQSPPLSRGLEYNEN VTLDLQVVFHAYVLIK FANSRPRDLWVLSRMDPGRTYQPWQFFAS SKRDCLERFGPQTLERITRDDAAICTTEYSRIVPLENGEIVVSLVNGRPG AMNFSYSPLLREFTKATNVR LFLRTNTLLGHLMGKALRDPVTTRY YYSIKDISIGGRVCVGHADACDAKDPDPFR LQCTCQHNTCGGTCDR CCPGFNQQPWKPATANSANECQSCNCYGHATDCYDPEVDRRRASQ SLDGTYQGGVICDCQHHTTGVNCCERCLPGFYRSPNHPLDSPHVCRRC NCESDFTDGTCEDLTGRCYCRPNFSGERCDCVCAEGFTGFPSCYPTPSS NDTREQVLPAGQIVNDCSAAGTQGNACRDPVGRCLCKPNFQGT CELCAPGFYGPQCQCS SPGVADDRCDPDTGQCRVGFEGATCD RCAPGYFHFP LQC LCGCSPAGTLEPEGCEAGRCLCQPEFAGPHCDRCR PGYHGFPCQACTCDPRGALDQLCGAGGLCRCPGYTGTAQCQECSPG FHGFPCVPCCHCSAEGSLHAACDPRSGQCS CRPRVTGLRCDTCVPGAY NFPYCEAGSCHPAGLAPVDPALPEAQVPCMCRHAHVEGSPCDRCKPGF WGLSPSNPEGCTRCSDLRGTLGGVAECQPGTGCFCFKPHVCGQACA SCKGEEGLDQADYFGCRS CRCDIGGALGQSC EPRTGVCRCRPNTOGP TCS EPARDHYLPDLHHLRLEEEAATPEGHAVRFGFNPLEFENFSWRG YAQMAMPVQPRIVARLNLTS PDLFWLVFRYVNRGAMSVSGRVSVREEG RSATCANCTAQSQPVAFPPSTEPAFITVPRGEGEPEVLNPGTWALRVE

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Human Laminin	Sequence
	AEGVLLDYVLLPSAYYEALLQLRVTEACTYRPSAQOSGDNCLLYT HPLDGFPSAAGLEALCRQDNLPRPCPTQLSPSHPLITCTGSDVDV QLQVAVPQPGRYALVVEYANEDARQEVGVAVHTPQRAPOQGLLSLH PCLYSTLCRGRTARDTQDHLAVFHLDS EASVRLTAEQARFFLHGVTLPV IEEEEPEFVEPRVSCIS SHGAFGPN SAACLP SRFPKPPQPI ILRDCQVIPLE PGLPLTHAQDLTPAMSPAGPRPRPPTAVDPDAEPTLLREFPQATVVFTTH VPTLGRYAELLHGYPAEI PTEPVEVLINAGR VVQGHANASFCPHGYG CRTLVVCEGQALLDVTHSELTVTVRV PKGRWLWLDYVLVVPEVNS FGYLREEPLDKSYDFISHCAAQGYHISPSSSSLCR NAASLSLFYNNG ARPCCGHEVGATGPTCEPFGGQCPCHAHVI GRDCSRCATGYWGFNC RPCDCGARL CDEL TGQCICPPRTIPPDCLLCQPQTFGCHPLVGC EECNC SGPGIQELTDPTCDTDSGQCKCRPNVTGRRCDTCSPGFHGYPRCRPCD CHEAGTAPGVCDPLTGQCYKENVQGPCKDQC SLGTFSLDAANPKGC TRCF CFGATERCRSSSYTRQEFVDMEGWVLLS TDRQVVPHERQPGE MLRADLRHVPEAVPEAFPELYWQAPP SYLGRVSSYGGTLRYELHSE TQRGDV FVPMESRPDVVLQGNQMSITFLEPAYPTPGHVHRGQLQVLE GNFRTETRNVTVSREELMMVLASLEQLQIRALFSQISSAVFLRRVALE ASPAQGALASNVELCLCPASYRGDS CQECAPGFYRDVKGLFLGRCV PCQCHGHSDRCLPGSGV CVDCQHNTGGAHCER CQAGFVSRDDPSAP CVSCPCPLSVSPNNFAEGCVLRGGRTQCLCKPGYAGASCERCAPGFFG NPLVLGSSCQPCDCSNGDNP LLFSDCDPLTGACRGLRHTTGPRCEIC APGFYGNALLPGNCTRCDC TPCGTEACDPHSGHCLCKAGVTGRRCDR CQEGHFGEDGCGGCRPCACGPAEAGS ECHPQSGQCHCRPMTGMPQCR ECAPGYWGLPEQGCRCQCPCGGRCDPHTGR CNCPGLSGERCDC TCSQ QHQVVPVGGPVGHSIHCEVCDHCVLLDDDLERAGALLPAIHEQLRGI NASSMAWARLHRLNASIADLQSQLRSLGPRHETAQCLEVLEQQS TSL GQDARRLGGQAVGTRDQASQLLAGTEATLGHAKTLLAAIRAVDR TLS ELMSQTGHLGLANASAPSGEQLLRTLAEVERLLWEMRARDLGAPQAA ABAAELAAARLLARVQEQLSLWEEENQALATQTRDR LQAHEAGLMD LREALNRAVDATRAEQELN SRNQERLEEALQRKQELSRDNATLQATL HAARDTLASVFRLLHSLDQAKEELERLAASLDGARTPLLQRMQTFSPA GSKLRLVEAAEBAHAQQLGQ LALNLSII LDVNDRLTQRAI EASNAYS RILQAVQAAEDAAGQALQADHTWATVVRQGLVDRACQLLANSTAL EAMLQEQQR LGLVMAALQGARTQLRDRVRAKQDLEAHTIQAQAM LAMDTDETSKKIAHAKAVAAEAQDTATRVQS QLQAMQENVERWQG QYEGLRGQDLGQAVLDAGHSVSTLEKTL PQLLAKLSILENRGVHNASL ALSASIGRVRELI AQARGAASKVKVPMKFNGRSGVQLRTPRDLADLA AYTALKFYLQGPPEPGQGTEDRFVMYMGSRQATGDMGVSLRDKK VHWVYQLGEAGPAVLSIDEDI GEQFAAVSLDR TLQFGHMSVTVRQM IQETKGD TVAPGAEGLLNRPD DFFVYVGGYPTFTFPPLLRFPYGRG IEMDTLNEEVVSLYNEERTEQLD TAVDRPCARSKSTGDPWLT DGSYLD GTGEARISED SQISTTKREEQLRLVSYSGVLEELKQSQQLCLAVQEGS LVLLYDFGAGLKKAVPLQPPPLTSASKAIQVFLGGSRRKRVLVRVER ATVYSVEQDNDLELADAYYLG GVPDQLPPSLRRLFPPTGGSVRCVK GIKALGKYVDLKR LNTTGV SAGCTADLLVGRAMTFHGHGFLRLALS VAPLTGNVYSFGFHSADQSALLYRASPDGLCQVSLQQGRVSLQLL RTEVKTQAGFADGAPHYVAFYSNATGVWLVYDDQLQMQM KPHRGPPP ELQPQEGPRLLLGLLPESGTIYNE SGCI SNVFORLLGQRVDFDQQ NLGSVNVSTGCAPALQAQTPGLGPRGLQATARKASRRSRQPARHPAC MLPPLHRTTRDSYQGGSLSSHLEFVGI LARHRNWP SLSMHVLP RSSR GLLLF TARLRPGSPSLALFLSNGHFVAQMRGLGTRLRQAQRQR SRPGR WHKVSVRWEKNRI LLVTDGARAWSQEGPHRQHQA EHPQHTL FVG GLPASSHSSKLPVTVGFSGVKRLRLHGRPLGAPTRMAGVTPCILGPLE AGLFFPGSGGVI TLDLPGATLPDVGLELEVRPLAVTGLI FHLGQARTPP YLQLQVTEKQVLLRADDGAGEFSTSVTRPSVLCDGQWHR LAMKSG NVLRLEVDAQSNHTVGPLLAAAAGAPAPLYLGGLEPEPMAVQPWPPAY CGCMRRLAVNRSVPAMTRSVEVHGAVGASGCPAA
laminin subunit beta-1 precursor (LAMB1); SEQ ID NO: 37	MGLLQLLAFSFLALCRARVRAQEPEFSYGC AEGSCYPATGDL LIGRAQ KLSVTS TCGLHKPEPYCIVSHLQEDKKCFI CNSQDPYHETLNPDSHLIE NVVTFAPNRLKI WQSENGVENVTIQLDLEAEFHFTHLIMTFKTRFP AAMLIERSDFPKTWGVYRYFYDCEASFPGISTGPMKKVDDIICDSR YSDIEPSTEGEVI FRALDPAFKIEDPYSRIQNL LKINTLR IKFVKLHTL DNLLDSRMEIREKYYAVYDMVVRGNCF CYGHASECAPVDGFNEEV EGMVHGHCMRHNTKGLNCELCMDFYHDL PWRPAEGRNSNACKKC NCNEHSISCHFDMAVYLATGNVSGV CDDCQHNTMGRNCEQCKPFY YQHPERDIRDPNFCERC TCDPAGSQNEGICDSYDFSTGLIAGQCRCKL NVEGEHCDVCKEGFYDLSSDPFGCKSCACNPLGTIPGGNCPDSETGH CYCKRLVTGQHCDQCLPEHWGLSNDLDGCRPCDCLGGALNNSCFA ESGQCSCRPHMIGRQCNEVEFGYFATLDHYLYEAEANLGPVGSIVE RQYIQDRIPSWTGAGFVRVPEGAYLEFFIDNIPYSMEYDILIRYEPQLPD HWEKAVITVQRPGR IPTSSRCGNTIPDDDNQVVSLSPGSRVYVLRPRVC FEKGTNYTVRLELPQYTS SDSLVE SPYTLIDS LVLMYPYCKSLDIFTVGG SGGGVV TNSAWETFORYRCLENSRSVVKTPMTDVCRNII FSI SALLHOT GLACECDPQGSLSVCDENGGQCQCRPNVVGRTCNRCAPGTFGFGPS GCKPCECHLQGSVNAFCNPVTGQCHCFQGVYARQCDRCLPGHWGFFS

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Human Laminin	Sequence
	CQPCQCNGHADDCPVTGECLNCQDYTMGHNCERCLAGYYGDFIIGS GDHCRPCPCPDGPDSDGRQFARSCYQDPVTLQLACVCDPGYIGSRCDCC ASGYFGNPEVGGSCQPCQCHNNIDTTPDPEADKTKETGRCLKLYHTEG EHCQFCRFYGYGDALQQDCRKCVCNYLGTVQEHNGSDCQCDKATG QCLCLPNVIGQNCDCRCAFNWQLASGTGCDPCNCNAAHSGFSPSCNEF TGCCQCMPPGFGGRTCSQCQLFWGDDPVECRACDCDPRGIETPQCDQ STGQCVCVEGVEGPRCDKTRGYSVFPDCTPCHQCFALWDVIAELT NRTHRFLEKAKALKISGVI GPYRETVDVSVERKVS EIKDILAQSPAEP KNIGNLFEEAEKLIKDVTEMAQVEVKLSDTTSQSNSTAKELDSLQTE AESLDNTVKELAEQLEFIKNSDIRGALDSITKYFQMSLEAEERVNASTT EPNSTVBEQALMRDRVEDVMMERESQFKEKQEEQARLLDELAKLQS LDLSAAAEMTCGTPPGASCSETECGGPNCRDTEGERKCGGPGCGGLV TVAHNAWQKAMDLDQDVLSEALAEVQLSKMSVSAKLRADAEKQSA EDILKKNATKEKMDKSNELRNLIKQIRNFLTQDSADLDSIEAVANEV LKMMPSTPQQQLQNLTEDIRERVESLSQVEVILQHSAAIARAEMLLEE AKRASKSATDVKVTADMVKEALEEAEKAQVAEKAIKQADEDIQGT QNLLTSHESETAASEETLFNASQRISELERNVEELKRKAQNSGEAEYIE KVYYTVKQSAEDVKKTLDELDEKYKVENLIIAKKTEESADARRKAE MLQNEAKTLAQANSKLQLKDLERKYEDNQRYLEDKAQELARLEG EVRSLKDISQKVAVYSTCL
laminin subunit beta-2 precursor (LAMB2); SEQ ID NO: 38	MELTSRERGRGQPLPWELRLGLLSVLAATLAQAPADVPGCSRGSCY PATGDLVLVGRADRLTASSTCGLNGPQPYCIVSHLQDEKKCFLCDSRFP FSARDNPHSHRIQNVVTSFAPQRRAAWQSENGIPAVTIQLDLEAEFH PHTLIMTFKTRPAAMLVERSADPGRTHVYRYFSYDCGADPPGVPL APPRHDDVVCESTRYSEIEPSTEGEVIYRVLDPAIPIPDYSSRIQNLKIKI TNLRVNLTRLHTLGDNLDPREIREKYIYALYELVVRGNCFCYGHGA SECAPAPGAPAHAEQVMEVHGACICKHNTRGLNCEQCQDFYRDLFPWRPA EDGSHACRCKCECHGHTSCHFDMAVYLAGNVS GGVCDCGQHNTA GRHCELCRPFYRDP TKDLRDPVCRSCDCDPMGSDQGGRCDSHDDP ALGLVSGQCRCKEHVVGTRCQCQCRDGFGLSISDRLGCRRCCQCNARG TVPGSTPCDPNSGSCYCKRLVTGRGCDRCLPGHWGLSHDLLGCRPCD CDVGGALDPQDEGTGQCHCRQHVMVGRRCQVQPGYFRPFLDHLIW EAEDTRGQVLDVVERLVTPGETPSWTGSGFVRLQEGQTLFLVAVSPK AMDYDLLRLLEPQVPEQWAELELIVQRPVPAHSLCGHLVPKDDRIQ GTLQPHARYLIFPNPVCLEPGISYKHLHLKLVRTGGSAQPETPYSGPGLLI DSLVLPRVLVLEMFSGGDAALERQATPERYQCHEEGLVPSKTSPE ACAPLLISLSTLIYNGALPCQCNPQGLSSECNPHGGQCLCKPGVVGRR CDLCPAGYGGFGPTGCQACQCSHEGALSSLCEKTSQCLCRTGAFGLR CDRCQRGQWGFPSCRPCVCNGHADECNHTGACLGCRDHTGGEHCE RCIAGFHGDPRLPYGGQCRPCPCPEGPGSRHFATSCHQDEYSQQIVC HCRAGYTGRLCEACAPGHFGDPSRPGGRQCQLECSGNIDPMDPDACD PHTGQCLRLHHTEGPHCAHCKPGFHQAARQSCRCTCNLGTNPQ QCPSPDQCHCDPSGGQPCLEPNVQGPSCDRCAPNFWNLTSGHGCQPCA CHPSRARGPTCNEFTGQCHCRAGFGGRTCSQCQLHWGDPGLQCHAC DCDSRGIDTPQCHRFTGHCSCRPGVSGVRCDCQARGFSGIFPACHPCH ACFGDWDVVQDLAARTQRLQRAQELQQTGVLGAFESSFWHMQEK LGIQVIGVARNSTAASATLQLEATEELRREI GEATEHLTQLEADLTDV QDENFNANHALSGLERDRLALNLTLRQLDQHLDDLKHSNFLGAYDSIR HAHSQSAEAEERRANT SALAVSPVNSASARHRTALMDAQKEDFNS KHMANTRALGKLSAHTHTLSLTDINELVCGAPGDAPCATSPCGGAGC RDEDGQPRCGGLSNGAAATADLALGRARHTQAEQALAEAGGSILS RVAETRRQAS EAQQAQAALDKANASRGQVEQANQELQELIQSVKDF LNQEGADPDSIEMVATRVLELSIPASAEQIQHLAGAIAERVRSLADVDA ILARTVGDVRAEQQLQDARRARSWAEDEKQKAETVQAALAEQRA QGIAQGAIRGAVADTRDTEQTLYQVQERMAGAEALSSAGERARQLD ALLEALKLKRAGNSLAASTAEETAGSAQGRAQAEQLLRGPLGDQYQ TVKALAEKKAQGVLAQAQAEQLRDEARDLLQAAQDKLQRLQLELEG TYEENERALESKAAQLDGLAARMRSVLQAINLQVQIYNTCQ
laminin subunit beta-3 precursor (LAMB3); SEQ ID NO: 39	MRPFFLLCFALPGLLHAQQACSRGACYPVVDLLVGRTRFLRASSTCG LTKPEYCTQYGEWQMKCKCDSRQPHNYSHRVENVASSSGPMRW WQSQNDVNPVSLQLDLDRRFPQLQEVMMEFQGPMPAGMLIERSSDFG KTWRVYQYLAADCTSTFPRVRQGRPQSWQDVRCSLQRPQARNARLNG GKVLQNLMDLVSGIPATQSQKIQEVGEITNLRVNFTRLAPVPPQGYHP PSAYYAVSQRRLQGSFCFHGADRCAKPKGASAGPSTAVQVHDVVCV QHNTAGPNCERCAPPYNNRPRPAEGQDAHECCQDCNCHSSETCHF DPAVFAASQGAYGGVCDNCRDHTEGKNCECQLHYFRNRRPGASIQE TCISCECDPDGAVPGAPCDPVTGQCVCHEVQGERCDLCKPGFTGLTY ANPQGCHRCDNI LGSRRDMPDEESGRCLCLPNVVGPKCDQCAPYH WKLASGQCEPCACDPHNSLSPQCNQFTGQCPCREGFGGLMCSAAAI RQCPDRTYGDVATGCRACDCDFRGTGPGCDKASGRCLCRPGLTGPR CDQCQRGYCNRYPVVCAHPCFQTYDADLREQALRFGRLRNATASL WSPGLBEDRGLASRI LDKASKIEQIRAVLS SPAVTEQVEVAQVASA ILSL RRTLQQLQLDLPLEEETLSLPRDLES LDRS FNGLLTMQRKREQFEKIS SADPSGAFRMLSTAYEQSAQAQVSDSSRLDQLRDSRREARLVR

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Human Laminin	Sequence
	QAGGGGTGSPKLVLRLEMSLPLDTPFNKLCGNSRQMACTPI SCP GELCPQDNGTACGSRGVLPRAGGAFMAGQVAEQLRGFNAQLQR TRQMI RAAEESASQIQSSAQRLETVSASRSQMEEDVRRTRLLIQVVR DFLTDPDPTDAATI QEVSEAVLALWLPDTSATV LQKMNEIQAIAARLPN VDLVLSQTKQDIARARRLQAEAEARSRAHVEGQVEDVVGNLRQGT VALQEAQDTMQGTSRSLRLIQDRVAEVQVLRPAEKLVTSMTKQLGD FWTRMEELRHQARQQGAEAVQAQQLAEGASEQALSAQEGFERIKQK YAE LKDR LGQSSMLGEQGARIQSVKTEAEELFGETMEMMDRMKDME LELLRGSQAIMLRADLTGLEKRV EQIRDHINGRVLVYYATCK
laminin subunit beta-4 isoform 1 precursor (LAMB4-isoform 1); SEQ ID NO: 40	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWQSENGLDHVSIRLDLEALFRFSHLILTFKTRPAAMLVE RSTDYGHNWKVKYFAKDCATSFNITSGQAQGVGDIVCDSKYSIDIEP STGGEVVLKVLDP SFEIENPYSPIQDLVTLTNLRINFTKLHTLGDALLG RRQNDSLDKYYALYEMIVRGSFCFNHASECRPMQKMRGDFVSPPG MVHGQVCQHNTDGPNCERCKDFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTGQHCDRCRPLFYRDP LKTISDPYACIPCECDPDGTISGGICVSHSDPALGSAQGLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCS YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAAGYFFAPLNFYLYEAEAEATTLQGLAPLGSETFGQ SPAVHVVLGEPVGNPVTWTGPGFARVLPAGALRFVANNIPFPVDFTI AIHYETQSAADWTVQIVVNPFGGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGESHAHSHVLDVSLGLIPQINSL ENF CSKQDLDEYQLHNCVEIASAMGPQVLPGACERLIISMSAKLHDGAVAC KCHPQGSVGS SCSRLGGQCCKPLVVGRCDCRSTG SYDLGHHGCHP CHCHPQGSKDTVCDQVTGQCPCHGEVSGRRCDRCLAGYFGFPSC HPC PCNRF AELCDPETGSCFNCGGFTTGRNCERCIDGYYGNPSSGQPCRPL CPDDPSSNQYFAHSCYQNLWSDVICNCLQGYTGTCQCECSTGFYGNP RISGAPCQPCACNNDIVTDPESCSRVTGECLRCLHNTQGANCLCKP GHYGSALNQT CRRCSCHASGVSPMECPGGGACLCDPVTGACPCLEPN VTGLACDRCADGYWNLVPGRCQSCDCDPRTSQSSHCDQLTGQCP KLG YGGKRCSECEENYVGDPPGRICIPDCNRACTQKPICDPDTGMCR CREGVSQRCDRCARGHSQEFPTCLQCHLCFDQWDHTISSLSKAVQG LMRLAANMEDKRETLVPEADFKDLRGNVSEIERILKHPVFPSPGKFLK VKDYHDSVRRQIMQLNEQLKAVYEFQDLKDTIERAKNEADLLEDLQ EEIDLQSSVLNASIADSS ENIKKYYHISSSAEKKINETSSTINTSANTRND LLTILDLT LTKGNLSLERL KQIKIPDIQLNEKVCGDGPNVPCVPLPCGG ALCTGRKGRKCRGPGCHGSLT LSTNALQKAQEA KSIIRNLDKQVRGL KNQIESISEQAEVSKNNALQLREKLGNI RNQSDSEENINLFIKVKFNFL LEENVPPEDEK VANGVLDIHLPIPSQNLTDDELVKIQKHMQLCEDYRTD ENRLENEADGAQKLLVKAKAAEKAANILNLNDKTLNQLQQAQITQGR ANSTITQLTANITKIKKNVLQAEENQ TREMKSELELAKQRSGL EDGLSLL QTKLQRHQDHAVNAKVAESAQHQAQGSLEKEFEV LKQYAILQRKTS TTGLTKETL GKVKQLKDAAEKLAGDTEAKIRRIDLERKIQDLNLSRQ AKADQLRILELDQVVAIKNETIVEQEKKYARCYS
laminin subunit beta-4 isoform 2 precursor (LAMB4-isoform 2); SEQ ID NO: 41	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWQSENGLDHVSIRLDLEALFRFSHLILTFKTRPAAMLVE RSTDYGHNWKVKYFAKDCATSFNITSGQAQGVGDIVCDSKYSIDIEP STGGEVVLKVLDP SFEIENPYSPIQDLVTLTNLRINFTKLHTLGDALLG RRQNDSLDKYYALYEMIVRGSFCFNHASECRPMQKMRGDFVSPPG MVHGQVCQHNTDGPNCERCKDFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTGQHCDRCRPLFYRDP LKTISDPYACIPCECDPDGTISGGICVSHSDPALGSAQGLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCS YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAAGYFFAPLNFYLYEAEAEATTLQGLAPLGSETFGQ SPAVHVVLGEPVGNPVTWTGPGFARVLPAGALRFVANNIPFPVDFTI AIHYETQSAADWTVQIVVNPFGGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGESHAHSHVLDVSLGLIPQINSL ENF CSKQDLDEYQLHNCVEIASAMGPQVLPGACERLIISMSAKLHDGAVAC KCHPQGSVGS SCSRLGGQCCKPLVVGRCDCRSTG SYDLGHHGCHP CHCHPQGSKDTVCDQVTGQCPCHGEVSGRRCDRCLAGYFGFPSC HPC PCNRF AELCDPETGSCFNCGGFTTGRNCERCIDGYYGNPSSGQPCRPL CPDDPSSNQYFAHSCYQNLWSDVICNCLQGYTGTCQCECSTGFYGNP RISGAPCQPCACNNDIVTDPESCSRVTGECLRCLHNTQGANCLCKP GHYGSALNQT CRRCSCHASGVSPMECPGGGACLCDPVTGACPCLEPN VTGLACDRCADGYWNLVPGRCQSCDCDPRTSQSSHCDQARYFKAY
laminin subunit beta-4 isoform 3 precursor	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWQSENGLDHVSIRLDLEALFRFSHLILTFKTRPAAMLVE RSTDYGHNWKVKYFAKDCATSFNITSGQAQGVGDIVCDSKYSIDIEP

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Human Laminin	Sequence
(LAMB4-isoform 3); SEQ ID NO: 42	STGGEVVLKVLDPSEFEIENPYSPYIQDLVTLTNLRIINFTKLHTLGDALLG RRQNDSLDKYYYALYEMIVRGSCFCNGHASECRPMQMRGDVFSPPG MVHGQCVCQHNTDGPNCERCKDFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTGQHCDCRPLFYRDP LKTI SDPYACIPCECDPDGTISGGICVSHSDPALGSVAGQCLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCLS YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAAGYFPAPLNFYLYEAEAEATLQGLAPLGSSETFGQ SPAVHVVLGEPVGNPVTWTGPGFARVLPAGALRFVANNIPFPVDFTI AIHYETQSAADWTQIVVNPFGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGE SHAHSHVLVDSAAVQWHNLGSL QPPPECKQFSCFSFSPSSWDYREIPPHLANFCIFSRDGVSPHWPQWSQT PDLR
laminin subunit gamma-1 precursor (LAMC1); SEQ ID NO: 43	MRGSHRAAPALRPRGLWPVLAVLAAAAAGCAQAAMDECTDEGG RPQRCPMEFVNAAFNVTVVATNTCGTPPEEYCVQTVGTGVTKSCHLG DAGQPHLQHGAAFLTDYNNQADTTWWQSQTMLAGVQYPSINLTLH LGKAFDITYVRLKFHTSRPESFAIYKRTREDGPWIPYQYYSGCENTYS KANRGFIRTGDEQOALCTDEFSDISPLTGGNVAFSTLEGRPSAYNFDN SPVLQEWVTA TDIRVTLNRLNMTFGDEVFNPKVLKSYVYAI SDFAVGG RCKCNGHASECMKNEFDKLV CNCKHNTYGVDCCKLPPFNDRPWR ATAESASECLPCDCNGRSQECYFDPPELYRSTGHGGHCTNCQDNTDGA HCECRENFPRLGNNACSSCHCSFVGSLS TQCD SYGRCSCKPGVMGD KDCRCQPGFHSLEAGCRPCSCDPSGSDICENIETGRVCCKDNVEGFNC ERCKPGFNFLESSNPRGCTPCFCFGHSSVCTNAVGVSVYSISSTPQIDED GWRAEQRDGS EASLEWSSERQDI AVI SDSYFPRYFIAPAKFLGKQVLSY GQNL SFSFRVDRRDLRLS AEDLVLEGAGLRVSVPLIAQGN SYPSETTV KYVFRLEHATDYPWRPALTPPEFQKLLNNTS I KIRGTY SERSAGYLLD VTLASARPGPGVPATWVESCTCPVGYGGQFCMCLSGYRRETPNLPG YSPCVLCA CNGHSETCDEPETGVCMCRDNTAGPHCEKCS DGYGDSTA TSSDCQPCPCPGSSCAVVPKTKEVVCTNCPGTGTTKRCELCDGDFY GDPLGRNGPVR LCR LQCSDNI DPNAVGNCRNLTGCECLKCI YNTAGFY CDRC KDGFGNPLAPNPADKCKACNCLNYGTMKQOQSSCNPVGTQCE CLPHVTGQDCGACDPGFYNLQSGQGERCDCHALGSTNGQCDIRTGQ CECQPGITGQHCEVNHFGFPEGCKPCDCHPEGSLS LQCKDDGRC ECREGFVGNRCQCEENYFYNRSWPGCQCEPCACYRLVKDKVADHRV KLQELLES LIANLGTGDEMVTDAQAFEDRLKEABREVMDDLREAOQVVD VDQNLMDRLQRVNNLTSSQISRLQNI RNTI EETGNLAEQARAHVENTE RLIETASRELEKAKVAANVSVTQPESTGDPNNMTLLAEERKLAERH KQEAADDIVRVAKTANDTSTEAYNLLRLTAGENQTA FEI EELNRKYEQ AKNI SQDLEKQAAARVHEEAKRAGDKAVEIYASVAQLSPLDSE TLENEA NNIKMEAENLEQLIDQKLDKDYEDLREDMRGKELEVNKLEKGTBEQ TADQLLARADA AAKALAEAAKGRD TLQEAENDILNLLKDFDRRVND NKTAEEALR KIPAINQTI TEANEKTREAOQALGSAADATEAKNKAH EAERIASAVQKNATSKAEAEERTFAEVTDLDNEVNNMLKQLOEAEKE LKRKQDDADQMMAGMASQAAQEAENARKAKNSVTSLLS I INDL LEQLGQLD TVDLNKLNEIEGTLNKAKDEMKVSDLDRKVS DLENEAKK QEAAIMDYNRDIEEIMKDIRNLEDIRKTLPSGCFNTPSIEKP
laminin subunit gamma-2 isoform a precursor (LAMC2- isoform a); SEQ ID NO: 44	MPALWLGCCCLCFSLLLPAARATSRRVCD CNGKSRQCFDRELHRQTG NGFRCLNCDNDTGIHCEKCKNGFYRHRERDRCLPCNCSKGSLSAR CDNSGRCSCKPGVTGARCDRCLPGFHMLTDAGCTQDQRLDLSKDCD PAGIAGPCDAGRCVCKPAVTGERCDRCRSGYINLDGGNPEGCTQCFC YGHASACRSSAEYSVHKITSTFFHQVDVGKAVQRNGSPAKLQWSQRH QDVFSSAQRLDPVYFVAPAKFLGNQVSYGQSLSFYRVRDRGGRHPS AHDVILEGAGLRI TAPLMLGKTLPCGLTKTYTFRLNEHPSNNWSPQLS YFEYRRLRLNLTALRIRATYGEYSTGYIDNVTLSI SARPVSGAPAPWVEQ CICPVGYKGFQPCDCASGYKRDSARLPGFGTCIPCNQGGGACDPDTG DCYSGDENPDI ECADCP1GFYNDPHDPRSCKPCCHNGFSCSVMPETEE VVCNNCPGVTGARCEL CADGYGDFPGEHGPVRPCQPCQNNNVDP SASGNCDRLTGRCLKCIHNTAGIYCDQCKAGYFGDPLAPNPADKCRAC NCNPMGSEPVGCRSDGTVCVKPGFGGPNCEHGAFSPACYNQVKIQ MDQPMQQLQRMEALI SKAQGGDGVVDPTELEGRMQQAEQALQDI LR DAQISEGASRLGLQLAKVRSQENSYSRLDD LKMTVERVRALGSQY QNRVRDTHRLITQMQLS LAESEALSGNTNIPASDHVYGPNGFKSLAQE ATRLAESHVESASNMEQLTRETEDYSKQALS LVRKALHEGVGSGSGSP DGAVVQGLVEKLEKTKSLAQQLTREATQAEI EADRSYQHSRLDLSVS RLQGVSDQSPQVEAKRIKQKADSLSLVTRHMDPEFKRTQKNLGNWK EAAQQLLQNGKSGREKSDQLLSRANLAKSRAQEA LSGMGNATFYEVEI LKNLREFDLQVDRKAEAEAMKRLSYISQKVS DSDKTAQERALG SAAAADAQRKNGAGEALEI SSEIEQETIGSLNLEANVTADGALAMEKGL ASLKSEMEVEGELERKELEFDTNMDAVQMI TEAQKVDTRAKNAG VTIQDTLNTLDGLLHLMQPLSVDEEGLVLEQKLSRAKTQINSQLRP MMSLEERARQQRGHLHLETSIDGILADVKNLENIRDNLP GCYNTQ ALEQQ

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Human Laminin	Sequence
laminin subunit gamma-2 isoform b precursor (LAMC2-isoform b); SEQ ID NO: 45	<p>MPALWLGCCLCFSLLLPAARATSRRVCDNCGKSRQCI PDRELHRQTG NGFRCLNCNDNTDGIHCEKCKNGFYRHRERDRCLPCNCNSKGSLSAR CDNSGRCSCKPGVTGARCDRCLPGFHM LTDAGCTQDQRLDLSKDCD PAGIAGPCDAGRVCCKPAVTGERCDRCRSGYNYLDGNGPEGCTQCFC YGHSASCRSSAEYSVHKITSTFHQDVGWKAQVRNGSPAKLQWSQRH QDVFSSAQRLDPVYFVAPAKFLGNQQVSYGQSLSFYRVDGRGRHPS AHDVILEGAGLRI TAPLMP LKGLTLPCLTKTYTFRLNEHPSNNWSPQLS YFEYRLLRNL T ALRIRATYGEYSTGYIDNVTLISARPVSGAPAPWVEQ CIPCVPVYKQFCQDCASGYKRDSARLGPFGTCIPCNQGGGACDPDTG DCYSGDENPDIECADCP1GFYNDPHDPRSCPKPCCHNGFSCSVMPETEE VVCNNCPPGVTGARCEL CADGYFGDPFGEHGPVVRPCQPCQNNVDP SASGNCDRLTGRCLKCIHNTAGIYCDQCKAGYFGDPLAPNPADKCFRA CNCNPMGSEPVGCRSDGTCVCKPGFGGPNCEHGAFSPACYNQVKIQ MDQFMQQLQRMEALI SKAQGGDGVVDPTELEGRMQQAEQALQDILR DAQISEGASRSLGLQ LAKVRSQENSYSRLLDDLKMTVERVRALGSQY QNRVRDTHRLITQMQLSLAESEASLGNTNIPASDHVYVGNPFKSLAQE ATRLAE SHVESASNMEQLTRETEDYSKQALSLVRKALHEGVGSGSGSP DGAVVQGLVEKLEKTKSLAQQLTREATQAEIEADRSYQHSRLDLSVS RLQGVSDQSFQVEAKRIKQKADSLSLVTRHMEDEFKRTQKNLGNWK EEAQQLLQNGKSGREKSDQLLSRANLAKSRAQEALSMGNATFYEVES I LKNLREFDLQVNRKAEAEAMKRLSYISQKVSADSKTQQAERALG SAAADAQRAKNGAGEALEISSEIEQEIGSLNLEAVNTADGALAMEKGL ASLKSEMREVEGELERKELEFDTNMDAVQMVITEAQKVDTRAKNAG VTIQDTLNTLDGLLHLMGM</p>
laminin subunit gamma-3 precursor (LAMC3); SEQ ID NO: 46	<p>MAAAALLLGLALLAPRAAGAGMGACYDAGRPRCLPFVFNAAFGR LAQASHTCGSPPEDFCPHVGAAGAGAHQCQRCDAADPQRHEINASYLT DFHSQDESTWQSPSMAFGVQYPTSVNITLRLKGAIEITYVRLKPHTS RPESFAIYKRSRADGPWEPYQFYASQCCKTYGRPEGQYLRPGEDERVA FCTSEFSDISPLSGGNVAFSTLEGRPSAYNFEESPLQEWVSTELLISL DRLNTFGDDIFKDPKVLQSYAVSDPFSVGGRCCKNGHASECGPDVA GQLACRCQHNTTGTD CERCLPFFQDRPWARGTAEAAHECLPCNCSGR SEECTFDRELFRSTGHGGRCHCRDHTAGPHCERCQENFYHWDPRMP CQPCDCQSGAGSLHLQCDDTGTACKPTVTGWKCDRCLPGFHSLSEGG CRPCTCNPAGSLDTC DPRSGRCPCKENVGNLDCDRCPGT FNLPQHNP AGCSSCFYGHSKVCASTAQFQVHHILSDPHQGAEGWARSVGGSEH PPQWSPNGVLLSPEDEEELTAPEKFLGDQRFSGQPLILTFRVPPGDSPL PVQLRLEGTGLALSRLHSSLSGPQDAGHPREVELRFHLQETSEDVAPPL PPFHFQRLANLTLRLRVSPGSPAGPVFLTEVRLTSARPGLSPPASW VEICSCPTGYTGQFCESCAPGYKREMPQGGPYASCVPCTCNQHGTCDP NTGICVCSHHTEGPSCERCLPGFYGNPFAGQADDQPCPCPGQSACTTI PESREVVCTHCPPGQRGRRCVCDGFFGDPLGLFGHPQCHQCQCSG NVDNPAVGNCDPLSGHCLRCLHNTTGDHCEHCQEGFYGSALAPRPAD KMPCCSCHPQGSVSEMPCDPVTGQCSCLPHVTARDCSRCPYGGFFDL QPGRGCRSCKCHPLGSDQEDQCHPKTGQCTCRPGVTGQACDRCLGFF GFSIKGCRACRCSPLGAASAQCHENGTCVCRPGFEGYKCDRCHDNFFL TADGTHCQCPSCYALVKEEAALKARLTLTEGWLQGSDCGSPWGPL DILLGEAPRGDVIYQGH EILLPGAREAFLEQMSLEGAVKAAREQLQRL NKGARCAQAGSQKTCTQLADLEAVLESSEEEI LHAAAILASLEIPQEGP SQPTKWSHLATEARALARSHRDTATKIAATAWRALLASNTSYALLWN LLEGRVALETQRDLEDRYQEVAQAQKALRTAVAEVLP EAESVLATVQ QVGADTAPYLALLASPGALPQKRAEDLGLKAKALEKTVASWQHMA TEAARTLQTAQAATLRQTEPLTKLHQEARAALTAASSSVQAATVTVM GARTLLADLEGMKLQFPRPKDQAALQRKADSVSDRLADTRKKTQ AERMLGNAAPLSSAKKKGREAEVLAKDSAKLAKALLRERKQAHRR ASRLTSQTQATLQQAQQVLA SEARRQEEEAERVGAGLSEMEQQIRE SRISLEKDIETLSELLARLGLDTHQAPAQALNETQWALERLRLQLGSP GSLQRKLSLLEQESQQQLQIQGFESDLAETRADKQNL EAILHSLPENC ASWQ</p>

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Further exemplary peptides useful in the methods and compositions of the disclosure include:

SEQ ID NO:	Name (location) length	Peptide sequence
1	$\alpha 3_{3043-3067}$ (LG4) 25 aa.	RLV FALGTDGKKLR IKSKEKNDGK
9	$\alpha 3_{3031-3043}$ (LG4) 13 aa.	KNSFMALYLSKGR
2	$\alpha 3_{2932-2951}$ (Linker) 20 aa.	PPFLMLLKGSTRFNKTKTFR
3	$\alpha 4_{1521-1543}$ (LG4) 23 aa.	TLFLAHGRLVYMFNVGHKKLKIR
4	$\alpha 4_{1408-1434}$ (Linker) 27 aa.	PLFLLHKKGNLSKPKASQNKKGKSK
5	$\alpha 5_{3539-3550}$ (LG5) 12 aa.	TLPDVGLELEVR
6	$\alpha 5_{3417-3436}$ (LG4) 20 aa.	RQRSRPGRWHKVSVRWEKNR
10	$\alpha 5_{3312-3325}$ (Linker) 14 aa.	ARKASRRSRQPARH
7	$\alpha 5_{3300-3330}$ (Linker) 31 aa.	TPGLGPRGLQATARKASRRSRQPARHPACML
8	$\alpha 2PI_{1-8}$ $\alpha 3_{3043-3067}$ 33 aa.	NQEQVSPRLRVFALGTDGKKLR IKSKEKNDGK
11	$\alpha 2PI_{1-8}$ $\alpha 5_{3312-3325}$ 22 aa.	NQEQVSP LARKASRRSRQPARH
12	$\alpha 2PI_{1-8}$	NQEQVSP L
49	vWF A1	YIGLKDRKRPSELRR IASQVKYAC

In some embodiments, the compositions and methods comprise a peptide from a LG4 domain or fragment thereof. Exemplary LG4 domains are shown below:

SEQ ID NO:	Name	Sequence
13	LAMA3_ Human, LG4 domain aa2986-aa3150 (UniprotKB database Q16787)	ALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQT TSSRGLVFHTGTKN SFMALYLSKGR LVFALGTDGKKLR IKSKEKNDGKWH TVVFGHDGEGKRLVV DGLRAREGSLPGNST I S IRAPVYLGSPSPGKPK SLPTNSFVGC LKNFQLDSKPLYTPSSSFGVSSC
14	LAMA4_ Human, LG4 domain aa1469-aa1640	AYQYGGTANSRQEF EHLKGD FGA KSQFSIRLRT RSSHGMIFVVS DQEENDFM TLF LAHGRLVYMFNVGHKKLKIRS QEKYNDGLWHDVIFIRERS SGR LVIDGLRVLEESLP PTEATWIKGPIYLGGVAPG KAVKNVQINSIYSFSGCLSNLQ LNGASITSASQ

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SEQ ID NO:	Name	Sequence
5	(UniprotKB database Q16363)	TFSVTPC
15	LAMA5_ Human, LG4 domain aa3340-aa3513 (UniprotKB database O15230)	SYQFGGSLSSHLEFVGI LARHRNWPSLSMHVLP RSSRGLLLFTARLRPGSPSLALFLSNGHFVAQM EGLGTRLR AQSRQSRPGRWHKVSVRWEKNRIL LVTDGARAWSQEGPHRQH QGA EHPQPTL FVGG LPASSHSSKLPVTVGFSGCVKRLRLRHGRPLGAP TRMAGVTPC

In some embodiments, the compositions and methods include an engineered Laminin peptide comprising a factor XIIIa transglutaminase substrate domain from the $\alpha 2$ -plasmin inhibitor. Such exemplary peptides are described below:

SEQ ID NO:	Name	Sequence
25	16 Human $\alpha 2PI_{1-8}$ LAMA3_ LG4 ₂₉₈₆₋₃₁₅₀	NQEQVSP LGGSGALQFGDIPTSHLLFKLP QELLKPRSQFAVDMQTSSRGLVFHTGTKN SFMALYLSKGR LVFALGTDGKKLR IKSKEKNDGKWH TVVFGHDGEGKRLVV DGLRAREGSLPGNST I S IRAPVYLGSPSPGKPKSLPTNSFVGC LKNFQLDSKPLYTPSSSFGVSSC
30	17 Human $\alpha 2PI_{1-8}$ LAMA4_ LG4 ₁₄₆₉₋₁₆₄₀	NQEQVSP LGGSGAYQYGGTANSRQEF EHLKGD FGA KSQFSIRLRT RSSHGMIFVVS DQEENDFM TLF LAHGRLVYMFNVGHKKLKIRS QEKYNDGLWHDVIFIRERS SGR LVIDGLRVLEESLP PTEATWIKGPIYLGGVAPG KAVKNVQINSIYSFSGCLSNLQ LNGASITSASQ TFSVTPC
40	18 Human $\alpha 2PI_{1-8}$ LAMA5_ LG4 ₃₃₄₀₋₃₅₁₃	NQEQVSP LGGSGSYQFGGSLSSHLEFVGI LARHRNWPSLSMHVLP RSSRGLLLFTARLRPGSPSLALFLSNGHFVAQM EGLGTRLR AQSRQSRPGRWHKVSVRWEKNRIL LVTDGARAWSQEGPHRQH QGA EHPQPTL FVGG LPASSHSSKLPVTVGFSGCVKRLRLRHGRPLGAP TRMAGVTPC

In some embodiments, the compositions and methods comprise peptides comprising a collagen binding peptide. Exemplary collagen binding peptides are shown below.

SEQ ID NO:	Name	Sequence
55	47 vWF A3 domain	CSQPLDVILLLD GSSSFPAS YFDEMKSFAKAFISK ANIGPRLTQVSVLQY GSI TTIDV PWNVPEKAHLLS LVDVMQREGGSPS IQGDLGFAVRVYLTSEM HGAR PGASKAVVILVTDVSVDSV DAAAADAARSNRVTV FPIGIGDRYDAAQLRILAGPAGDSNVV KLR IEDLPTMVT LGNSFLHKLCSGFVRICTG
60	48 Decorin	CGPFQQRGLFDFMLEDEASGIGPEVPD RDRDFE PSLGPVCFRCQCHLRV VQCSDLGLDKVPKDLPPD TLLDLQNNKI TEIKD GDFKNLKNLHALLLVNNKISK VSPGAF TPLVKLERLYLSKNQLKELPEKMPKTLQ ELRAHENEI TKVRKVT FNGNLNQMIVI ELGTNPLKS SGIENGAFQGMKLSYIRIADTNI TSI PQGLPPSLTE LHL DGNKISRVDAA SLKGLN LAKLGLS FNSISAV

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SEQ ID NO.	Name	Sequence
		DNGSLANTPHLRELHLDNNKLTRVPGGLAEHKYI QVVYLHNNNI SVVGSSDFCPPGHNTKKASYSGVS LFSNFPVQYWEIQPSTFRFCVYVRSIAIQLGNYK

The growth factor-binding peptide may be a peptide with 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identity (or any derivable range therein) to a peptide of the disclosure, such as peptides, proteins, or polypeptides defined by any one of SEQ ID NOS:1-50. The peptide or polypeptide may have one or more conservative or non-conservative substitutions. Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide, with or without the loss of other functions or properties. Substitutions may be conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine. Alternatively, substitutions may be non-conservative such that a function or activity of the polypeptide is affected. Non-conservative changes typically involve substituting a residue with one that is chemically dissimilar, such as a polar or charged amino acid for a nonpolar or uncharged amino acid, and vice versa.

Embodiments of the disclosure include a peptide/polypeptide that is at least, at most, or exactly 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical (or any derivable range therein) to a peptide or polypeptide/polypeptide that has at least, at most, or exactly 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein to a peptide/polypeptide that starts at position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16,

17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, or 450 of any one of SEQ ID NOS:1-50.

The polypeptides or peptides described herein may include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more (or any derivable range therein) variant amino acids within at least, or at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein, of a peptide or polypeptide of the disclosure, such as peptides, proteins, or polypeptides defined by any one of SEQ ID NOS:1-50.

A polypeptide segment as described herein may include 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85,

86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein of a peptide or polypeptide of the disclosure, such as peptides, proteins, or polypeptides defined by any one of SEQ ID NOS:1-50.

The polypeptides or peptides described herein may be of a fixed length of at least, at most, or exactly 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more amino acids (or any derivable range therein) or a peptide or polypeptide of the disclosure, such as peptides, proteins, or polypeptides defined by any one of SEQ ID NOS:1-50.

A linker sequence may be included in the peptide construction. For example, a linker having at least, at most, or exactly 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more amino acids (or any derivable range therein) may separate a peptide of the disclosure, such as peptides, proteins, or polypeptides defined by any one of SEQ ID NOS:1-50, to an attached moiety, such as a transglutaminase-reactive peptide, a collagen binding peptide, cell adhesion moiety, tag, or functional moiety. In some embodiments, the linker comprises a glycine serine linker. In some embodiments, the linker comprises (GSGG)_x (SEQ ID NO:60), wherein x=1-6. In some embodiments, x=2. In some embodiments, x=1, 2, 3, 4, 5, or 6 (or any derivable range therein). In some embodiments, the linker comprises GSGGGSGG (SEQ ID NO:61).

B. Exemplary Attachments to the Growth Factor Binding Peptides/Polypeptides

Embodiments include a growth factor binding peptide attached to moieties such as a functional moiety. In some

embodiments, the functional moiety may be a therapeutic agent, marker, cell adhesion molecule, antigen, protein, protein drug, or cytokine. In some embodiments, the growth factor binding peptide is attached to a second growth factor binding peptide. In some embodiments, the growth factor binding peptide is attached to a chemical moiety, such as a marker or fluorescent marker. The fusion comprises the peptides conjugated directly or indirectly to each other. The peptides may be directly conjugated to each other or indirectly through a linker. The linker may be a peptide, a polymer, an aptamer, a nucleic acid, or a particle. The particle may be, e.g., a microparticle, a nanoparticle, a polymersome, a liposome, or a micelle. The polymer may be, e.g., natural, synthetic, linear, or branched. A fusion protein that comprises the first peptide and the second peptide is an example of a molecular fusion of the peptides, with the fusion protein comprising the peptides directly joined to each other or with intervening linker sequences and/or further sequences at one or both ends. The conjugation to the linker may be through covalent bonds. Methods include preparing a molecular fusion or a composition comprising the molecular fusion, including such a composition in a pharmaceutically acceptable form.

Embodiments include a molecular fusion of a polypeptide that comprises a growth factor binding peptide and a transglutaminase (TG)-reactive peptide. An embodiment of a TG-reactive peptide is a peptide that comprises residues 1-8 of alpha 2-plasmin inhibitor (NQEQVSPL) (SEQ ID NO:12). In some embodiments, the TG-reactive peptide is at the amino terminus of the growth factor binding peptide. In some embodiments, the TG-reactive peptide is at the carboxy terminus of the growth factor binding peptide. Embodiments include such a polypeptide being a recombinant fusion polypeptide. The molecular fusion may be further comprising a cell adhesion moiety having a specific binding affinity for a cell adhesion molecule. Various cell adhesion moieties are known, for instance, wherein the cell adhesion moiety comprises a ligand for a glycoprotein or a cell surface receptor. Or the cell adhesion moiety may comprise a ligand with specific binding to the cell adhesion molecule and the cell adhesion molecule is a cell surface receptor chosen from the group consisting of an integrin, and a cadherin. Or the cell adhesion moiety may comprise an integrin-binding peptide such as Tenascin III3, an RGD sequence.

In some aspects, the peptide or polypeptide of the disclosure is attached to a tag. The tag may be a purification tag, a signaling sequence, a detectable marker, a post-translational modifier, or a targeting moiety. In some embodiments, the peptide or polypeptide is attached to a functional moiety such as an enzyme, a fluorescent compound, or a therapeutic agent. Detectable markers include, for example, a radioactive atom, a chromophore, a fluorophore, or the like. Other examples of tags or functional moieties include enzymes, radioisotopes, fluorochromes, chemiluminescent compounds, dyes, and proteins. Examples of luminescent labels that produce signals include, but are not limited to bioluminescence and chemiluminescence. Detectable luminescence response generally comprises a change in, or an occurrence of, a luminescence signal. Suitable methods and luminophores for luminescently labeling assay components are known in the art and described for example in Haugland, Richard P. (1996) Handbook of Fluorescent Probes and Research Chemicals (6.sup.th ed.). Examples of luminescent probes include, but are not limited to, aequorin and luciferases. Examples of suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhod-

amine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue™, and Texas Red. Other suitable optical dyes are described in the Haugland, Richard P. (1996) Handbook of Fluorescent Probes and Research Chemicals (6.sup.th ed.). In another aspect, the fluorescent label is functionalized to facilitate covalent attachment to a cellular component present in or on the surface of the cell or tissue such as a cell surface marker. Suitable functional groups, including, but not are limited to, isothiocyanate groups, amino groups, haloacetyl groups, maleimides, succinimidyl esters, and sulfonyl halides, all of which may be used to attach the fluorescent label to a second molecule. The choice of the functional group of the fluorescent label will depend on the site of attachment to either a linker, the agent, the marker, or the second labeling agent. Attachment of a tag or functional moiety may be either directly to the cellular component or compound or alternatively, can be via a linker. Suitable binding pairs for use in indirectly linking the fluorescent label to the intermediate include, but are not limited to, antigens/antibodies, e.g., rhodamine/anti-rhodamine, biotin/avidin and biotin/streptavidin.

In some embodiments, the functional moiety comprises an imaging agent. Exemplary imaging agents include gadolinium, iodine, barium, or a radio pharmaceutical such as calcium-47, carbon-11, carbon-14, chromium-51, cobalt-57, cobalt-58, erbium-169, fluorine-18, gallium-67, gallium-68, hydrogen-3, indium-111, iodine-123, iodine-125, iodine-131, iron-59, krypton-81m, nitrogen-13, oxygen-15, phosphorus-32, radium-223, rubidium-82, samarium-153, selenium-75, sodium-22, sodium-24, strontium-89, technetium-99m, thallium-201, xenon-133, and yttrium-90.

The term molecular fusion, or the term conjugated, refers to direct or indirect association by chemical bonds, including covalent, electrostatic ionic, or charge-charge. In some embodiments, the conjugation is through a peptide bond. The conjugation creates a unit that is sustained by chemical bonding. Direct conjugation refers to chemical bonding to the agent, with or without intermediate linkers or chemical groups. Indirect conjugation refers to chemical linkage to a carrier. The carrier may largely encapsulate the agent, e.g., a polymersome, a liposome or micelle or some types of nanoparticles, or have the agent on its surface, e.g., a metallic nanoparticle or bead, or both, e.g., a particle that includes some of the agent in its interior as well as on its exterior. The carrier may also encapsulate an antigen for immunotolerance. For instance a polymersome, liposome, or a particle may be made that encapsulates the antigen. The term encapsulate means to cover entirely, effectively without any portion being exposed, for instance, a polymersome may be made that encapsulates an antigen or an agent.

Conjugation may be accomplished by covalent bonding of the peptide to another molecule, with or without use of a linker. The formation of such conjugates is within the skill of artisans and various techniques are known for accomplishing the conjugation, with the choice of the particular technique being guided by the materials to be conjugated. The addition of amino acids to the polypeptide (C- or N-terminal) which contain ionizable side chains, i.e. aspartic acid, glutamic acid, lysine, arginine, cysteine, histidine, or tyrosine, and are not contained in the active portion of the polypeptide sequence, serve in their unprotonated state as a potent nucleophile to engage in various bioconjugation reactions with reactive groups attached to polymers, i.e. homo- or hetero-bi-functional PEG (e.g., Lutolf and Hubbell, *Biomacromolecules* 2003; 4:713-22, Hermanson, *Bioconjugate Techniques*, London. Academic Press Ltd; 1996).

In some embodiments, a soluble polymer linker is used, and may be administered to a patient in a pharmaceutically acceptable form. Or a drug may be encapsulated in polymersomes or vesicles or covalently attached to the peptide ligand.

The molecular fusion may comprise a particle. The growth factor binding peptide may be attached to the particle. An antigen, agent, or other substance may be in or on the particle. Examples of nanoparticles, micelles, and other particles are found at, e.g., US 2008/0031899, US 2010/0055189, US 2010/0003338, which applications are hereby incorporated by reference herein for all purposes, including combining the same with a ligand as set forth herein; in the case of conflict, however, the instant specification controls.

Nanoparticles may be prepared as collections of particles having an average diameter of between about 10 nm and about 200 nm, including all ranges and values between the explicitly articulated bounds, e.g., from about 20 to about 200, and from about 20 to about 40, to about 70, or to about 100 nm, depending on the polydispersity which is yielded by the preparative method. Various nanoparticle systems can be utilized, such as those formed from copolymers of poly(ethylene glycol) and poly(lactic acid), those formed from copolymers of poly(ethylene oxide) and poly(beta-amino ester), and those formed from proteins such as serum albumin. Other nanoparticle systems are known to those skilled in these arts. See also Devalapally et al., *Cancer Chemother Pharmacol.*, Jul. 25, 2006; Langer et al., *International Journal of Pharmaceutics*, 257:169-180 (2003); and Tobio et al., *Pharmaceutical Research*, 15(2):270-275 (1998).

Larger particles of more than about 200 nm average diameter incorporating the growth factor binding peptides may also be prepared, with these particles being termed microparticles herein since they begin to approach the micron scale and fall approximately within the limit of optical resolution. For instance, certain techniques for making microparticles are set forth in U.S. Pat. Nos. 5,227,165, 6,022,564, 6,090,925, and 6,224,794.

Functionalization of nanoparticles to employ targeting capability requires association of the targeting polypeptide with the particle, e.g., by covalent binding using a bioconjugation technique, with choice of a particular technique being guided by the particle or nanoparticle, or other construct, that the polypeptide is to be joined to. In general, many bioconjugation techniques for attaching peptides to other materials are well known and the most suitable technique may be chosen for a particular material. For instance, additional amino acids may be attached to the polypeptide sequences, such as a cysteine in the case of attaching the polypeptide to thiol-reactive molecules.

The molecular fusion may comprise a polymer. The polymer may be branched or linear.

The molecular fusion may comprise a dendrimer. In general, soluble hydrophilic biocompatible polymers may be used so that the conjugate is soluble and is bioavailable after introduction into the patient. Examples of soluble polymers are polyvinyl alcohols, polyethylene imines, and polyethylene glycols (a term including polyethylene oxides) having a molecular weight of at least 100, 400, or between 100 and 400,000 (with all ranges and values between these explicit values being contemplated). Solubility in this context refers to a solubility in water or physiological saline of at least 1 gram per liter. Domains of biodegradable polymers may also be used, e.g., polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polycaprolactones, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, and polycyanoacylates.

II. NUCLEIC ACIDS

In certain embodiments, the current disclosure concerns recombinant polynucleotides encoding the proteins, polypeptides, and peptides of the disclosure.

As used in this application, the term “polynucleotide” refers to a nucleic acid molecule that either is recombinant or has been isolated free of total genomic nucleic acid. Included within the term “polynucleotide” are oligonucleotides (nucleic acids of 100 residues or less in length), recombinant vectors, including, for example, plasmids, cosmids, phage, viruses, and the like. Polynucleotides include, in certain aspects, regulatory sequences, isolated substantially away from their naturally occurring genes or protein encoding sequences. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be RNA, DNA (genomic, cDNA or synthetic), analogs thereof, or a combination thereof. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide.

In this respect, the term “gene,” “polynucleotide,” or “nucleic acid” is used to refer to a nucleic acid that encodes a protein, polypeptide, or peptide (including any sequences required for proper transcription, post-translational modification, or localization). As will be understood by those in the art, this term encompasses genomic sequences, expression cassettes, cDNA sequences, and smaller engineered nucleic acid segments that express, or may be adapted to express, proteins, polypeptides, domains, peptides, fusion proteins, and mutants. A nucleic acid encoding all or part of a polypeptide may contain a contiguous nucleic acid sequence of: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1000, 1010, 1020, 1030, 1040, 1050, 1060, 1070, 1080, 1090, 1095, 1100, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 9000, 10000, or more nucleotides, nucleosides, or base pairs, including all values and ranges there between, of a polynucleotide encoding one or more amino acid sequence described or referenced herein. It also is contemplated that a particular polypeptide may be encoded by nucleic acids containing variations having slightly different nucleic acid sequences but, nonetheless, encode the same or substantially similar protein.

In particular embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode a polypeptide or peptide of the disclosure. The term “recombinant” may be used in conjunction with a polynucleotide or polypeptide and generally refers to a polypeptide or polynucleotide produced and/or manipulated *in vitro* or that is a replication product of such a molecule.

In other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode a polypeptide or peptide of the disclosure.

The nucleic acid segments used in the current disclosure can be combined with other nucleic acid sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary con-

siderably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant nucleic acid protocol. In some cases, a nucleic acid sequence may encode a polypeptide sequence with additional heterologous coding sequences, for example to allow for purification of the polypeptide, transport, secretion, post-translational modification, or for therapeutic benefits such as targeting or efficacy. As discussed above, a tag or other heterologous polypeptide may be added to the modified polypeptide-encoding sequence, wherein “heterologous” refers to a polypeptide that is not the same as the modified polypeptide.

In certain embodiments, the current disclosure provides polynucleotide variants having substantial identity to the sequences disclosed herein; those comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher sequence identity, including all values and ranges there between, compared to a polynucleotide sequence of this disclosure using the methods described herein (e.g., BLAST analysis using standard parameters).

The disclosure also contemplates the use of polynucleotides which are complementary to all the above described polynucleotides.

A. Vectors

Polypeptides of the disclosure may be encoded by a nucleic acid molecule comprised in a vector. The term “vector” is used to refer to a carrier nucleic acid molecule into which a heterologous nucleic acid sequence can be inserted for introduction into a cell where it can be replicated and expressed. A nucleic acid sequence can be “heterologous,” which means that it is in a context foreign to the cell in which the vector is being introduced or to the nucleic acid in which is incorporated, which includes a sequence homologous to a sequence in the cell or nucleic acid but in a position within the host cell or nucleic acid where it is ordinarily not found. Vectors include DNAs, RNAs, plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (e.g., YACs). One of skill in the art would be well equipped to construct a vector through standard recombinant techniques (for example Sambrook et al., 2001; Ausubel et al., 1996, both incorporated herein by reference). In addition to encoding a polypeptide of the disclosure, the vector can encode other polypeptide sequences such as a one or more other bacterial peptide, a tag, or an immunogenicity enhancing peptide. Useful vectors encoding such fusion proteins include pIN vectors (Inouye et al., 1985), vectors encoding a stretch of histidines, and pGEX vectors, for use in generating glutathione S-transferase (GST) soluble fusion proteins for later purification and separation or cleavage. In some embodiments, the vector comprises pSeqTag-A or pcDNA3.1.

The term “expression vector” refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. Expression vectors can contain a variety of “control sequences,” which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described herein.

B. Promoters and Enhancers

A “promoter” is a control sequence. The promoter is typically a region of a nucleic acid sequence at which

initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors. The phrases "operatively positioned," "operatively linked," "under control," and "under transcriptional control" mean that a promoter is in a correct functional location and/or orientation in relation to a nucleic acid sequence to control transcriptional initiation and expression of that sequence. A promoter may or may not be used in conjunction with an "enhancer," which refers to a cis-acting regulatory sequence involved in the transcriptional activation of a nucleic acid sequence.

Naturally, it may be important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type or organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters, enhancers, and cell type combinations for protein expression (see Sambrook et al., 2001, incorporated herein by reference). The promoters employed may be constitutive, tissue-specific, or inducible and in certain embodiments may direct high level expression of the introduced DNA segment under specified conditions, such as large-scale production of recombinant proteins or peptides.

Various elements/promoters may be employed in the context of the present invention to regulate the expression of a gene. Examples of such inducible elements, which are regions of a nucleic acid sequence that can be activated in response to a specific stimulus, include but are not limited to Immunoglobulin Heavy Chain (Banerji et al., 1983; Gilles et al., 1983; Grosschedl et al., 1985; Atchinson et al., 1986, 1987; Imler et al., 1987; Weinberger et al., 1984; Kiledjian et al., 1988; Porton et al.; 1990), Immunoglobulin Light Chain (Queen et al., 1983; Picard et al., 1984), T Cell Receptor (Luria et al., 1987; Winoto et al., 1989; Redondo et al.; 1990), HLA DQ α and/or DQ β (Sullivan et al., 1987), β Interferon (Goodbourn et al., 1986; Fujita et al., 1987; Goodbourn et al., 1988), Interleukin-2 (Greene et al., 1989), Interleukin-2 Receptor (Greene et al., 1989; Lin et al., 1990), MHC Class II 5 (Koch et al., 1989), MHC Class II HLA-DR α (Sherman et al., 1989), β -Actin (Kawamoto et al., 1988; Ng et al.; 1989), Muscle Creatine Kinase (MCK) (Jaynes et al., 1988; Horlick et al., 1989; Johnson et al., 1989), Prealbumin (Transthyretin) (Costa et al., 1988), Elastase I (Ornitz et al., 1987), Metallothionein (MTII) (Karin et al., 1987; Culotta et al., 1989), Collagenase (Pinkert et al., 1987; Angel et al., 1987), Albumin (Pinkert et al., 1987; Tronche et al., 1989, 1990), α -Fetoprotein (Godbout et al., 1988; Campere et al., 1989), γ -Globin (Bodine et al., 1987; Perez-Stable et al., 1990), β -Globin (Trudel et al., 1987), c-fos (Cohen et al., 1987), c-Ha-Ras (Triesman, 1986; Deschamps et al., 1985), Insulin (Edlund et al., 1985), Neural Cell Adhesion Molecule (NCAM) (Hirsh et al., 1990), α 1-Antitrypsin (Latimer et al., 1990), H2B (TH2B) Histone (Hwang et al., 1990), Mouse and/or Type I Collagen (Ripe et al., 1989), Glucose-Regulated Proteins (GRP94 and GRP78) (Chang et al., 1989), Rat Growth Hormone (Larsen et al., 1986), Human Serum Amyloid A (SAA) (Edbrooke et al., 1989), Troponin I (TN I) (Yutzey et al., 1989), Platelet-Derived Growth Factor (PDGF) (Pech et al., 1989), Duchenne Muscular Dystrophy (Klamut et al., 1990), SV40 (Banerji et al., 1981; Moreau et al., 1981; Sleigh et al., 1985; Firak et al., 1986; Herr et al., 1986; Imbra et al., 1986; Kadesch et al., 1986; Wang et al., 1986; Ondek et al., 1987; Kuhl et al., 1987; Schaffner et al., 1988), Polyoma (Swartzendruber et al., 1975; Vasseur et al., 1980; Katinka et al., 1980, 1981; Tyndell et al., 1981;

Dandolo et al., 1983; de Villiers et al., 1984; Hen et al., 1986; Satake et al., 1988; Campbell et al., 1988), Retroviruses (Kriegler et al., 1982, 1983; Levinson et al., 1982; Kriegler et al., 1983, 1984a, b, 1988; Bosze et al., 1986; Miksicek et al., 1986; Celander et al., 1987; Thiesen et al., 1988; Celander et al., 1988; Choi et al., 1988; Reisman et al., 1989), Papilloma Virus (Campo et al., 1983; Lusky et al., 1983; Spandidos and Wilkie, 1983; Spalholz et al., 1985; Lusky et al., 1986; Cripe et al., 1987; Gloss et al., 1987; Hirochika et al., 1987; Stephens et al., 1987), Hepatitis B Virus (Bulla et al., 1986; Jameel et al., 1986; Shaul et al., 1987; Spandau et al., 1988; Vannice et al., 1988), Human Immunodeficiency Virus (Muesing et al., 1987; Hauber et al., 1988; Jakobovits et al., 1988; Feng et al., 1988; Takebe et al., 1988; Rosen et al., 1988; Berkhout et al., 1989; Laspia et al., 1989; Sharp et al., 1989; Braddock et al., 1989), Cytomegalovirus (CMV) IE (Weber et al., 1984; Boshart et al., 1985; Foecking et al., 1986), Gibbon Ape Leukemia Virus (Holbrook et al., 1987; Quinn et al., 1989).

Inducible elements include, but are not limited to MT II—Phorbol Ester (TFA)/Heavy metals (Palmiter et al., 1982; Haslinger et al., 1985; Searle et al., 1985; Stuart et al., 1985; Imagawa et al., 1987; Karin et al., 1987; Angel et al., 1987b; McNeall et al., 1989); MMTV (mouse mammary tumor virus)—Glucocorticoids (Huang et al., 1981; Lee et al., 1981; Majors et al., 1983; Chandler et al., 1983; Lee et al., 1984; Ponta et al., 1985; Sakai et al., 1988); β -Interferon—poly(rI)/poly(rc) (Tavernier et al., 1983); Adenovirus 5 E2—E1A (Imperiale et al., 1984); Collagenase—Phorbol Ester (TPA) (Angel et al., 1987a); Stromelysin—Phorbol Ester (TPA) (Angel et al., 1987b); SV40—Phorbol Ester (TPA) (Angel et al., 1987b); Murine MX Gene—Interferon, Newcastle Disease Virus (Hug et al., 1988); GRP78 Gene—A23187 (Resendez et al., 1988); α -2-Macroglobulin—IL-6 (Kunz et al., 1989); Vimentin—Serum (Rittling et al., 1989); MEW Class I Gene H-2kb—Interferon (Blanar et al., 1989); HSP70—E1A/SV40 Large T Antigen (Taylor et al., 1989, 1990a, 1990b); Proliferin—Phorbol Ester/TPA (Mordacq et al., 1989); Tumor Necrosis Factor—PMA (Hensel et al., 1989); and Thyroid Stimulating Hormone α Gene—Thyroid Hormone (Chatterjee et al., 1989).

The particular promoter that is employed to control the expression of peptide or protein encoding polynucleotide of the invention is not believed to be critical, so long as it is capable of expressing the polynucleotide in a targeted cell, preferably a bacterial cell. Where a human cell is targeted, it is preferable to position the polynucleotide coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include either a bacterial, human or viral promoter.

C. Initiation Signals and Internal Ribosome Binding Sites (IRES)

A specific initiation signal also may be required for efficient translation of coding sequences. These signals include the ATG initiation codon or adjacent sequences. Exogenous translational control signals, including the ATG initiation codon, may need to be provided. One of ordinary skill in the art would readily be capable of determining this and providing the necessary signals.

In certain embodiments of the invention, the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988; Macejak and

Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message (see U.S. Pat. Nos. 5,925,565 and 5,935,819, herein incorporated by reference).

D. Selectable and Screenable Markers

In certain embodiments of the invention, cells containing a nucleic acid construct of the current disclosure may be identified *in vitro* or *in vivo* by encoding a screenable or selectable marker in the expression vector. When transcribed and translated, a marker confers an identifiable change to the cell permitting easy identification of cells containing the expression vector. Generally, a selectable marker is one that confers a property that allows for selection. A positive selectable marker is one in which the presence of the marker allows for its selection, while a negative selectable marker is one in which its presence prevents its selection. An example of a positive selectable marker is a drug resistance marker. As an alternative, 2A peptides could be used to introduce ribosomal skips to enable expression of multiple polypeptidic or protein sequences.

E. Host Cells

As used herein, the terms "cell," "cell line," and "cell culture" may be used interchangeably. All of these terms also include their progeny, which is any and all subsequent generations. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations. In the context of expressing a heterologous nucleic acid sequence, "host cell" refers to a prokaryotic or eukaryotic cell, and it includes any transformable organism that is capable of replicating a vector or expressing a heterologous gene encoded by a vector. A host cell can, and has been, used as a recipient for vectors or viruses. A host cell may be "transfected" or "transformed," which refers to a process by which exogenous nucleic acid, such as a recombinant protein-encoding sequence, is transferred or introduced into the host cell. A transformed cell includes the primary subject cell and its progeny.

Host cells may be derived from prokaryotes or eukaryotes, including bacteria, yeast cells, insect cells, and mammalian cells for replication of the vector or expression of part or all of the nucleic acid sequence(s). Numerous cell lines and cultures are available for use as a host cell, and they can be obtained through the American Type Culture Collection (ATCC), which is an organization that serves as an archive for living cultures and genetic materials (www.atcc.org).

F. Expression Systems

Numerous expression systems exist that comprise at least a part or all of the compositions discussed above. Prokaryote- and/or eukaryote-based systems can be employed for use with the present invention to produce nucleic acid sequences, or their cognate polypeptides, proteins and peptides. Many such systems are commercially and widely available.

The insect cell/baculovirus system can produce a high level of protein expression of a heterologous nucleic acid segment, such as described in U.S. Pat. Nos. 5,871,986, 4,879,236, both herein incorporated by reference, and which can be bought, for example, under the name MAXBAC® 2.0 from INVITROGEN® and BACPACK™ BACULOVIRUS EXPRESSION SYSTEM FROM CLONTECH®.

In addition to the disclosed expression systems of the invention, other examples of expression systems include STRATAGENE®'s COMPLETE CONTROL™ Inducible

Mammalian Expression System, which involves a synthetic ecdysone-inducible receptor, or its pET Expression System, an *E. coli* expression system. Another example of an inducible expression system is available from INVITROGEN®, which carries the T-REX™ (tetracycline-regulated expression) System, an inducible mammalian expression system that uses the full-length CMV promoter. INVITROGEN® also provides a yeast expression system called the *Pichia methanolica* Expression System, which is designed for high-level production of recombinant proteins in the methylotrophic yeast *Pichia methanolica*. One of skill in the art would know how to express a vector, such as an expression construct, to produce a nucleic acid sequence or its cognate polypeptide, protein, or peptide.

III. COMPOSITIONS

In some embodiments, pharmaceutical compositions are administered to a subject. Different aspects involve administering an effective amount of a composition to a subject. In some embodiments, a composition comprising a peptide of the disclosure may be administered to the subject or patient to treat wounds or facilitate wound, tissue, or bone repair. Additionally, such compositions can be administered in combination with an additional therapy.

A. Carriers and Excipients

Pharmaceutically acceptable carriers or excipients may be used to deliver embodiments as described herein. Excipient refers to an inert substance used as a diluent or vehicle for a therapeutic agent. Pharmaceutically acceptable carriers are used, in general, with a compound (eg. peptide of the disclosure) so as to make the compound useful for a therapy or as a product. In general, for any substance, a carrier is a material that is combined with the substance for delivery to an animal. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. In some cases the carrier is essential for delivery, e.g., to solubilize an insoluble compound for liquid delivery; a buffer for control of the pH of the substance to preserve its activity; or a diluent to prevent loss of the substance in the storage vessel. In other cases, however, the carrier is for convenience, e.g., a liquid for more convenient administration. Pharmaceutically acceptable salts of the compounds described herein may be synthesized according to methods known to those skilled in the arts. Thus a pharmaceutically acceptable compositions are highly purified to be free of contaminants, are sterile, biocompatible and not toxic, and further may include a carrier, salt, or excipient suited to administration to a patient. In the case of water as the carrier, the water is highly purified and processed to be free of contaminants, e.g., endotoxins.

The compounds described herein may be administered in admixture with suitable pharmaceutical diluents, excipients, extenders, or carriers (termed herein as a pharmaceutically acceptable carrier, or a carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. Thus the deliverable compound may be made in a form suitable for oral, rectal, topical, intravenous injection, intra-articular injection, intradermal, intramuscular, and/or parenteral administration. Carriers include solids or liquids, and the type of carrier is chosen based on the type of administration being used. Suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents may be included as carriers, e.g., for pills. For instance, an active component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as

lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. The compounds can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. The active compounds can also be administered parentally, in sterile liquid dosage forms. Buffers for achieving a physiological pH or osmolarity may also be used.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should 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 also 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), suitable mixtures thereof, and vegetable oils. 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. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the 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, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. The term "pharmaceutically acceptable carrier," means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali

or organic salts of acidic residues such as carboxylic acids; and the like. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods.

B. Dosage

Some variation in dosage will necessarily occur depending on the condition of the subject. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. An effective amount of therapeutic or prophylactic composition is determined based on the intended goal. The term "unit dose" or "dosage" refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the composition calculated to produce the desired responses discussed above in association with its administration, i.e., the appropriate route and regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the effects desired. Precise amounts of the composition also depend on the judgment of the practitioner and are peculiar to each individual. Factors affecting dose include physical and clinical state of the subject, route of administration, intended goal of treatment (alleviation of symptoms versus cure), and potency, stability, and toxicity of the particular composition.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically or prophylactically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above.

Typically, for a human adult (weighing approximately 70 kilograms), from about 0.1 mg to about 3000 mg (including all values and ranges there between), or from about 5 mg to about 1000 mg (including all values and ranges there between), or from about 10 mg to about 100 mg (including all values and ranges there between), of a compound are administered. It is understood that these dosage ranges are by way of example only, and that administration can be adjusted depending on the factors known to the skilled artisan.

In certain embodiments, a subject is administered about, at least about, or at most about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 410, 420, 425, 430, 440, 441,

450, 460, 470, 475, 480, 490, 500, 510, 520, 525, 530, 540, 550, 560, 570, 575, 580, 590, 600, 610, 620, 625, 630, 640, 650, 660, 670, 675, 680, 690, 700, 710, 720, 725, 730, 740, 750, 760, 770, 775, 780, 790, 800, 810, 820, 825, 830, 840, 850, 860, 870, 875, 880, 890, 900, 910, 920, 925, 930, 940, 950, 960, 970, 975, 980, 990, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, 4100, 4200, 4300, 4400, 4500, 4600, 4700, 4800, 4900, 5000, 6000, 7000, 8000, 9000, 10000 milligrams (mg) or micrograms (mcg) or $\mu\text{g}/\text{kg}$ or micrograms/kg/minute or $\text{mg}/\text{kg}/\text{min}$ or micrograms/kg/hour or $\text{mg}/\text{kg}/\text{hour}$, or any range derivable therein of an agent of the disclosure (e.g. growth factor, cytokine, peptide, polypeptide, functional moiety, etc. . . .).

A dose may be administered on an as needed basis or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, or 24 hours (or any range derivable therein) or 1, 2, 3, 4, 5, 6, 7, 8, 9, or times per day (or any range derivable therein). A dose may be first administered before or after signs of a condition. In some embodiments, the patient is administered a first dose of a regimen 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours (or any range derivable therein) or 1, 2, 3, 4, or 5 days after the patient experiences or exhibits signs or symptoms of the condition (or any range derivable therein). The patient may be treated for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more days (or any range derivable therein) or until symptoms of the condition have disappeared or been reduced or after 6, 12, 18, or 24 hours or 1, 2, 3, 4, or 5 days after symptoms of an infection have disappeared or been reduced.

C. Growth Factors and Cytokines

Certain embodiments of the disclosure relate to compositions, molecular complexes, biomaterials, and implants comprising growth factors and cytokines. Exemplary non-limiting growth factors and cytokines include mammalian proteins such as ANG-1, ANG-2, EGF, EPO, NGF, FGF-2, FGF-4, FGF-6, FGF-7, FGF-10, FGF-17, FGF-18, TGF- α , TGF- β , TGF- β 1, TGF- β 2, TGF- β 3, NGF, NT-3, BDNF, PIGF-1, PIGF-2, PIGF-3, BMP-2, BMP-7, BMP-9 PDGF-AA, PDGF-AB, PDGF-BB, PDGF-DD, VEGF-A165, VEGF-A121, VEGF-B, VEGF-C, VEGF-D, IGF-1, IGF-BP3, IGF-BP5, HGF, EGF, HB-EGF, CXCL12, or CXCL11. In some embodiments, the growth factor or cytokine is a mammalian growth factor or cytokine. In some embodiments, the growth factor or cytokine is a human, mouse, pig, monkey, horse, goat, rabbit, sheep or rat growth factor or cytokine. In some embodiments, one or more of ANG-1, ANG-2, EGF, EPO, NGF, FGF-2, FGF-4, FGF-6, FGF-7, FGF-10, FGF-17, FGF-18, TGF- α , TGF- β , TGF- β 1, TGF- β 2, NT-3, BDNF, PIGF-1, PIGF-2, PIGF-3, BMP-2, BMP-7, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-DD, VEGF-A165, VEGF-A121, VEGF-B, VEGF-C, IGF-1, IGF-BP3, IGF-BP5, or HGF are specifically excluded from the compositions, molecular complexes, scaffolds, implants, or matrices described herein. In some embodiments, at least, at most, or exactly, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or 30 (or any derivable range therein) of ANG-1, ANG-2, EGF, EPO, NGF, FGF-2, FGF-4, FGF-6, FGF-7, FGF-10, FGF-17, FGF-18, TGF- α , TGF- β , TGF- β 1, TGF- β 2, NT-3, BDNF, PIGF-1, PIGF-2, PIGF-3, BMP-2, BMP-7, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-DD, VEGF-A165, VEGF-A121, VEGF-B, VEGF-C, IGF-1, IGF-BP3, IGF-BP5, or HGF is included in the embodiments of the disclosure

IV. BIOMATERIAL SCAFFOLD AND IMPLANTS

Certain embodiments of the disclosure relate to biomaterial scaffolds or matrix comprising the peptide or polypeptides of the disclosure. The term matrix refers to a three-dimensional structure, including a block, gel, sheet, or film; it is a term used in contrast to a soluble or fluid material. The scaffolds have to withstand mechanical loads, contain suitable degradation kinetics, and present bioactive molecules. Scaffolds function as a fusion of cell carrier and drug delivery device for the purpose of tissue engineering. To mimic the natural microenvironment for cells in order to induce tissue repair and regeneration, synthetic materials can be modified with ECM fragments. ECM fragments described herein may be designed to form a molecular fusion with a transglutaminase (TG) peptide at the N or C terminus. In some embodiments, the TG-reactive peptide consists of residues 1-8 of the protein α 2 plasmin inhibitor (α ₂PI₁₋₈, NQEQVSPL (SEQ ID NO:12)). Factor XIIIa can therefore be used as a transglutaminase to catalyze the reaction between the glutamines of this sequence (NQEQVSPL (SEQ ID NO: 12)) and the lysines of different biomaterials. The coagulation enzyme, factor XIIIa, will covalently bind the free amine group of the lysines (Lys) to the gamma-carboxamid group of glutamine (Gln), resulting in bonds that exhibit high resistance to proteolytic degradation. For example, natural fibrin hydrogels are cross-linked by this mechanism and TG-TNC III1-5 can therefore be cross-linked inside the gel (Schense and Hubbell, 1999).

Modification of synthetic hydrogels is possible by engineering counter-substrates for transglutaminases, such as lysines inside poly ethylene glycol (PEG-Lys) hydrogels. PEG is modified with lysines by chemically cross-linking a lysine containing peptide that includes The SH group of the cysteine functions as nucleophile (Mikael donor) in a Mikael type addition, with VS functioning as Michael acceptor (Lutolf, Lauer-Fields, et al., 2003). This technology has been used to make TG-PEG gels, which are cross-linked by two multi-arm PEG-peptide conjugates, PEG-Lys and PEG-Gln, in the presence of factor XIII, which allows for incorporation of other proteins containing a TG substrate (Ehrbar, Rizzi, et al., 2007). Alternatively, chemical crosslinking through cysteine residues may be used to attach proteins, peptides, and polypeptides to polymeric compositions and gels.

The peptide, polypeptides, compositions, and molecular complexes of the disclosure can be further immobilized into biomaterial matrices, forming additional embodiments. The peptides and polypeptides can be fused to a transglutaminase substrate that can covalently bind to natural protein biomaterials such as fibrin or to synthetic biomaterials engineered to comprise counter-substrates for transglutaminases.

Biomaterial scaffolds useful in the embodiments of the disclosure may comprise ceramics, synthetic polymers, and/or natural polymers. Ceramic scaffolds include, for example, hydroxyapatite (HA) and tri-calcium phosphate (TCP). Ceramic scaffolds are typically characterized by high mechanical stiffness (Young's modulus), very low elasticity, and a hard brittle surface. Examples of synthetic polymers include polystyrene, poly-L-lactic acid (PLLA), polyglycolic acid (PGA) and poly-DL-lactic-co-glycolic acid (PLGA). Exemplary natural polymers include collagen, proteoglycans, alginate-based substrates, and chitosan. Natural polymers are biologically active and typically promote excellent cell adhesion and growth. Furthermore, they are also biodegradable and so allow host cells, over time, to

produce their own extracellular matrix and replace the degraded scaffold. In some embodiments, the biomaterial scaffold may comprise different components such as ceramics and natural or synthetic polymers.

According to a further aspect of the present invention, the biomaterial scaffold or implant comprises synthetic cartilage, bone, ligament, tendon, meniscus, periodontal tissue, dentine, enamel, intervertebral disc, annulus fibrosus, or nucleus pulposus implant, graft, substitute, scaffold, filler, coating or cement.

The biomaterial or implants may further comprise cells. The cells may be stem or progenitor cells, differentiated cells, terminally differentiated cells, or combinations thereof. The cells may be totipotent, pluripotent or unipotent stem cells, or induced pluripotent stem cells. The cells may be human embryonic stem cells, derived via a technology which does not necessitate the destruction of the human embryo, for example via an established cell line. Mesenchymal stem cells (also referred to as marrow stromal cells, multipotent stromal cells, or MSCs) are pluripotent stem cells which can differentiate into a variety of cell types including osteoblasts, tenocytes, chondrocytes, myocytes, adipocytes. These cell types have the ability to generate bone, tendon, ligament, cartilage, muscle, and fat. The cells may be MSCs or any cell within the MSC lineage. Progenitor cells can go through several rounds of cell division before terminally differentiating into a mature cells, and the cells may be these intermediary cells. The cells may be selected from the group consisting of: MSCs (marrow stromal cells, mesenchymal stem cells, multipotent stromal cells), chondrocytes, fibrochondrocytes, osteocytes, osteoblasts, osteoclasts, synoviocytes, adipocytes, bone marrow cells, mesenchymal cells, stromal cells, genetically transformed cells, or combinations thereof. The cells may be autologous or heterologous.

In some embodiments, the biomaterial scaffold comprises fibrin. Other materials may also be engineered to include peptides of the disclosure. Such materials are described in U.S. Pat. Nos. 7,241,730, 6,331,422, 6,607,740, 6,723,344, US Pub 2007/0202178, US Pub 2007/0264227, which are hereby incorporated herein by reference for all purposes.

In some embodiments, the biomaterial scaffold comprises collagen. Collagen scaffolds are described in, for example, US Publications: 2017/0182212, 20170173216, 20160199538, and 20150367030, which are hereby incorporated herein by reference for all purposes.

V. THERAPEUTIC METHODS

After damage, tissue repair or regeneration is the result of a spatio-temporal coordination of cell fate processes that are controlled by a multitude of cell-signaling events coming from the extracellular microenvironment and recruited cells at the site of injury (Gurtner, Werner, et al., 2008). To site few, tissue healing processes such as angiogenesis (Herbert and Stainier, 2011), stem cells homing (Karp and Leng Teo, 2009), or inflammation (Eming, Hammerschmidt, et al., 2009) are all tightly coordinated and controlled by a cascade of cell-signaling events. Angiogenesis, the formation of new blood vessels, is crucial to provide oxygen and nutrients to the regenerating tissue. Various approaches have been made with a goal of providing amenable and tissue-specific matrices to control cell processes, such as adhesion, migration, proliferation, differentiation (Lutolf and Hubbell, 2005; Atala, 2008; Huebsch and Mooney, 2009). A goal is to provide matrices to contain signals that directly act on tissue-damaged cells, attract regeneration-competent cells,

block regeneration-suppressing signals, and guide cell fate. Powerful molecules to control these processes are secreted cell-signaling molecules such as morphogens (Affolter and Basler, 2007), cytokines (Vilcek and Feldmann, 2004), and growth factors (Cross and Dexter, 1991).

The embodiments of the disclosure may facilitate these processes and can be used to assist in the healing of normal wounds, including those resulting from accidents, surgery or failure of healing of a surgical wound (e.g., a dehiscent wound). Certain aspects of the disclosure will accelerate wound healing, reduce scarring and ultimately promote repair, regeneration and restoration of structure and function in all tissues.

The embodiments of the disclosure can be used to treat external wounds caused by, but not limited to scrapes, cuts, lacerated wounds, bite wounds, bullet wounds, stab wounds, burn wounds, sun burns, chemical burns, surgical wounds, bed sores, radiation injuries, all kinds of acute and chronic wounds, wounds or lesions created by cosmetic skin procedures and also ameliorate the effects of skin aging. The embodiments of the disclosure may accelerate wound healing in all kinds of external wounds and improve the cosmetic appearance of wounded areas, and skin subject to aging and disease. In certain embodiments, the composition, peptide, polypeptide, implant, molecular complex, scaffold, or matrix of the disclosure may be provided directly, as a pre-treatment, as a pre-conditioning, coincident with injury, pre-injury, or post-injury. The composition be used to treat internal injury caused by, but not limited to, disease, surgery, gunshots, stabbing, accidents, infarcts, ischemic injuries, to organs and tissues including but not limited to heart, bone, brain, spinal cord, retina, peripheral nerves and other tissues and organs commonly subject to acute and chronic injury, disease, congenital and developmental malformation and aging processes. Injury to internal organs causes a fibrotic response, which leads to loss of structure and function in organ systems.

In certain aspects, regenerative processes aided by the compositions peptides, polypeptides, implants, molecular complexes scaffolds, or matrices of the disclosure may include, but are not limited to internal and external injury, regeneration of tissues, organs, or other body parts, healing and restoration of function following vascular occlusion and ischemia, brain stroke, myocardial infarction, spinal cord damage, brain damage, peripheral nerve damage, ocular damage (e.g., to corneal tissue), bone damage and other insults to tissues causing destruction, damage or otherwise resulting from, but not limited to, injury, surgery, cancer, congenital and developmental malformation, and diseases causing progressive loss of tissue structure and function, including but not limited to diabetes, bacterial, viral and prion-associated diseases, Alzheimer's disease, Parkinson's disease, AIDS and other genetically determined, environmentally determined or idiopathic disease processes causing loss of tissue/organ/body part structure and function. In addition, the compositions described herein can be administered with drugs or other compounds promoting tissue and cellular regeneration including, but not limited to, trophic factors in processes including, but not limited to, brain, retina, spinal cord and peripheral nervous system regeneration (e.g., NGFs, FGFs, Neurtrophins, Neuregulins, Endothelins, GDNFs, BDNF, BMPs, TGFs, Wnts), as well as pre-conditioning factors or stimuli e.g., hypoxia, norepinephrine, bradykinin, anesthetics, nitrate, ethanol, Alda-1, ALDH2 antagonists, PKC-epsilon agonists, exogenous ligands that activate opioid receptors (DPDPE, deltorphin II, methadone, SNC-80, BW373U86, DPI-287, DPI-3290)

delivered in a prospective pre-treatment prior to a surgery of other procedure disrupting tissue in a subject.

Embodiments of the disclosure further include the use of the peptides, compositions, polypeptides, implants, molecular complexes, scaffolds, or matrices of the disclosure to aid in the healing of pathological wounds, such as through use of a contractile toroid for assisting the closure of slow healing wounds e.g., diabetic wounds. Diabetic wounds are examples of difficult to heal wound can include, for example, a wound that is often characterized by slower than normal re-epithelialization/closure inflammatory phase and delayed formation and remodeling of extracellular matrix.

The present disclosure can also assist in the healing of chronic wounds or wounds that do not heal. Wounds that have not healed within three months, for example, are said to be chronic. Chronic wounds include, diabetic, diabetic foot, ischemic, venous, venous stasis, arterial, pressure, vasculitic, infectious, decubitis, burn, trauma-induced, gangrenous and mixed ulcers. Chronic wounds include, wounds that are characterized by and/or chronic inflammation, deficient and overprofuse granulation tissue differentiation and failure of re-epithelialization and wound closure and longer repair times. Chronic wounds can include ocular ulcers, including corneal ulcers. Use of the disclosed embodiments in wound healing and tissue regeneration would include in humans and agricultural, sports and pet animals.

VI. EXAMPLES

The following examples are included to demonstrate preferred embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Example 1—Laminin Heparin-Binding Peptides Bind to Several Growth Factors and Enhance Diabetic Wound Healing

1. Results

a. Multiple GFs Bind to Multiple Isoforms of Laminin

The inventors first examined the capacity of a variety of full-length laminin isoforms (-111, -211, -332, -411, -421, -511, and -521) to bind GFs from the VEGF/PDGF, FGF, BMP, NT, IGF, EGF and CXCL chemokine families, for which the inventors have previously observed binding to other ECM proteins, including fibronectin, vitronectin, tenascin-C, osteopontin, and fibrinogen, as well as that reportedly modulate wound-healing. Binding of laminin to absorbed GFs was detected using an antibody against laminin, and signals greater than 0.1 were considered to be indicative of a binding event. Overall, it was found that multiple GFs strongly bound to all tested laminin isoforms (FIG. 1A). Specifically, from the VEGF/PDGF family, VEGF-A165, PIGF-2, PDGF-AA, PDGF-BB, and PDGF-CC bound to all isoforms of laminin, in contrast to VEGF-A121, PIGF-1, and PDGF-DD which did not show binding. From the FGF family, the inventors observed that FGF-2, FGF-7, FGF-10, and FGF-18 bound to all laminin isoforms, whereas FGF-1, FGF-6, and FGF-9 did not. Among the BMPs, BMP-2 and BMP-3 showed binding to laminins, but

not BMP-4 and BMP-7. NT-3 and BDNF showed strong binding towards all tested laminin isoforms, while β NGF bound only weakly. Neither IGF-1 nor IGF-2 displayed significant binding to laminins. In addition, HB-EGF weakly bound to laminins. As to the tested chemokines, CXCL-12 γ bound to all laminin isoforms, whereas CXCL-11 and CXCL-12a bound weakly to laminin-332 but not to the other isoforms.

Next, the inventors measured the affinities between laminin-521, as an example, and VEGF-A165, PIGF-2, and PDGF-BB using surface plasmon resonance (SPR). SPR chips were functionalized with laminin-521, and growth factors were flowed over the surface. The obtained binding curves were fitted with Langmuir binding kinetics to calculate specific dissociation constants (K_D) (FIG. 1B). K_D values were 5.8 nM for VEGF-A165, 12.9 nM for PIGF-2, and 24.2 nM for PDGF-BB. The nM range of K_D values demonstrated the strong binding affinities of laminin-521 to the selected GFs.

b. GFs Bind to the HBDs of Laminin

Because the GFs that bound to laminins have also been previously reported to bind to other ECM glycoproteins through HBDs, it was hypothesized that HBDs of laminins might be responsible for the interactions between GFs and laminin. To address this hypothesis, ELISA assays were repeated for VEGF-A165, PIGF-2 or FGF-2 in the presence of heparin added in excess (10 μ M). As a result, the inventors observed that excess heparin inhibited GF binding to laminin (FIG. 2A-C), supporting that laminin HBDs mediated interactions with GFs. To further confirm this, the inventors tested direct GF binding to the LG domains from human laminin α 3, α 4 and α 5, within which HBDs of laminin were localized. It was found that VEGF-A165, PIGF-2, PDGF-BB, and FGF-2 bound to laminin LG domains α 3₂₉₂₈₋₃₁₅₀, α 4₈₂₆₋₁₈₁₆ and α 5₃₀₂₆₋₃₄₈₂, in contrast to VEGF-A121 and PIGF-1 which did not show any binding (FIG. 3A-C), as tested by ELISA. The binding affinities between α 3₂₉₂₈₋₃₁₅₀ and VEGF-A165 or PDGF-BB were then measured by SPR, and K_D values were 1.2 nM for VEGF-A165, and 10.2 nM for PDGF-BB (FIG. 3D). These data again demonstrated the strong affinities of the laminin LG domain to the tested GFs.

The inventors next examined the binding of GFs to chemically synthesized laminin LG domain peptides, the sequences of which are all derived from human laminin sequences (Table 1, FIG. 4A). These peptides are putative HBDs; they were determined based on previous reports with mouse or human HBD sequences, or are positively charged sequences located within the linker domain between the LG3 and LG4 domains in laminin α 3, α 4 and α 5 chains. Of 9 tested peptides, 6 bound to heparin (i.e. HBDs), namely α 3₂₉₃₂₋₂₉₅₁, α 3₃₀₄₃₋₃₀₆₇, α 4₁₄₀₈₋₁₄₃₄, α 4₁₅₂₁₋₁₅₄₃, α 5₃₃₀₀₋₃₃₃₀, and α 5₃₄₁₇₋₃₄₃₆ among which α 3₂₉₃₂₋₂₉₅₁, α 4₁₄₀₈₋₁₄₃₄, and α 5₃₃₀₀₋₃₃₃₀ are derived from the LG3-LG4 linker. Interestingly, α 5₃₃₁₂₋₃₃₂₅, which is a subdomain of α 5₃₃₀₀₋₃₃₃₀, did not bind to heparin.

Finally, the affinities of VEGF-A, PIGF, PDGF-BB, and FGF-2 to these peptides were examined (FIG. 4B-F). The inventors observed that all heparin-binding peptides showed significant binding to some GFs. Indeed, α 3₃₀₄₃₋₃₀₆₇, α 4₁₄₀₈₋₁₄₃₄ and α 5₃₄₁₇₋₃₄₃₆ bound to VEGF-A165, PIGF-2, PDGF-BB, and FGF-2. α 4₁₅₂₁₋₁₅₄₃ showed similar results except for the binding to PDGF-BB, which was not statistically significant. α 3₂₉₃₂₋₂₉₅₁ and α 5₃₃₀₀₋₃₃₃₀ preferentially bound to VEGF-A165 and FGF-2, and VEGF-A165 and PIGF-2 respectively. As to the non-heparin-binding peptides, α 5₃₃₁₂₋₃₃₂₅ did not show particular binding to any

tested GF. Interestingly, $\alpha 5_{3539-3550}$, which did not show binding to heparin, significantly bound to all tested GFs, and $\alpha 3_{3031-3043}$ bound to VEGF-A165. None of the tested laminin-derived peptides bound to VEGF-A121 nor to PIGF-1, consistent with the results obtained in FIG. 1 and FIG. 3. To examine sequence specificity of this binding to GFs, the inventors produced a scrambled sequence $\alpha 3_{3043-3067}$ peptide (FIG. 9); scrambling the sequence of $\alpha 3_{3043-3067}$ decreased the binding signals between $\alpha 3_{3043-3067}$ and VEGF-A165, PIGF-2, PDGF-BB, and FGF-2, compared to its native form. Taken together, these data suggest that GFs bind to the HBDs of laminin, located in the LG3-LG4 linker or in LG4-LG5 domains.

c. Laminin HBD Peptides Promote Adhesion of Multiple Types of Cells

Because the laminin HBDs have been reported to bind to syndecan, a key cell surface adhesion molecule, the inventors tested syndecan binding to the synthesized laminin-derived peptides (FIG. 5A-D). $\alpha 3_{3043-3067}$, $\alpha 4_{1521-1543}$, $\alpha 4_{1408-1434}$, $\alpha 5_{3417-3436}$, and $\alpha 5_{3300-3330}$ showed significant binding to all isoforms of recombinant syndecans, i.e. syndecan 1-4. $\alpha 3_{2932-2951}$, $\alpha 3_{3031-3043}$, and $\alpha 5_{3312-3325}$ showed weak binding to the tested syndecans, while $\alpha 5_{3539-3550}$ did not show binding to any syndecan isoform. Because laminin-derived peptides that interact with syndecans may further promote cell adhesion by providing binding substrates, the inventors tested fibroblasts and HUVEC adhesion to plates coated with these peptides. The inventors observed enhancement of fibroblast attachment on $\alpha 3_{2932-2951}$, $\alpha 3_{3031-3043}$, $\alpha 3_{3043-3067}$, $\alpha 4_{1521-1543}$ and $\alpha 5_{3417-3436}$ -coated surfaces (FIG. 6A). Fibroblast binding was observed even in the presence of EDTA, consistent with syndecan function (FIG. 6B). Of these peptides, $\alpha 3_{2932-2951}$, $\alpha 3_{3043-3067}$, and $\alpha 4_{1521-1543}$ also promoted HUVEC attachment (FIG. 6C), even in the presence of EDTA in the case of $\alpha 3_{3043-3067}$ (FIG. 6D). Interestingly, peptides that promoted both fibroblast and HUVEC adhesion in vitro through syndecan binding were those that the inventors previously found to be laminin HBDs (FIG. 4A). VEGF-A165 increases the degree of migration of HUVEC cells in vitro (FIG. 10). However, both in the presence and absence of VEGF-A165, $\alpha 3_{3043-3067}$ did not increase the degree of cell migration.

d. Retention of VEGF-A165 and PDGF-BB in Fibrin Matrix is Increased by the Incorporation of Laminin HBD Peptides

The inventors then sought to determine whether laminin HBD peptides, which showed binding to GFs, were able to improve the retention of VEGF-A165 and PDGF-BB within fibrin matrix. VEGF-A165 and PDGF-BB are both crucial factors for angiogenesis. These GFs are known to be quickly released from fibrin matrices upon delivery, which limits their wound healing efficacy in vivo. For this purpose, the inventors selected $\alpha 3_{3043-3067}$ and $\alpha 5_{3417-3436}$ laminin HBD peptides, and fused them to a transglutaminase-reactive sequence from the α_2 -plasmin inhibitor to allow their covalent incorporation by factor XIIIa into fibrin matrices during polymerization. GF release from fibrin matrices containing $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$, $\alpha_2\text{PI}_{1-8}-\alpha 5_{3417-3436}$ or no laminin-derived peptide were then monitored daily and quantified by ELISA (FIG. 7A, B). As expected, the inventors observed that VEGF-A165 and PDGF-BB were quickly released from the fibrin matrix (>85% released after 24 h). However, incorporation of either $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ or $\alpha_2\text{PI}_{1-8}-\alpha 5_{3417-3436}$ allowed significant retention of VEGF-A165 and PDGF-BB into matrices, which were respectively released after 5 days, for VEGF-A165 ($\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$: 25%, $\alpha_2\text{PI}_{1-8}-\alpha 5_{3417-3436}$: 31%) and for PDGF-BB ($\alpha_2\text{PI}_{1-8}-$

$\alpha 3_{3043-3067}$: 45%, $\alpha_2\text{PI}_{1-8}-\alpha 5_{3417-3436}$: 47%). This data highlights the key biological role of laminin in sequestering GFs into ECM, and demonstrates the potential of laminin HBD peptides to control GF delivery from fibrin biomaterials (FIG. 7A, B). The inventors next evaluated the effect of $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ on GF retention in diabetic wounds in the type 2 diabetic db/db mouse in vivo (FIG. 7C). Incorporation of $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ into fibrin matrices significantly enhanced the amount of VEGF-A165 remaining in the wounds 3 days after treatment, showing that incorporation of $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ prolongs retention of GFs in vivo.

e. Laminin HBD-Functionalized Fibrin Matrices Potentiate GFs and Promote Wound Healing In Vivo

Although the etiology of non-healing wounds is multifaceted in diabetes, the progression to a non-healing phenotype is related to poor blood vessel formation. Thus, induction of mature blood vessels is a crucial step for diabetic wound-healing. Previous studies have reported a synergistic effect between angiogenesis inducers VEGF-A165 and PDGF-BB in wound healing, more precisely topical application of VEGF-A165 improves wound closure and PDGF-BB promotes the amount of granulation tissue in the type 2 diabetic db/db mouse. The inventors further evaluated whether fibrin matrices engineered with laminin-HBD peptides could enhance skin repair in a model of delayed wound healing, by controlling the release of VEGF-A165 and PDGF-BB in vivo. VEGF-A165 (100 ng/wound) and PDGF-BB (50 ng/wound) were co-delivered from fibrin matrix onto full-thickness back-skin wounds in db/db mice, which provides a well-established and clinically-relevant model of impaired wound healing. Here, the inventors particularly functionalized fibrin with the laminin peptide $\alpha 3_{3043-3067}$, since it bound to GFs and syndecans, and promoted fibroblast and endothelial cells adhesion in vitro (FIG. 4-6). Four groups were tested: fibrin only, fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$, fibrin containing GFs, and fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ and containing GFs. Wound histology was analyzed after 4, 7 and 10 days, considering that wounds are normally fully closed after 15 days when treated with fibrin matrix. As a result, wounds that received fibrin matrices containing GFs or $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ peptide only did not differ from wounds treated with fibrin alone on day 7, neither in amount of granulation tissue nor in extent of wound closure (FIG. 8A-C). In contrast, the co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ led to a significantly faster wound closure after 7 days, as well as a significant increase in granulation tissue formation (FIG. 8A-C). GFs alone improved the amount of granulation tissue but not wound closure on day 10, suggesting that $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ peptide speeds the wound healing process by these GFs. Representative wound morphology for all four treatments is presented in FIG. 8D. Clear differences in granulation tissue thickness and extent of re-epithelialization can be visualized when GFs were delivered within the $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ peptide-functionalized fibrin matrix compared to the other conditions.

Angiogenesis is a crucial step of wound-healing in diabetic wounds, and both VEGF-A165 and PDGF-BB are angiogenesis inducers. The inventors next examined endothelial cell proliferation (FIG. 8E). Co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha 3_{3043-3067}$ led to a significantly increased frequency of Ki67⁺, a proliferation marker, within CD31⁺ CD45⁻ endothelial cells compared to other treatment groups on day 5. This is consistent with the increase in granulation

tissue observed on day 7 as a result of delivery of GFs in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ (FIG. 8C).

Immune cells play crucial role in wound-healing regulation. The inventors next examined the immune cell population in the wound in each treatment group. Delivery of GFs in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ slightly decreased the frequency of neutrophils within CD45⁺ cells compared to other treatment groups. On the other hand, delivery of GFs in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ increased the frequency of monocytes within CD45⁺ cells compared to other treatment groups. Among immune cells, neutrophils migrate first into wounds and then monocytes appear^{43,44}. Therefore, this set of data suggests that delivery of GFs in fibrin functionalized with $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ promotes wound healing immunologically as well. Inclusion of $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ improved the GF delivery capacity of fibrin *in vivo*, resulting in an accelerated wound healing.

2. Discussion

It was unexpectedly found that GF binding to laminin does not seem to be limited to HBDs, as a few non-heparin binding peptides also bound to some GFs, notably $\alpha_3_{3031-3043}$ and $\alpha_5_{3539-3550}$. These peptides are human alignments of reported mouse HBD peptides, called A3G75 and A5G94 respectively. Thus, the mechanism of GF-binding to laminin still remains incompletely clarified and may be resolved by further crystallography studies of GF-laminin complex.

Physiologically, proteolytic cleavage of LG4 and LG5 domains is crucial for the deposition of laminin in the native ECM. Upon tissue injury, laminin is overexpressed, and LG4-LG5 domains accumulate in wounds, wherein they promote tissue healing mechanisms. In this study, the inventors characterized laminin-derived peptides that are located just before the proteolytic cleavage site, in the linker between the LG3 and LG4 domains, or within the LG4-LG5 domains (Table. 2, FIG. 4A). On one side, the inventors discovered 3 novel heparin-, GF- and syndecan-binding peptides within the LG3-LG4 linker regions of α_3 , α_4 , and α_5 chains, namely $\alpha_3_{2932-2951}$, $\alpha_4_{1408-1434}$ and $\alpha_5_{3300-3330}$ identifiable through their highly cationic sequences (FIG. 4). Since α_3 , α_4 and α_5 chains are known to be predominantly present in their processed form (i.e. lacking LG4-LG5) in mature, unwounded skin, it is likely that these peptides are exposed *in vivo* under homeostatic conditions, thus providing both GF ligands and cell adhesion sites in basement membranes. Interestingly, laminin α_1 chain, which is not proteolytically processed, and α_2 chain do not contain such cationic sequences in the LG3-LG4 linker region, which might reflect functional differences between α chain isoforms. On the other side, the inventors identified 5 peptides in the LG4 and LG5 domains of α_3 , α_4 and α_5 chains that displayed specific binding to GFs, in particular to VEGF-A165. Among them, $\alpha_3_{3043-3067}$, $\alpha_5_{3539-3550}$ and $\alpha_5_{3417-3436}$ additionally bound to PDGF-BB, FGF-2 and PIGF-2 with high affinities (FIG. 4). These growth factors are well-known as key regulators of the wound healing cascade, and are particularly involved in wound angiogenesis. Therefore, it is proposed that the reported positive effects of LG4-LG5 domains during wound healing might be related to promiscuous interactions with GFs, in addition to binding to syndecans and release of laminin-derived pro-angiogenic peptides.

In this study, the inventors identified 5 laminin HBDs that are able to bind to both GFs and syndecan cell-surface receptors (FIGS. 4 and 5), among which $\alpha_3_{3043-3067}$, $\alpha_4_{1521-1543}$ and $\alpha_5_{3417-3446}$ further promoted cell attachment (FIG. 6). Although syndecans are not known to directly

activate major signaling pathways, they support cell adhesion and integrin signaling. Moreover, direct binding of laminin peptides from LG domains to integrins has also been reported; for example, the integrin $\alpha_3\beta_1$ binds to $\alpha_3_{2932-2943}$. Nevertheless, in the assays, EDTA did not abolish cell adhesion, suggesting that initial cell attachment was mediated by syndecans rather than integrins (the binding of which is Ca²⁺-dependent). Consequently, and considering the short length of the laminin HBD peptides, it is unlikely that laminin HBD peptides can enhance GF signaling via synergy with integrins. It is believed that GF binding properties, more than cell adhesion properties, of laminin HBDs in fibrin matrices substantially contribute to the promotion of wound healing.

Although GFs are promising drugs for tissue regeneration, their uncontrolled delivery upon application on wounded tissue has limited their clinical efficacy and safety to date. For example, recombinant human VEGF-A has not been approved for clinical use by the U.S. Food and Drug Administration (FDA) due to a negative result in phase II clinical trials. PDGF-BB (Regranex in the clinic) has shown clinical efficacy, but safety issues such as cancer risk have been flagged, potentially due to high dosing. Because 20 μg per wound of VEGF-A165 applied topically for five consecutive days were known to promote wound healing in the db/db mouse and 10 μg per wound of PDGF-BB did not significantly enhance wound healing, the inventors treated full-thickness back-skin wounds with a roughly 40- to 250-fold lower dose of GFs (combination of 100 ng VEGF-A165 and 50 ng of PDGF-BB) delivered once in a fibrin matrix. Thus, controlling GF delivery to improve efficacy and dose reduction seems essential in future GF-based therapies and could be achieved by use of biomaterials matrices.

Here, the inventors showed that covalent incorporation of an engineered GF-binding domain derived from laminin, $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$, into fibrin matrix significantly enhanced the effect of VEGF-A165 and PDGF-BB on skin wound healing, by highly increasing GF retention into fibrin both *in vitro* and *in vivo* (FIG. 8). In contrast, wounds treated with fibrin matrix containing GFs only, in which PDGF-BB and VEGF-A165 were not specifically retained in the fibrin matrices, had no detectable effect on wound healing at the tested dose (FIG. 8). Wounds treated with fibrin matrix containing $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ only promoted wound-closure slightly. This might be the result of trapping endogenous GFs. Considering the importance of angiogenesis in diabetic wounds and the inventors' observation of increased Ki67⁺ within CD31⁺CD45⁻ endothelial cells, the healing process induced by fibrin matrix containing $\alpha_2\text{PI}_{1-8}-\alpha_3_{3043-3067}$ and GFs was driven by enhanced angiogenesis in the wounds. Improved angiogenesis, which sustains the newly formed granulation tissue, resulted from effective sequestration of VEGF-A165 and PDGF-BB (FIG. 7). Granulation tissue morphogenesis translated to improved morphogenesis at the level of the dermal epithelium, as reflected by faster wound closure.

One advantage of using the laminin HBD peptide for wound healing, is production simplicity: the laminin HBD peptide is short enough to be chemically synthesized in large scale, rather than requiring recombinant expression. Furthermore, the inventors showed that a laminin HBD can functionalize fibrin matrix in both aspects as a GF reservoir and an adhesion-promoting cell scaffold (FIGS. 6 and 7).

In conclusion, the inventors found that multiple isoforms of laminin promiscuously bind GFs from the VEGF/PDGF, FGF, BMP, and NT families, in addition to HB-EGF and

CXCL12 γ , through their HBDs. By engineering a fibrin matrix displaying the α_3 ³⁰⁴³⁻³⁰⁶⁷ laminin HBD, as a demonstrative example, the inventors have shown that the laminin HBD peptide promotes skin wound closure in the db/db mouse, as a model of delayed wound healing, when associated with VEGF-A165 and PDGF-BB. In addition to highlighting a GF-modulating function for laminin, an important tissue homeostasis and repair protein, the inventors show that both GF- and cell-binding characters of a laminin HBD can promote tissue repair when incorporated within fibrin matrix, which may be clinically useful.

3. Tables

TABLE 1

The sequences of laminin-derived peptides.	
Name (location) length	Peptide sequence
α_3 ²⁹³²⁻²⁹⁵¹ (Linker) 20 aa.	PPFLMLLKGSTRFNKTKTFR (SEQ ID NO: 2)
α_3 ³⁰³¹⁻³⁰⁴³ (LG4) 13 aa.	KNSFMALYLSKGR (SEQ ID NO: 9)
α_3 ³⁰⁴³⁻³⁰⁶⁷ (LG4) 25 aa.	RLVFALGTDGKKLRIKSKKENDGK (SEQ ID NO: 1)
α_4 ¹⁴⁰⁸⁻¹⁴³⁴ (Linker) 27 aa.	PLFLLHKKGNLSPKASQNKKGKSK (SEQ ID NO: 4)
α_4 ¹⁵²¹⁻¹⁵⁴³ (LG4) 23 aa.	TLFLAHGRLVYMFNVGHKKLKIR (SEQ ID NO: 3)
α_5 ³³⁰⁰⁻³³³⁰ (Linker) 31 aa.	TPGLGPRGLQATARKASRRSRQPARHPACML (SEQ ID NO: 7)
α_5 ³³¹²⁻³³²⁵ (Linker) 14 aa.	ARKASRRSRQPARH (SEQ ID NO: 10)
α_5 ³⁴¹⁷⁻³⁴³⁶ (LG4) 20 aa.	RQRSRPRGWHKVSVRWEKNR (SEQ ID NO: 6)
α_5 ³⁵³⁹⁻³⁵⁵⁰ (LG5) 12 aa.	TLPDVGLELEVR (SEQ ID NO: 5)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr1 25 aa.	RLVKALKTDKFLGRIGSEKCNKDKG (SEQ ID NO: 74)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr2 25 aa.	RKTDALVFLKGGIGSKKCNDKR (SEQ ID NO: 75)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr3 25 aa.	CRKKKKKKKALLGIGDFNSEVTDG (SEQ ID NO: 76)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr4 25 aa.	KKRKLVALTDPLGICSENDGRKKK (SEQ ID NO: 77)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr5 25 aa.	LVRAKLTDKFLGKRIGSKECNKDKG (SEQ ID NO: 78)
α_3 ³⁰⁴³⁻³⁰⁶⁷ Scr6 25 aa.	ALLLIGRDFNKKRKKSEVTDGC (SEQ ID NO: 79)
α_2 PI1-8- α_3 ³⁰⁴³⁻³⁰⁶⁷ 33 aa.	NQEQVSPRLRVFALGTDGKKLRIKSKKENDGK (SEQ ID NO: 8)
α_2 PI1-8- α_5 ³¹²⁻³³²⁵ 22 aa.	NQEQVSPARKASRRSRQPARH (SEQ ID NO: 11)

TABLE 2

Summary of laminin-derived peptide interactions.					
Laminin-derived peptides	Interaction with			Cell adhesion	
	Heparin	GFs	Syndecans	Fibroblasts	HUVECs
α_3 ²⁹³²⁻²⁹⁵¹	++	+	+	+	+
α_3 ³⁰³¹⁻³⁰⁴³		+	+	+	
α_3 ³⁰⁴³⁻³⁰⁶⁷	++	++	++	++	++
α_4 ¹⁴⁰⁸⁻¹⁴³⁴	++	++	++		
α_4 ¹⁵²¹⁻¹⁵⁴³	++	+	++	+	+
α_5 ³³⁰⁰⁻³³³⁰	++	+	++		
α_5 ³³¹²⁻³³²⁵			+		
α_5 ³⁴¹⁷⁻³⁴³⁶	++	++	++	+	
α_5 ³⁵³⁹⁻³⁵⁵⁰		+			

++ indicates high affinities, + indicates medium/low affinities. The laminin-derived peptide tested in vivo is highlighted in bold.

4. Materials and Methods

a. Growth Factors and Chemokines

All growth factors (GFs) and chemokines were purchased in their mature forms, highly pure (>95% pure), carrier-free, and lyophilized¹. Vascular endothelial growth factor (VEGF)-A121, VEGF-A165, placental growth factor (PIGF)-1, PIGF-2, platelet-derived growth factor (PDGF)-AA, PDGF-BB, PDGF-CC, PDGF-DD, fibroblast growth factor (FGF)-1, FGF-2, FGF-6, FGF-7, FGF-9, FGF-10, FGF-18, bone morphogenetic protein (BMP)-2, BMP-3, BMP-4, BMP-7, β -nerve growth factor (NGF), neurotrophin (NT)-3, brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF)-1, IGF-2, heparin-binding epidermal growth factor (HB-EGF), C—X—C motif ligand (CXCL)-11, and CXCL-12 α were purchased from Peprotech. CXCL-12 γ was purchased from R&D systems. Except for PDGF-DD and BMP-7, which were produced in eukaryotic cells, all GFs were produced in *Escherichia coli* and thus were not glycosylated. All GFs were reconstituted and stored according to the provider's instructions to regain full activity and prevent loss of protein.

b. Detection of Laminin Binding to Recombinant GFs

ELISA tests were performed as previously reported. In brief, ELISA plates (med-binding, Greiner Bio-One) were coated with 50 nM GFs at 37° C. for more than 2 hrs. After blocking with 2% BSA solution containing PBS and 0.05% Tween 20 (PBS-T), 10 nM recombinant human laminin isoforms (-111, -211, -332, -411, -421, -511, and -521) (>95% purity tested by SDS-PAGE, BioLamina) were added. Bound laminin was detected with rabbit anti-human laminin γ 1 chain antibody (1:1000 dilution, Assay biotech) or rabbit anti-human laminin α 3 chain antibody (1:1000 dilution, Assay biotech). After incubation with biotinylated anti-rabbit antibody for 60 min at room temperature (RT), HRP conjugated streptavidin (Jackson ImmunoResearch) was added. After 60 min of incubation at RT, 50 μ L TMB substrate (Sigma-Aldrich) was added. The reactions were stopped by adding 25 μ L of 2N H₂SO₄. Subsequently, the absorbance at 450 nm was measured with a reference of 570 nm.

c. Production and Purification of Recombinant Laminin α_3 ²⁹²⁸⁻³¹⁵⁰ Protein

Protein production and purification were performed as described previously¹. The sequence encoding for human laminin alpha 3 LG domain Ser2928-Cys3150 (linker domain and LG4 domain) was synthesized and subcloned into the mammalian expression vector pcDNA3.1(+) by Genscript. A sequence encoding for 6 His (SEQ ID NO: 80) was added at the N-terminus for further purification of the recombinant protein. Suspension-adapted HEK-293F cells

were routinely maintained in serum-free FreeStyle 293 Expression Medium (Gibco). On the day of transfection, cells were inoculated into fresh medium at a density of 1×10^6 cells/mL. 1 $\mu\text{g/mL}$ plasmid DNA, 2 $\mu\text{g/mL}$ linear 25 kDa polyethylenimine (Polysciences), and OptiPRO SFM media (4% final concentration, Thermo Fisher) were sequentially added. The culture flask was agitated by orbital shaking at 135 rpm at 37° C. in the presence of 5% CO₂. 6 days after transfection, the cell culture medium was collected by centrifugation and filtered through a 0.22 μm filter. Culture media was loaded into a HisTrap HP 5 mL column (GE Healthcare), using an ÄKTA pure 25 (GE Healthcare). After washing of the column with wash buffer (20 mM imidazole, 20 mM NaH₂PO₄, 0.5 M NaCl, pH 7.4), protein was eluted with a gradient of 500 mM imidazole (in 20 mM NaH₂PO₄, 0.5 M NaCl, pH 7.4). The elution solution was further purified with size exclusion chromatography using a HiLoad Superdex 200PG column (GE healthcare). All purification steps were carried out at 4° C. The expression of laminin LG domain was determined by western blotting using anti-His tag antibody (BioLegend) and the proteins were verified as >90% pure by SDS-PAGE.

d. Surface Plasmon Resonance (SPR)

SPR analysis was performed as described previously². In brief, measurements were made with a Biacore 3000 SPR system (GE Healthcare). Laminin-521 or laminin $\alpha 3_{2928-3150}$ was immobilized via amine coupling on a C1 chip (GE Healthcare) for ~2000 or ~1000 resonance units (RU), respectively, according to the manufacturer's instructions. VEGF-A165, PDGF-BB, or PIGF-2 was flowed at increasing concentrations in the running buffer at 20 $\mu\text{L}/\text{min}$. The sensor chip was regenerated with 50 mM NaOH for every cycle. Specific bindings of GFs to laminin were calculated by comparison to a non-functionalized channel used as a reference. Experimental results were fitted with Langmuir binding kinetics using BIAevaluation software (GE Healthcare).

e. Inhibition of Laminin-GF Binding by Heparin

ELISA plates (med-binding) were coated with 10 $\mu\text{g/mL}$ laminin isoforms (-111, -211, -221, -411, -421, -511, and -521) in PBS for 2 hrs at 37° C. Then, wells were blocked with 2% BSA-containing PBS-T and further incubated with 1 $\mu\text{g/mL}$ each of VEGF-A165, PIGF-2, or FGF-2 for 60 min at RT with 10 μM heparin. Next, the wells were incubated with biotinylated anti-VEGF, anti-PIGF, or anti-FGF-2 antibodies (R&D Systems). The antibodies were detected by streptavidin-HRP (R&D Systems). Signals were revealed and measured as described above.

f. Detection of GF Binding to Recombinant Laminin LG Domain Protein and the Synthesized Laminin HBD Peptides

ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 $\mu\text{g/mL}$ of laminin alpha 3 LG domain recombinant protein, laminin alpha 4 LG domain recombinant protein (R&D systems), laminin alpha 5 LG domain recombinant protein (LD BioPharma), or laminin peptide (sequences are described in Table 1, chemically synthesized by Genscript) in PBS for 2 hrs at 37° C. 1 $\mu\text{g/mL}$ of BSA served as non-binding protein control. After blocking with 2% BSA PBS-0.05% Tween 20 (PBS-T) solution, 1 $\mu\text{g/mL}$ of the recombinant human proteins (VEGF-A121, VEGF-A165, PIGF-1, PIGF-2, PDGF-BB or FGF-2) or 10 $\mu\text{g/mL}$ of biotinylated heparin (Sigma-Aldrich) were added. Bound GF was detected with biotinylated antibodies for human VEGF, PIGF, PDGF-BB, or FGF-2 (R&D Systems). The antibodies were detected by streptavidin-HRP (R&D Systems). Signals were revealed and measured as described above.

g. Detection of Recombinant Syndecan Binding to the Synthesized Laminin HBD Peptides

ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 $\mu\text{g/mL}$ laminin peptide (sequences are described in Table 1, chemically synthesized by Genscript) in PBS for 2 hrs at 37° C. 1 $\mu\text{g/mL}$ of BSA served as non-binding protein control. After blocking with 2% BSA PBS-T solution, 1 $\mu\text{g/mL}$ of the recombinant human syndecan-1, syndecan-2, syndecan-3, syndecan-4 (all syndecan proteins are histidine-tagged; SinoBiological) were added. Bound GF was detected with anti-histidine tag antibody (1:1000 dilution, BioLegend). Signals were revealed and measured as described above.

h. Cell Adhesion Assay

96-well plates (non-tissue culture treated, Greiner Bio-one) were pre-coated with 1 $\mu\text{g/mL}$ with laminin HBD peptides in PBS for 2 hrs at 37° C., followed by blocking with 2% BSA PBS for 1 h at RT. Cell adhesion assays were performed using human lung fibroblasts (Lonza) in FGM-2 medium (Lonza) or human umbilical vein endothelial cells (HUVEC; Lonza) in EGM-2 medium (Lonza) supplemented with 1% fetal bovine serum (FBS) and 100 $\mu\text{g/mL}$ VEGF-A165, with or without 5 mM EDTA (Sigma-Aldrich). Cells were plated at 3000 cells/well on laminin peptide pre-coated plates and incubated for 30 min at 37° C., 5% CO₂. Then, the medium was removed, and wells were quickly washed three times with PBS. Cell numbers were quantified using a CyQUANT assay, according to the manufacturer's instructions (Invitrogen). All cell lines were checked for mycoplasma contamination and used in passages from 5 to 8.

i. Migration Assay

A migration assay was performed as described previously³. A QCM 24-Well Colorimetric Cell Migration Assay kit was used to perform migration assay. Both sides of inserts were coated with 0.1 μM of bovine collagen I (C4243, Sigma-Aldrich) for 1 hr at 37° C. Then, the inserts were washed with water, dried in a laminar flow cabinet and disposed on 24-well cell culture plate covers. Solutions containing 30 ng/mL of VEGF-A165 preincubated with or without 0.1 μM of $\alpha 3_{3043-3067}$ peptide in medium (MCDB-131, 0.05% BSA) were added to the bottom side of the transwell (500 $\mu\text{L}/\text{well}$). Directly thereafter, HUVEC cells in medium containing 0.05% BSA (300 $\mu\text{L}/\text{transwell}$, 4×10^4 cells/transwell) were added to the transwell upper parts. After 6 hr, migrated cells were stained and absorbance at 560 nm was measured according to the manufacturer's instructions.

j. Release of GF from Fibrin Matrix

Fibrin matrices were generated with human fibrinogen (VWF and fibronectin depleted, Enzyme Research Laboratories) as described previously¹. In brief, fibrin matrices were generated with 8 mg/mL fibrinogen, 2 U/mL human thrombin (Sigma-Aldrich), 4 U/mL factor XIIIa (Fibrogamin; Behring), 5 mM calcium chloride (Sigma-Aldrich), 2 μM $\alpha_2\text{PI}_{1-8}$ -laminin peptide (sequences are described in Table 1, chemically synthesized by Genscript), and 500 ng/mL recombinant human VEGF-A165 or PDGF-BB. Thus, the peptides were incorporated into the 3D fibrin matrix through enzymatic coupling, via the coagulation transglutaminase factor XIIIa, of the $\alpha_2\text{PI}_{1-8}$ peptide sequence (NQEQVSPL (SEQ ID NO: 12)) fused to the laminin peptide. Fibrin matrix was polymerized at 37° C. for 1 hr and transferred into 24-well Ultra Low Cluster plates (Corning) containing 500 μL of buffer (20 mM Tris-HCl, 150 mM NaCl, and 0.1% BSA; pH 7.4). A control well that served as a 100% released control contained only the GF in 500 μL of buffer. Every 24 hrs, buffers were removed, stored

at -20° C., and replaced with fresh buffer. For the 100% released control well, 20 μ L of buffer was removed each day and stored at -20° C. After 5 days, the cumulative release of GF was quantified by ELISA (DuoSet; R&D Systems), using the 100% released control as a reference.

k. Retention of VEGF-A165 at the Wound Site

Retention assays were performed as previously reported¹. Briefly, C57BLKS/J-m/Lepr db (db/db) mice ages 10 to 11 wks were used. Their backs were shaved and four full-thickness punch-biopsy wounds (6 mm in diameter) were created in each mouse. Directly after, fibrin matrices [80 μ L total, fibrinogen (10 mg/mL), 2 U/mL human thrombin, 4 U/mL factor XIII, 5 mM calcium chloride, 2 μ M α_2 PI₁₋₈- α_3 ₃₀₄₃₋₃₀₆₇, 200 ng of recombinant human VEGF-A165] were polymerized on the wounds. To avoid drying of the matrices, the wounds were covered with non-adhering dressing (Adaptic, Johnson & Johnson), and then with adhesive film dressing (Hydrofilm, Hartmann). After 3 or 6 days, mice were sacrificed. The wounds were punched again, in order to recover the fibrinous matrices. Moreover, the tissue surrounding the wounds (2 mm beyond the wound margin) was removed. The tissue was transferred in 0.9 mL of tissue T-PER Tissue Protein Extraction Reagent (Thermo Scientific) containing 1 mg/mL of collagenase IV (Sigma-Aldrich), and homogenized with a tissue homogenizer. The tissue lysate was incubated 1 hr at 37° C. and 100 μ L of a 5 M NaCl solution containing protease inhibitors (1 tablet of protease inhibitor cocktail for 10 mL) was added to the lysate. The samples were centrifuged at 10000xg for 5 min, and the supernatants were stored at -80° C. Recombinant human VEGF-A165 remaining in the fibrinous matrix and in the tissue surrounding the wound were quantified by ELISA (DuoSet, R&D Systems), using 200 ng of recombinant human VEGF-A165 as 100%.

l. Mouse Skin Chronic Wound Healing Model

Skin wound healing assays were performed as previously reported¹. Briefly, C57BLKS/J-m/Lepr db (db/db) male mice were 10 to 12 wks old at the start of the experiments. Their backs were shaved and four full-thickness punch biopsy wounds (6 mm in diameter) were created in each mouse. Directly after, fibrin matrices [80 μ L total, fibrinogen (10 mg/mL), 2 U/mL human thrombin, 4 U/mL factor XIII, 5 mM calcium chloride, 2 μ M α_2 PI₁₋₈- α_3 ₃₀₄₃₋₃₀₆₇, 100 ng of VEGF-A165, and 50 ng of PDGF-BB] were polymerized on the wounds. The wounds were covered with adhesive film dressing. Mice were single-caged after the wound surgery. After 4, 7, 10 days, mice were euthanized and the skin wounds were carefully harvested for histological analysis.

m. Histomorphometric Analysis of Wound Tissue Sections

Histomorphometric analyses were performed as previously reported¹. Briefly, an area of 8 mm in diameter, which includes the complete epithelial margins, was excised. Wounds were cut in the center into two and embedded into paraffin. Histological analysis was performed on 5 μ m serial sections. Images were captured with an EVOS FL Auto microscope (Life Technologies). The extent of re-epithelialization and granulation tissue formation was measured by histomorphometric analysis of tissue sections (H&E stain) using ImageJ software (NIH). For analysis of re-epithelialization, the distance that the epithelium had traveled across the wound was measured; the muscle edges of the panniculus carnosus were used as indicator for the initial wound edges; and re-epithelialization was calculated as the percentage of the distance of edges of the panniculus carnosus muscle. For granulation tissue quantification, the area covered by a highly cellular tissue was determined.

n. Flow Cytometric Analysis of the Wounds

Skin wounds were treated with fibrin matrices as described above. After 5 days, the wounded skins were removed as described above, cut into small pieces (<0.5 mm²) and transferred to 1 mL of an enzyme solution (collagenase D (1 mg/mL)) and agitated for 1 hr at 37° C. Then, the cells from digested wounds were re-suspended in PBS, passed through a cell strainer and centrifuged. Then, cells were stained for 15 min in 100 μ L of FACS buffer containing antibodies: anti-CD31 (MEC13.3, BD Biosciences), anti-Ki67 (B56, BD Biosciences), anti-CD45 (30-F11), anti-Ly6G (1A8), anti-Ly6C (HK1.4), and anti-CD11b (M1/70). All antibodies were purchased from BioLegend if not otherwise described. Fixable live/dead cell discrimination was performed using Fixable Viability Dye eFluor 455 (eBioscience) according to the manufacturer's instructions. Intracellular staining was performed using the Intracellular Staining Permeabilization Wash Buffer according to manufacturer's instructions (BioLegend). Cells were analyzed using a Fortessa (BD Biosciences) flow cytometer and analyzed using FlowJo software (FlowJo, LLC).

o. Statistical Analysis

Statistical methods were not used to predetermine necessary sample size, but sample sizes were chosen based on estimates from pilot experiments and previously published results such that appropriate statistical tests could yield significant results. Statistically significant differences between experimental groups were determined by one-way ANOVA followed by Tukey's HSD post hoc test with Prism software (v7, GraphPad). Variance between groups was found to be similar by the Brown-Forsythe test. For non-parametric data, the Kruskal-Wallis test followed by Dunn's multiple comparison test was used. For ELISA data, the two-tailed Mann-Whitney U test was used. For the animal studies, experiments were not performed in a blinded fashion. Mice were randomized into treatment groups within a cage immediately before the wound surgery and treated in the same way. All animal experiments were performed with approval from the Veterinary Authority of the Institutional Animal Care and Use Committee of the University of Chicago. GF-laminin binding ELISA assays were repeated 4 times. Wound healing assays were repeated 3 times. The P values less than 0.05 are considered to be significantly different. The P values less than 0.05 and 0.01 indicate symbols * and **, respectively.

Example 2—Use of Recombinant Laminin A-Chain LG4 Domain for Controlled Delivery of Growth Factor/Chemokines from Biomaterials

Controlling the release kinetic of therapeutic proteins, such as growth factors (GFs) and chemokines, is essential to fully exploit their biological effects. In regenerative medicine, for example, GFs that are rapidly release from an injured site showed very modest clinical efficacy, thus implying their use at supra-physiological doses. As a consequence of such high non-physiological dosing, several GF-based therapies received safety warnings due to serious side effects directly related to the GF activity (e.g. ectopic tissue growth, tumor development). In this context, it has been demonstrated that engineering the slow-release of therapeutic proteins from biomaterials significantly increase their biological effects at reduced doses.

The inventors showed that LG4 domains located in the α -chain of the different laminin isoforms strongly bind to multiple GFs and chemokines. In this example, the use of these high affinity and promiscuous interactions between the

laminin α -chain LG4 domains and GFs/chemokines to control GFs/chemokines delivery from biomaterials is described. Indeed, the incorporation of the LG4 domains in biomaterials can substantially increase retention of GF/chemokines, by providing high-affinity binding substrates.

Experimental design: Here, the incorporation of recombinant laminin LG4 domains into biomaterials through enzymatic cross-linking within the biomaterial is exemplified. More precisely, the LG4 domain of α_3 , α_4 or α_5 -chain isoforms of laminin can be incorporated into fibrin-containing biomaterials through enzymatic crosslinking by the factor XIIIa during fibrin polymerization.

Other incorporation methods may include direct chemical conjugation of recombinant laminin LG4 to the biomaterial, or fusion of LG4 domains to protein sequences displaying strong but non-covalent binding to the biomaterial.

Methods: In this approach, the DNA sequence encoding for the transglutaminase substrate domain of the α_2 -plasmin inhibitor, named α_2PI_{1-8} (amino acid sequence: NQEQVSPL (SEQ ID NO: 12)), followed by the DNA sequence of a short GGSG linker (SEQ ID NO: 81), can be fused to the 5'-end of the DNA sequence encoding for a LG4 domain of laminin α_3 , α_4 or α_5 -chains; so that the end construct will be α_2PI_{1-8} -GGSG (SEQ ID NO: 81)-LG4 (see sequences below).

Modified recombinant LG4 domains sequences can be then inserted into a DNA plasmid suitable for protein production. For production in mammalian cells, plasmids generally contain a Kozak sequence, a start codon and a signal sequence for protein secretion (e.g. IgGk signal sequence), downstream of a strong ubiquitous promoter (e.g. CMV). The termination of the protein is achieved by a stop codon added at the C-terminus of the DNA sequence. An additional tag, such as a 6x histidine-tag (SEQ ID NO: 80), can be added at the N-terminus of the recombinant protein (i.e. after the signal sequence) or at its C-terminus (i.e. before the stop codon), to further facilitate protein purification. Following this design, recombinant LG4 domains will be produced by transient transfection of HEK293F cells over 7 days, and directly purified from the cell supernatant by affinity chromatography (e.g. to the histidine tag, to heparin) and/or physicochemical-based chromatography (e.g. size exclusion or ion-exchange chromatography). Final purity and identity of the recombinant laminin LG4 domain will be confirmed by SDS-PAGE and western blot analyses.

Results: Recombinant LG4 domains fused to the α_2PI_{1-8} domain can be first assessed for their ability to remain incorporated into fibrin matrix. This is commonly achieved by performing release assays; after incorporation, the amount of recombinant LG4 domain released from fibrin matrix can be daily quantified either by ELISA or by fluorescence measurements, considering that LG4 domains could be fluorescently-labeled prior to incorporation.

As soon as the functionality of the α_2PI_{1-8} domain as a substrate for crosslinking into fibrin can be established, the retention of GF/chemokines into fibrin containing laminin LG4 domains (versus fibrin alone) can be evaluated by ELISA-based release assays. Upon confirmation of successful GF/chemokines retention into fibrin by the recombinant laminin LG4 domains, fibrin matrices containing LG4 domains can be further characterized as a GF/chemokines delivery system in vivo, similarly to what was done in Example 1 with the α_2PI_{1-8} -fused LG4-derived peptides.

Interpretation: This molecular engineering of LG4 domains of α_3 , α_4 and α_5 -chains of human laminin illus-

trates the use of recombinant LG4 domain as an additive to biomaterials, to enhance pharmacokinetic properties of biomaterials in delivering of GF/chemokines. Particularly in this example, the fusion of LG4 domains with the transglutaminase substrate sequence from α_2 -plasmin inhibitor could leverage the GF/chemokines delivery properties of fibrin. Fusion of recombinant LG4 domains to other peptidic biomaterials able to be sequestered into natural or synthetic biomaterials could be similarly envisioned.

1. Native Human Sequences of Laminin α -Chain Isoforms

LAMA3 Human, LG4 domain aa2986-aa3150 (UniprotKB database Q16787):

(SEQ ID NO: 13)
ALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVVFHTGTKNSFM
ALYLSKGRLVFALGTDGKLLRIKSKEKCNKDKWHTVVFGHDGEGKRLVVD
GLRAREGSLPNSTISIRAPVYLGSPSPGKPKSLPTNSFVGCLKNFQLDS
KPLYTPSSSFGVSSC

NCBI-CCDS database (CCDS11880.1):

(SEQ ID NO: 19)
GCCCTCCAGTTTGGGGACATTCCACCAGCCACTTGCTATTCAAGCTTCC
TCAGGAGCTGCTGAAACCCAGGTCACAGTTTGCTGTGGACATGCAGACAA
CATCCTCCAGAGGACTGGTGTTCACACGGGCACTAAGAACTCCTTTATG
GCTCTTTATCTTTCAAAGGACGCTGGTCTTTGCACTGGGGACAGATGG
GAAAAAATTGAGGATCAAAGCAAGGAGAAATGCAATGATGGGAAATGGC
ACACGGTGGTGTGGCCATGATGGGAAAAGGGCGCTTGGTTGTGGAT
GGACTGAGGGCCCGGAGGGAAGTTTGCCTGGAACCTCCACCATCAGCAT
CAGAGCGCCAGTTTACCTGGGATCACCTCCATCAGGGAAACCAAAGAGCC
TCCCCACAAACAGCTTTGTTGGGATGCCTGAAGAACTTTCAGCTGGATTCA
AAACCTTGTATACCCCTTCTCAAGCTTCGGGTGTCTCTCTGC.

LAMA4 Human, LG4 domain aa1469-aa1640 (UniprotKB database Q16363):

(SEQ ID NO: 14)
AYQYGGTANSRQEFELKGFAGKSFQFIRLRTRSSHGMIFVSDQEEND
FMTLFLAHGRVYMFNVGHKKLIRSQEKYNDGLWHDVIFIRERSRGLV
IDGLRVLEESLPPTEATWIKIPYILGGVAPGKAVKNVQINSIYSFSGCL
SNLQLNGASITSASQTFVTPC.

NCBI-CCDS database (CCDS34514.1):

(SEQ ID NO: 20)
GCCTATCAATATGGAGGAACAGCCAACAGCCGCAAGAGTTTGAACACTT
AAAAGGAGATTTGGTGCCAAATCTCAGTTTCCATTCTGCTGAGAACTC
GTTCTCCCATGGCATGATCTTCTATGTCTCAGATCAAGAAGAGATGAC
TTCATGACTCTATTTTGGCCCATGGCCGCTGGTTTACATGTTAATGT
TGGTCACAAAAACTGAAGATTAGAAGCCAGGAGAAATACAATGATGGCC
TGTGGCATGATGTGATATTTATTCGAGAAAGGAGCAGTGGCCGACTGGTA
ATTGATGGTCTCCGAGTCTTAGAAGAAAGTCTTCTCCTCCTACTGAAGCTAC
CTGGAAAAACAAGGGTCCCATTATTTGGGAGGTGTGGCTCCTGAAAAGG
CTGTGAAAAATGTTTCAGATTAACCTCATCTACAGTTTGTAGTGGCTGTCTC

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AGCAATCTCCAGCTCAATGGGGCCTCCATCACCTCTGCTTCTCAGACATT
 CAGTGTGACCCCTTGC
 LAMA5_Human, LG4 domain aa3340-aa3513 (UniprotKB
 database O15230): (SEQ ID NO: 15)
 SYQFGSLSHLEFVGLARHRNWPSSLMHVLPSSRGLLFTARLRPGS
 PSLALFLSNGHFVAQMEGLGTRLRRAQSRQSRPGRWHKVSVRWEKNRILL
 VTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSHSSKLPVTVGFSG
 CVKRLRLHGRPLGAPTRMAGVTPC
 NCBI-CCDS database (CCDS33502.1): (SEQ ID NO: 21)
 TCCTACCAGTTTGGGGTTCCTGTCCAGTCACCTGGAGTTTGTGGGCAT
 CCTGGCCCACATAGGAAGTGGCCAGTCTCTCCATGCACGCTCCTCCCGC
 GAAGCTCCCGAGGCTCCTCCTTCACTGCCCCTGTGAGCCCGGCAGC
 CCCTCCCTGGCGCTTCTTCTGAGCAATGCCACTTCTGTCACAGATGGA
 AGGCCTCGGGACTCGCTCCGCGCCAGAGCCGCCAGCGCTCCCGCCTG
 GCCGCTGGCACAAGGTCTCCGTGCGCTGGGAGAAGACCGGATCCTGCTG
 GTGACGGACGGGGCCCGGGCTGGAGCCAGGAGGGCCGACCCGCGCAGCA
 CCAGGGGCGAGAGACCCCCAGCCCCACACCTCTTTGTGGGGCGGCTCC
 CGGCCAGCAGCCACAGTCCAAACTTCCGGTGACCGTCCGGTTCAGCGGC
 TGTGTGAAGAGACTGAGGCTGCACGGGAGGCCCTGGGGCCCCACAG
 GATGGCAGGGGTACACCCCTGC

2. Engineered Human Sequences of Laminin α -Chain Isoforms

Sequence design: The factor XIIIa transglutaminase substrate domain from the α_2 -plasmin inhibitor (NQEQVSPL—SEQ ID NO:12) was added at the N-terminus of laminin LG4 domains, and separated from the LG4 domain by a short linker GGSG (SEQ ID NO: 81). The α_2 -plasmin inhibitor domain (NQEQVSPL—SEQ ID NO:12) could have been alternatively added to the C-terminus of LG4 domains (sequences not shown).

Human $\alpha 2PI_{1-8}$ -LAMA3_LG4₂₉₈₆₋₃₁₅₀: (SEQ ID NO: 16)
 NQEQVSPLGGSGALQFGDIPTSHLLFKLPQELKPRSQFAVDMQTSSRG
 LVFHTGTKNSFMALYLSKGRLVFALGTDGKLRIRKSEKCNKGKWHVVF
 GHDGEGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPSPGPKSLPTNS
 FVGCLKNFQLDSKPLYTPSSSFGVSSC.

Possible DNA sequence of human
 $\alpha 2PI_{1-8}$ -LAMA3_LG4₂₉₈₆₋₃₁₅₀: (SEQ ID NO: 22)
 AACCAGGAGCAGGTGTCCCACTTGGTGGATCCGGCGCCCTCCAGTTTGG
 GGACATCCCACCAGCCACTTGCTATTCAAGCTTCTCAGGAGCTGCTGA
 AACCCAGGTACAGTTTTGCTGTGGACATGCAGACAACATCCTCCAGAGGA
 CTGGTGTTCACACGGCACTAAGAACTCCTTTATGGCTCTTTATCTTTC
 AAAAGGACGTCTGGTCTTTGCACTGGGACAGATGGGAAAAATTGAGGA
 TCAAAGCAAGGAGAAATGCAATGATGGGAAATGGCACACGGTGGTGT
 GGCCATGATGGGAAAAGGGCGCTTGGTTGTGGATGGACTGAGGGCCCG

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GGAGGGAAGTTTGCTTGGAACTCCACCATCAGCATCAGAGGCCAGTTT
 5 ACCTGGGATCACCTCCATCAGGGAAACCAAGAGCCTCCCCACAAACAGC
 TTTGTGGGATGCTGAAGAAGTTTCACTGAGTTCAAAACCTTGTATAC
 CCTTCTTCAAGCTTCGGGGTGTCTTCTCTGC.

Human $\alpha 2PI_{1-8}$ -LAMA4_LG4₁₄₆₉₋₁₆₄₀: (SEQ ID NO: 17)
 10 NQEQVSPLGGSGAYQYGGTANSRQEFHLKGDGFAKSSQFSIRLRTRSSHG
 MIFVYSDQEENDFMTLFLAHGRVYMFNVGHKKLIRSQEKYNDGLWHDV
 15 IFIRERSGRVLIDGLRVLEESLPTEATWKIKGPIYLGAVGKAVKNV
 QINSIYFSGCLSNLQNLNGASITSASQTFVSTPC.

Possible DNA sequence of human
 $\alpha 2PI_{1-8}$ -LAMA4_LG4₁₄₆₉₋₁₆₄₀: (SEQ ID NO: 23)
 20 AACCCAGGAGCAGGTGTCCCACTTGGTGGATCCGGCGCCTATCAATATGG
 AGGAACAGCCAACAGCCGCCAAGAGTTTGAACACTTAAAGAGGATTTTG
 GTGCCAAATCTCAGTTTTCCATTGCTGAGAACTCGTTCCTCCATGGC

25 ATGATCTTCTATGTCTCAGATCAAGAAGAGAAATGACTTCACTACTTAT
 TTTGGCCATGGCCGCTTGGTTTACATGTTTAAATGTGGTCAAAAAAAC
 TGAAGATTAGAAGCCAGGAGAAATACAATGATGGCCTGTGGCATGATGTG
 30 ATATTTATTCGAGAAAGGAGCAGTGGCCGACTGGTAATTGATGGTCTCCG
 AGTCTAGAGAAAGTCTTCTCTACTGAACTACCTGGAAAAATCAAGG
 GTCCCATTTATTTGGGAGGTGGTCTCCTGAAAGGCTGTGAAAAATGTT
 35 CAGATTAACCTCATCTACAGTTTTAGTGGTGTCTCAGCAATCTCCAGCT
 CAATGGGCTCCATCACCTCTGCTTCTCAGACATTCAGTGTGACCCCTT

gc
 40 Human $\alpha 2PI_{1-8}$ -LAMA5_LG4₃₃₄₀₋₃₅₁₃: (SEQ ID NO: 18)
 NQEQVSPLGGSGSYQFGSLSHLEFVGLARHRNWPSSLMHVLPSSRSG
 45 LLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRRAQSRQSRPGRWHK
 VSVRWEKNRILLVTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSH
 SSKLPVTVGFSGCVKRLRLHGRPLGAPTRMAGVTPC.

Possible DNA sequence of human
 $\alpha 2PI_{1-8}$ -LAMA5_LG4₃₃₄₀₋₃₅₁₃: (SEQ ID NO: 24)
 50 AACCCAGGAGCAGGTGTCCCACTTGGTGGATCCGGCTCCTACCAGTTTGG
 GGGTTCCTGTCCAGTACCTGGAGTTTGTGGCATCCTGGCCGACATA
 55 GGAAGTGGCCAGTCTCTCCATGCACGCTCCTCCCGAAGCTCCCGAGGC
 CTCTCTCTTCACTGCCCCTGAGGCCCCGACGCCCTCCTGGCGCT

60 CTTCTGAGCAATGCCACTTCGTTGCACAGATGGAAGGCTCGGGACTC
 GGCTCCGCGCCAGAGCCGCCAGCGCTCCCGGCTGGCCGCTGGACAAG
 GTCTCCGTGCGCTGGGAGAAGAACCGGATCCTGCTGGTACGGACGGGGC
 CCGGGCTGGAGCCAGGAGGGCCGACCCGGCAGCACAGGGGGCAGAGC
 65 ACCCCAGCCCCACACCTCTTTGTGGGGCGCTCCCGCCAGCAGCCAC

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AGCTCCAAACTTCCGGTGACCGTCGGGTTACAGCGGCTGTGTGAAGAGACT
 GAGGCTGCACGGGAGGCCCTCGGGGCCCCACACGGATGGCAGGGGTCA
 CACCCCTGC.

Example 3—Use of Recombinant Laminin α -Chain
 LG4 Domain (or Other ECM Protein-Derived
 Growth Factor-Binding Domain) for Controlled
 Release of the Bone Morphogenetic Protein from
 Collagen Biomaterials

Collagen biomaterials are widely used in regenerative medicine, serving as a biocompatible supporting scaffold to promote cell activities during tissue regeneration, and to modulate the release of drugs (e.g. growth factors) upon implantation. As an example, the clinical product InFUSE® Bone Graft (Medtronic) is composed of a bovine Type I collagen sponge laden with the bone morphogenetic protein-2 (BMP-2), a well-known growth factor promoting bone regeneration. In the clinic, delivery of supraphysiological doses of BMP-2 (order of milligrams) into patients raised serious side effects, including ectopic bone formation, nerve injuries and increased cancer risk. Consequently, engineering delivery systems to control the release of BMP-2, as well as other growth factors, from collagen biomaterials constitutes a strong matter of interest for therapeutic use of growth factors. Here, the inventors exemplified the use of the laminin α -chain LG4 domain (LamLG4) and the fibrinogen β -chain heparin-binding domain (FgHBD) (Martino et al., *PNAS*, 2012), as growth factor-binding domains, to control the retention of BMP-2 into collagen biomaterials, and subsequently slow down their release.

1. Protein Designs

The inventors have engineered bipartite «bridge» proteins composed of a growth factor-binding domain linked to a collagen I-binding domain, which are able to retain BMP-2 into collagen biomaterials via non-covalent interactions (FIG. 12). The growth factors binding domains, namely LamLG4 or FgHBD, display strong affinity to BMP-2, and the collagen I-binding domain display strong affinity to collagen biomaterials, more particularly to bovine type I collagen hydrogels and sponges. In this example, the collagen-binding domain is made of a human antigen-binding fragment Fab from an anti-collagen I antibody (here named FabCol) patented elsewhere (WO 2016016269 A1).

2. Materials and Methods

a. DNA Sequences Preparation

The sequences of the variable regions of FabCol were taken from the patent WO 2016016269A1 (clone C11) and synthesized by Genscript (USA), before being incorporated into a plasmid containing human Fab constant regions. Both recombinant light chain and heavy chain were placed under the control of CMV promoters. LamLG4 and p(FgHBD) sequences were synthesized by Genscript. To prepare the FabCol-LamLG4 recombinant fusion protein DNA sequence, LamLG4 domain was placed at the C-terminus of the FabCol heavy chain, and separated from it by an 8 amino acids glycine-serine linker. As to the FabCol-p(FgHBD) fusion protein, 3 copies of the FgHBD domain were inserted at the C-termini of both the light and the heavy chains of FabCol, each copy linked to another by a 8 amino acids glycine-serine linker.

b. Protein Production of FabCol, FabCol-LamLG4, FabCol-p(FgHBD)

DNA plasmids of FabCol, FabCol-LamLG4 and FabCol-p(FgHBD) were prepared using NucleoBond Xtra maxiprep kits (Macherey-Nagel, USA). Plasmids were then transfected into human embryonic kidney cells (HEK293-F) using polyethyleneimine-mediated transfection and 1.5 mg plasmid per L of culture. The cells were cultured in suspension for 7 days in Freestyle 293 medium (ThermoFisher Scientific, USA). The culture supernatant was then collected and purified using HiTrap Mab Select column and an Akta PureM25 fast protein liquid chromatography FPLC systems (GE Healthcare Life Sciences, USA) according to the manufacturer instructions. FabCol-LamLG4 and FabCol-p(FgHBD) recombinant fusion proteins were further purified using HiTrap Heparin HP columns (GE Healthcare). Proteins were then dialyzed in phosphate saline buffer (PBS; pH 7.4), sterile-filtered and stored at -80° C.

c. Chemical Conjugation of FgHBD to FabCol

FgHBD peptide (>95% pure) was synthesized by Genscript (USA). FgHBD was chemically conjugated to FabCol using sulfo-SMCC crosslinker (ThermoFisher Scientific). One mg of FabCol was incubated with 30-fold molar excess of the sulfo-SMCC in PBS at room temperature for 1 h, after what the excess crosslinker was removed using Zeba Spin desalting columns, 7K MWCO (ThermoFisher Scientific). FgHBD peptide was then added to the FabCol at 30-fold molar excess, and the mixture was incubated for 1 h at room temperature. Unconjugated peptides were then removed using an Amicon 30 kDa centrifugal filters by diluting FabCol-p(FgHBD) conjugates into PBS and re-concentrating them, in repeated cycles. The removal of unconjugated FgHBD was assessed by SDS-PAGE gel chromatography. The conjugates were kept at 4° C. for maximum 2 weeks prior to experimentation.

d. SDS-PAGE Analyses

SDS-PAGE was used to assess size of the different FabCol variants. Protein samples were diluted in Laemmli buffer and loaded on MiniProtean TGX precast gels (gradient 4-20%; BioRad, Hercules Calif., USA). Electrophoresis was run in Tris-Glycine-SDS buffer at 130 V for 1 h. Proteins were visualized using SimplyBlue SafeStain staining (ThermoFisher scientific).

e. Binding Assay to Bovine Type I Collagen

ELISA plates (NUNC MaxiSorp, ThermoFisher Scientific) were coated overnight with $10 \mu\text{g/mL}$ of bovine type I collagen (PureCol, Advanced BioMatrix, San Diego Calif., USA) at room temperature. The plate was further blocked using 2% bovine serum albumine (BSA) for 2 h at room temperature. Then, appropriate amount of the FabCol-FgHBD conjugates, FabCol-LamLG4 or FabCol-p(FgHBD) recombinant proteins were diluted in PBS-0.05% Tween (PBST)+0.1% BSA to reach concentrations ranging from 0.01 nM to 30 nM, and were incubated for 1 h at room temperature. The plate was washed thrice in PBST, and an horseradish peroxidase-conjugated anti-human Fab antibody (Jackson ImmunoResearch) was used to detect bound FabCol variants. The plate was revealed using TMB substrate solution, and stop with 1 M H₂SO₄. Absorbance at 450 nm was read using a Jackson ImmunoResearch, and corrected using the absorbance at 570 nm. Curve fits and dissociation constant KD were computed using Prism (GraphPad Software Inc., USA).

f. Binding Assay to rhBMP-2

ELISA plates (NUNC MaxiSorp) were coated with 50 nM of recombinant human BMP-2 (CHO produced, R&D Systems, Minneapolis Minn., USA) overnight at room temperature. The plate was then blocked using 2% BSA for 2 h at room temperature, after which the plate was washed in

PBST and incubated with 50 nM of the FabCol-FgHBD conjugates, FabCol-LamLG4 or FabCol-p(FgHBD) recombinant proteins diluted in PBS-0.05% Tween (PBST)+0.1% BSA. Bound FabCol variants were detected and revealed as described above.

g. Binding Assay to Engineered Super-Affinity Growth Factors

Engineered super-affinity growth factors and mouse wild-type VEGF-C were produced as described in Martino et al., *Science*, 2014. Other wild-type recombinant human growth factors were purchased from R&D Systems or Peptotech (Rocky Hill N.J., USA). Growth factors were coated on medium-binding plates (Greiner) at a concentration of 100 nM for 1 h at 37° C. Plates were then blocked with 2% BSA in PBS for 2 h at room temperature. Then, the FabCol variants (100 nM) were diluted in 1% BSA and incubated in the wells for 1 h at room temperature. The plate was washed four times in PB ST and an HRP-anti-human Fab antibody was used to detect bound FabCol variants. Plate absorbance was read as described above.

h. Release from Collagen Matrix

Collagen hydrogels of 150 μ L were prepared using PureCol bovine type I collagen (Advanced BioMatrix). FabCol variants (120 nM) and rhBMP-2 (500 ng/mL) were mixed with collagen (2.4 mg/mL) and 1 \times Minimum Essential Medium (MEM), used as a pH indicator. Under agitation, the pH was neutralized by adding 1 M NaOH, after what the mixture was directly plated into a 48-well plate, previously blocked overnight with 2% BSA in PBS. Gels were then polymerized for 1 h at 37° C. Release buffer (1 mL; Tris 20 mM, NaCl 150 mM, 0.1% BSA, 1% Penicillin-Streptomycin) was then added to the wells, and the gels were gently detached from the plate. The release buffer was collected and refreshed daily, and stored at -20° C. until analysis. A well that contained only BMP-2 served as a 100% released control. The amount of released rhBMP-2 was quantified using human BMP-2 DuoSet ELISA kit (R&D Systems), according to the manufacturer's instructions.

i. Immunohistochemistry Assessment of rhBMP-2 Retention into Collagen Sponge

Recombinant human BMP-2 (0.1 mg/mL in PBS) mixed with the FabCol variants at a 1:1 molar ratio was dripped onto collagen sponges (7 μ L; Integra LifeSciences, Plainsboro Township N.J., USA), and further incubated 15 min at room temperature. Sponges were washed twice for 2.5 h in 10 mL of PBS containing 2% Fetal Bovine Serum (FBS). Sponges were then fixed in 2% paraformaldehyde (PFA) for 30 min. Sponges were again washed in PBS-2% FBS, and stained using a biotinylated anti-hBMP-2 (R&D Systems) and a streptavidin-AF594 using standard staining procedures. Sponges were imaged using a Leica DMi8 microscope (Leica, Wetzlar, Germany) and analysed using Fiji software (ImageJ, National Institute of Health, USA).

3. Results:

a. Conjugation of a Collagen-Binding Domain FabCol to a Growth Factor-Binding Domain FgHBD

In this example, fibrinogen-derived domain FgHBD is used as the growth factor binding domain. The laminin-derived growth factor binding domains, such as LamLG4 may also be used. To engineer a bridge protein able to link growth factors into collagen biomaterials, FgHBD was chemically conjugated to FabCol using a sulfo-SMCC linker (FIG. 13A). Conjugation was confirmed by SDS-PAGE analysis, which revealed a shift of about 35 kDa in size between the non-conjugated FabCol and the FabCol-FgHBD conjugates. Such a size difference suggests that multiple copies of the FgHBD peptides were conjugated to

the FabCol (FIG. 13B). After conjugation, the binding of FabCol-FgHBD conjugates to bovine type I collagen was preserved, although the affinity was reduced compared to non-conjugated FabCol. The dissociation constant K_D of FabCol-FgHBD conjugates to collagen I was determined by ELISA to be of high affinity, around 2.8 nM (FIG. 13C). In addition, FabCol-FgHBD conjugates strongly bound to rhBMP-2, whereas FabCol only did not (FIG. 13D).

b. FabCol-FgHBD Conjugates Increased Retention of rhBMP-2 into Collagen Biomaterials

When incorporated into collagen hydrogels, FabCol-FgHBD strikingly increased the retention of rhBMP-2 (FIG. 13E); indeed, only 20% of rhBMP-2 was released after 7 days, in contrast to 80% for the gels containing rhBMP-2 only or in presence of FgHBD peptides, and 50% for the gels containing FabCol. In collagen sponges, increased sequestration in presence of FabCol-FgHBD, added at a 1:1 molar ratio with rhBMP-2, was visualized by immunohistochemistry (FIG. 13F). Under the tested experimental conditions, rhBMP-2 showed some retention into collagen sponge, yet the presence of FabCol-FgHBD conjugates substantially increased this retention.

c. Engineering Recombinant Fusion Protein Linking a Collagen-Binding Domain FabCol to LamLG4 or FgHBD Growth Factor-Binding Domains to Sequester rhBMP-2 into Collagen Biomaterials

Two recombinant fusion proteins were made to bridge growth factors, particularly rhBMP-2, to collagen biomaterials (FIG. 14A). In a first design, 3 sequential repeats of FgHBD domain separated by glycine-serine linkers were fused to both C-termini of the FabCol light and heavy chains. In a second design, the LamLG4 domain was fused to the C-terminus of the FabCol heavy chain. Both fusion proteins were successfully produced in HEK293 cells and purified using protein A and heparin affinity, confirming the presence of FabCol and the growth factor-binding domains on the fusion proteins. Indeed, both FgHBD and LamLG4 were shown to bind to heparin (Ishihara et al., *Nature Communications* 2018; Martino et al., *PNAS* 2013). Purified proteins were analysed by SDS-PAGE, which revealed the presence of multiple bands around 75 kDa for the FabCol-p(FgHBD) variant, which theoretical size is 80 kDa. In contrast, FabCol-LamLG4 variant appeared as a single band around 80 kDa while its theoretical size is 71 kDa (FIG. 14B). Importantly, strong affinity of FabCol-p(FgHBD) and FabCol-LamLG4 to bovine type I collagen was observed by ELISA, with K_{DS} around 1.7 nM and 2.3 nM respectively (FIG. 14C). Similarly, both variants strongly bound to rhBMP-2, with FabCol-LamLG4 being superior to FabCol-p(FgHBD) (FIG. 14D). Finally, release tests showed that rhBMP-2 sequestration into type I collagen is substantially increased in presence of FabCol-LamLG4 (FIG. 14E).

d. Combining FabCol-LamLG4 Bridge Protein Technology with the Engineering of Super-Affinity ECM-Binding Growth Factors to Further Enhance Growth Factors Delivery

Interestingly, the inventors further assessed the affinity of FabCol-LamLG4 to other growth factors and growth factors engineered for super-affinity to the ECM (Martino et al. *Science*, 2014, WO2014006082A1). Super-affinity growth factors were engineered as fusion of wild-type growth factors with an ECM-binding domain derived from the placental growth factor-2, which allow their strong retention within physiological ECMs, mostly through interactions to glycoproteins (e.g. fibronectin, vitronectin, tenascin) and glycosaminoglycans (e.g. heparan-sulfates GAGs). Because LamLG4 is derived from laminin, a well-known ECM

protein of the basement matrix, PIGF-2 engineered growth factors are expected to exhibit higher affinities to FabCol-LamLG4 than the wild-type growth factors. Indeed, one can appreciate in FIG. 14F that the binding of FabCol-LamLG4 to PIGF-2-engineered growth factors was significantly higher than the one to non-engineered wild-type growth factors. This results would suggest that retention of growth factors into collagen biomaterials in presence of FabCol-LamLG4 might be further increased by the engineering of the growth factor using the PIGF-2-derived ECM-binding domain, and so that these two technologies could rationally be used in combination.

4. Sequences:

FabCol light chain with the human Fab constant region:

(SEQ ID NO: 62)
EIVLTQSPGTLTSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG
QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWK
 VDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQ
 GLSSPVTKSFNRGEC

Anti-Collagen light chain variable region:
 (SEQ ID NO: 63)

EIVLTQSPGTLTSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG
QGTKVEIK

FabCol heavy chain with the human Fab constant region:

(SEQ ID NO: 64)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEQVSA
ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKTL
AAFQDYWGQGLTQVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
 EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN
 VNHKPSNTKVDKRVPEPKSCGS

Anti-Collagen heavy chain variable region:
 (SEQ ID NO: 65)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEQVSA
ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKTL
AAFQDYWGQGLTQV

FgHBD (used for conjugation):
 (SEQ ID NO: 66)

GCGGSLRPAPPPISGGGYRARPAAKAAATQKKVERKAPDA
 (SEQ ID NO: 67)
SLRPAPPPISGGGYRARPAAKAAATQKKVERKAPDA

FabCol-LamLG4 heavy chain with the human Fab constant region (LamLG4 is displayed in italic):
 (SEQ ID NO: 71)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEQVSA
ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKTL
AAFQDYWGQGLTQVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
 EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN
 VNHKPSNTKVDKRVPEPKSCGSGGSGG**SLNKPPFLMLLKGSTRFNKT**
KTFRINQLLQDTPVASPRSVKVVQDACSPKPKTQANH

-continued

GALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGL
VFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEK
CNDGKWHVVFGHDGEGKRLVVDGLRAREGSLPG
NSTISIRAPVYLGSPSPGKPKSIP TNSFVGLKKNFQLDSKPL
YTPSSSFGVSSCTG.

LamLG4 : (SEQ ID NO: 68)
SLNKPPFLMLLKGSTRFNKTTFRINQLLQDTPVASPRSVKVVQDACSPK

PKTQANH GALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLV F H
TGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEK CNDGKWHVVFGHDG
EKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPSPGKPKSIP TNSFVGL
LKNFQLDSKPLYTPSSSFGVSSCTG.

20 FabCol-p (FgHBD) light chain with the human Fab constant region (the 3 repeats of p (FgHBD) are displayed in italic):
 (SEQ ID NO: 72)

EIVLTQSPGTLTSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG

QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWK
VDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGECGAGGGGGGHRPLDK

30 **GLSSPVTKSFNRGECGAGGGGGGHRPLDK**

KREEAPSLRPAPPPISGGGYRARPAAKAAATQKKVERKA
PDAGGGGGGGGGHRPLDKKREEAPSLRPAPPPISGGG
YRARPAAKAAATQKKVERKAPDAGGGGGGGGGHRPL
DKKREEAPSLRPAPPPISGGGYRARPAAKAAATQKK
VERKAPDAGGGT.

Three repeats of p (FgHBD):
 (SEQ ID NO: 69)

GHRPLDKKREEAPSLRPAPPPISGGGYRARPAAKAAATQKKVERKAPDAGG
GSGGGGGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAAKAAATQKKVE
RKAPDAGGGGGGGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAAK
AATQKKVERKAPDAGGGT
 or

(SEQ ID NO: 70)
GHRPLDKKREEAPSLRPAPPPISGGGYRARPAAKAAATQKKVERKAPDAGG
GSGGGGGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAAKAAATQKKVE
RKAPDAGGGGGGGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAAK
AATQKKVERKAPDAGGTG

55 FabCol-p (FgHBD) heavy chain with the human Fab constant region (the 3 repeats of p (FgHBD) are displayed in italic):
 (SEQ ID NO: 73)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEQVSA
ISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKTL
AAFQDYWGQGLTQVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN
VNHKPSNTKVDKRVPEPKSCGSGGSGGGHRPLDKKREEAPSLRPAPPP

65 **VNHKPSNTKVDKRVPEPKSCGSGGSGGGHRPLDKKREEAPSLRPAPPP**

-continued

SGGGYRARPAAATQKKVERKAPDAGGSGGGSG

GGHRPLDKKREAPSLRPAPPPISGGYRARPAA

ATQKKVERKAPDAGGSGGGSGGHRPLDKKREAPSLR

PAPPPISGGYRARPAAATQKKVERKAPDAGGTG.

Example 4: A Peptide from Von Willebrand Factor
that Functions as a Growth Factor Reservoir to
Promote Wound Healing

During wound healing, the distribution, availability and signaling of growth factors (GFs) are orchestrated by their binding to extracellular components in the wound microenvironment and provisional matrix. The hemostatic protein von Willebrand factor (vWF) regulates angiogenesis; its deficiency or dysfunction is associated with vascular malformations. This example shows that vWF deficiency delays wound healing accompanied by decreased angiogenesis and decreased amounts of vascular endothelial growth factor-A (VEGF-A) in the wound. In vitro, vWF binds to several GFs and vWF binds to GFs in human serum. Serum from a type 2B von Willebrand disease (vWD) patient carrying the R1341Q point mutation within the vWF peptide showed reduced vWF-GF associations. Incorporation of the vWF peptide into fibrin matrices enabled sequestration and slow release of incorporated GFs. Treatment of chronic skin wounds with VEGF-A165 and platelet derived growth factor (PDGF)-BB incorporated within vWF peptide-functionalized fibrin matrices accelerated wound healing, with increased angiogenesis and smooth muscle cell proliferation. Therefore, the vWF peptide can function as a GFs reservoir, leading to effective angiogenesis and tissue regeneration.

1. Materials and Methods

a. Wound-Healing of vWF-Deficient Mice

Mouse surgical preparation, wounding, splinting, and bandaging was performed as previously described. Briefly, vWF deficient and littermate control mice ages 20 to 24 wk were used. Their backs were shaved and two full-thickness punch biopsy wounds (6 mm in diameter) were created in each mouse. Donut-like silicone disc was used as a splint. The splint was placed on the wound and anchor the splint with 6-0 nylon sutures to ensure positioning. Then, wounds were covered with a adhesive film dressing (Hydrofilm, Hartmann). After 5 d, wounds were collected and used for further analysis. All animal experiments were performed with approval from the Veterinary Authority of the Institutional Animal Care and Use Committee of the University of Chicago and Imperial College London in accordance with the UK Animals (Scientific Procedures) act of 1986.

b. Histomorphometric Analysis of Wound Tissue Sections

Histomorphometric analyses were performed as previously reported. Briefly, an area of 8 mm in diameter, which includes the complete epithelial margins, was excised. Wounds were fixed with 2% PFA and cut in the center into two and embedded into paraffin. Histological analysis was performed on 5 μ m serial sections. Images were captured with an EVOS FL Auto microscope (Life Technologies). The extent of re-epithelialization and granulation tissue formation were measured by histomorphometric analysis of tissue sections (H&E staining) using ImageJ software. For analysis of re-epithelialization, the distance that the epithelium had traveled across the wound was measured; the

muscle edges of the panniculus carnosus were used as an indicator for the initial wound edges, and re-epithelialization was calculated as the percentage of the distance of edges of the panniculus carnosus muscle. For granulation tissue quantification, the area covered by a highly cellular tissue was determined.

c. Flow Cytometric Analysis of the Wounds

The wounded skins regions were removed, cut into small pieces (<0.5 mm²) and transferred to 1 mL of an enzyme solution (collagenase D (1 mg/mL)) and agitated for 1 hr at 37° C. Then, the cells from digested wounds were re-suspended in PBS, passed through a cell strainer, and centrifuged. Then, cells were stained for 15 min in 100 μ L of FACS buffer containing antibodies: anti-CD31 (MEC13.3, BD Biosciences), anti-Ki67 (B56, BD Biosciences), anti-CD45 (30-F11), anti- α -smooth muscle actin (SMA) (R & D systems). Fixable live/dead cell discrimination was performed using Fixable Viability Dye eFluor 455 (eBioscience) according to the manufacturer's instructions. Intracellular staining was performed using the Intracellular Staining Permeabilization Wash Buffer according to manufacturer's instructions (BioLegend). Cells were analyzed using a Fortessa (BD Biosciences) flow cytometer and data was analyzed using FlowJo software (FlowJo, LLC).

d. Quantification of VEGF-A in the Wounds

Wounds were harvested using an 8 mm diameter biopsy punch. The tissue was transferred in 0.9 mL of tissue T-PER Tissue Protein Extraction Reagent (Thermo Scientific) containing 1 mg/mL of collagenase IV (Sigma-Aldrich), and homogenized with a tissue homogenizer. The tissue lysate was incubated 1 hr at 37° C. and 100 μ L of a 5 M NaCl solution containing protease inhibitors (1 tablet of protease inhibitor cocktail for 10 mL) added to the lysate. The samples were centrifuged at 10000 \times g for 5 min, and the supernatants were stored at -80° C. Recombinant human VEGF-A165 in the wound tissue was quantified by ELISA (DuoSet, R&D Systems).

e. Mouse Diabetic Skin Wound Healing Model

Diabetic skin wound healing assays were performed in the mouse as previously reported. Briefly, C57BLKS/J-m/Lepr db (db/db) male mice were 10 to 12 wk old at the start of the experiments. Their backs were shaved and four full-thickness punch biopsy wounds (6 mm in diameter) were created in each mouse. Directly after, fibrin matrices [80 mL total, fibrinogen (10 mg/mL), 2 μ M α_2 PI₁₋₈-vWF peptide, 100 ng of VEGF-A165, and 50 ng of PDGF-BB] were polymerized on the wounds; the N-terminal α_2 plasmin inhibitor peptide (α_2 PI₁₋₈) is a substrate for factor XIIIa and provides covalent incorporation of the vWF peptide into fibrin during coagulation, as previously reported for other biomolecules. To avoid drying of the matrices, the wounds were covered with adhesive film dressing (Hydrofilm, Hartmann). Mice were single-caged after the wound surgery. After 7 d, mice were sacrificed and the skin wounds were carefully harvested for histological analysis.

f. Statistical Analysis

Statistically significant differences between experimental groups were determined by one-way ANOVA followed by Tukey's HSD post hoc test with Prism software (v7, Graph-Pad). For single comparisons, a two-tailed Student's t-test was used. The symbols * and ** indicate p values less than 0.05 and 0.01, respectively; N.S., not significant.

2. Results

a. vWF Deficiency Results in Delayed Wound Healing by Decreased Angiogenesis

The inventors first tested whether endogenous vWF plays a role in dermal wound healing. Full-thickness back-skin

wounds were made on vWF-deficient mice and littermate wild-type (WT) controls. After 5 d, wounds were analyzed (FIG. 15). As a result, vWF deficiency significantly delayed wound closure, which was associated with poor granulation tissue formation (FIG. 15A-B). vWF deficiency decreased the proliferation of CD31⁺ endothelial cells and smooth muscle cells (SMCs), in the wounds, suggesting impaired angiogenesis (FIG. 8C-D). The inventors next tested the amount of VEGF-A, a strong angiogenesis inducer, per wound. ELISA after homogenization of wound tissue samples revealed that vWF deficiency decreased the amount of the VEGF-A in the wounds (FIG. 15E). These results suggest that vWF contributes to skin tissue repair through angiogenesis and GF involvement.

b. vWF Binds to Multiple GFs

The inventors then tested the hypothesis that vWF promiscuously binds to GFs. A panel of GFs from the PDGF/VEGF, FGF, TGF β /bone morphogenetic protein (BMP), neurotrophin, and chemokine families were selected. VEGF-A121, which did not show significant binding to vWF by surface plasmon resonance (SPR) (FIG. 21), was used as non-binding reference. The results of the binding screening are shown (FIG. 16A-B). As a result, vWF bound to VEGF-A165, placenta growth factor (PlGF)-2, PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD, but not to VEGF-A121 or PlGF-1, neither of which bind heparin. From the FGF family, vWF bound to FGF-2, FGF-7, and FGF-18, but not to FGF-1 or FGF-6. Among the transforming growth factor (TGF) β /bone morphogenetic protein (BMP) family, vWF showed strong binding to TGF- β 1 and BMP-2, but not to TGF- β 3 or BMP-7. Regarding the neurotrophins, both nerve growth factor (β -NGF) and neurotrophin-3 (NT-3) showed relevant binding. Neither insulin-like growth factor-I (IGF-I) nor IGF-II bound to vWF. In addition, epidermal growth factor (EGF) did not show binding to vWF. From the chemokine family, CXCL-11 bound to vWF and CXCL-12 α did not, whereas its isoform CXCL-12 γ which has an additional HBD in its C-terminus, showed strong binding signal to vWF. These data indicate that vWF binds to multiple heparin binding GFs.

The binding affinity of vWF to VEGF-A165 and PDGF-BB was determined by SPR (FIG. 16C-D). The curves obtained for the specific binding signals were fitted with Langmuir binding kinetics. The binding affinity between VEGF-A165 and vWF was described by a single dissociation constant (K_D value) of 27 nM. PDGF-BB had two estimated binding sites, with the lowest K_D value of 24 nM. The nM range of K_D values demonstrate strong binding affinities of vWF to the tested heparin-binding GFs.

c. vWF Binds to VEGF-A in Human Serum

The inventors next tested the presence of the GF-vWF complex in pooled serum from healthy donors. Both sandwich ELISA and immunoprecipitation followed by Western blotting showed that vWF binds to VEGF-A in two different lots of pooled human serum (FIG. 17A-B). These data suggest that VEGF-A-vWF complexes are present in the circulation.

d. The HBD of vWF A1 Domain Binds to Multiple GFs

The inventors next investigated the domain within vWF responsible for association with GFs. ELISA assays for vWF binding to VEGF-A165, PlGF-2 or FGF-2, were carried out in the presence of excess (10 μ M) heparin. Excess heparin inhibited vWF binding to the GFs (FIG. 22), indicating involvement of HBDs. The HBD of vWF is located in the A1 domain (FIG. 18A); thus the inventors evaluated GF binding to the recombinant A1 domain. VEGF-A165, PlGF-2, PDGF-BB, FGF-2 and CXCL-12 γ showed strong binding to

recombinant A1 domain, as measured by ELISA (FIG. 18B). The inventors next used a chemically synthesized vWF HBD (24-amino acid peptide, Table 1). In these studies, VEGF-A165, PlGF-2, PDGF-BB, FGF-2 and CXCL-12 γ showed binding to the vWF HBD, whereas neither VEGF-A121 nor PlGF-1 were able to bind to the vWF HBD, consistent with the results in FIG. 16 (FIG. 18C). These data show that the vWF A1 peptide binds to GFs.

e. vWF Binds to Heparin-Binding VEGF-A Via the HBD within the A1 Domain

The inventors examined the association between multiple recombinant isoforms of VEGF-A and vWF domains (FIG. 23A). VEGF-A165 was found to bind plasma-derived purified vWF as well as immature, pro-peptide-containing recombinant vWF (FIG. 23B). Similarly, VEGF-A145, which also contains VEGF's HBD, bound to vWF (FIG. 23C), whilst VEGF-A121, which lacks a HBD, did not (FIG. 23D). The vWF A1 domain bound to VEGF-A165 and VEGF-A145. However, no binding of the vWF A2 or A3 domains to VEGF-A165 or VEGF-A145 was detected (FIG. 23B-C). The vWF A1 HBD peptide was also able to bind to VEGF-A165 and VEGF-A145, with a similar magnitude. Scrambling of the amino acid sequence of the vWF A1 HBD abolished the binding (FIG. 23B-C), suggesting that the sequence, not just the total charge, is crucial for the association with VEGF-A165 and VEGF-A145. In addition, substitutions of Arg with Ser in the vWF A1 HBD sequence impaired the binding (FIG. 23B-C), indicating that the positively charged residues are essential. These data demonstrate that the HBDs in vWF A1 domain and in VEGF-A are responsible for binding between the two proteins.

f. Type 2B vWD R1341 Mutation Impairs vWF Binding to GF In Vitro and in Human Serum

Missense point mutations within the A1 domain of vWF have been reported in patients with type 2B vWD, a subtype where the increased affinity of vWF for GPIIb α results in spontaneous platelet aggregation, loss of the most active high molecular weight vWF multimers, thrombocytopenia and bleeding. Type 2B mutations are clustered in exon 28 of the vWF gene, encoding the vWF A1 domain, and some map within the HBD. One such mutation, affecting R1341 within the HBD, has been reported in several patients with type 2B vWD (vWF Variant Database found on the world wide web at vwf.group.shef.ac.uk/), with substitutions to either Leu, Pro, Gln, or Trp. Because Arg in HBDs seems to be crucial for the GF binding (FIG. 23B-C), The inventors next investigated whether this mutation could affect vWF-GF binding. Mutation of R1341 to any of these residues, or Ser, abolished binding between the vWF A1 HBD and GFs (considering VEGF-A165, PDGF-BB, and FGF-2) (FIG. 19A). These data indicate that the R1341 residue is indispensable for binding between vWF A1 HBD and GFs. Crucially, the R1341Q mutation also decreased binding to GFs (i.e. VEGF-A165, PDGF-BB, and FGF-2) to full-length recombinant human vWF, compared to its WT form (FIG. 19B). Moreover, serum from a patient with type 2B vWD carrying the R1341Q mutation displayed decreased vWF binding to GFs (i.e. VEGF-A165, PDGF-BB, and FGF-2), compared to serum from healthy donors (FIG. 19C).

Next, the inventors examined whether vWF HBD peptide is able to improve GF retention within a fibrin matrix, using VEGF-A165 and PDGF-BB, which have been observed to be quickly released from fibrin. Fibrinogen solutions containing GFs and the vWF HBD with integrated factor XIIIa transglutaminase reactive substrate sequence, i.e. α_2 PI₁₋₈-vWF HBD, were polymerized to form a fibrin matrix using thrombin and factor XIII. GF release from the matrix was

determined by ELISA (FIG. 20A-B). As previously shown, VEGF-A165 and PDGF-BB were quickly released from the unmodified fibrin matrix (>85% released after 1 d). However, by incorporating the $\alpha_2\text{PI}_{1-8}$ -vWF HBD peptide, VEGF-A165 and PDGF-BB were retained within the fibrin matrices (45% and 52% retention on day 5, respectively). These results demonstrate that the vWF HBD enhances the function of a fibrin matrix as a GF reservoir. The inventors also observed the effect of vWF HBD on slow-release of other GFs (i.e. CXCL-12 γ and FGF-2) from a poly ethylene glycol (PEG)-based synthetic matrix, which has no intrinsic affinity for GFs (FIG. 24). These data show that vWF HBD serves as a GFs reservoir in multiple contexts and for multiple factors.

g. $\alpha_2\text{PI}_{1-8}$ -vWF HBD Peptide Functionalized Fibrin Matrix Promotes Chronic Wound Healing In Vivo.

The inventors hypothesized that fibrin matrices functionalized with the vWF HBD peptide could potentiate the effect of GFs due to GF sequestration and resulting slow release from matrices, resulted in enhancing skin wound healing in a delayed wound healing model. A genetic mouse model of type 2 diabetes provides a well-established and clinically relevant experimental system of delayed wound healing, and induction of angiogenesis reportedly promotes wound healing in this model. VEGF-A165 and PDGF-BB, which are crucial angiogenesis inducers and exhibited binding to the vWF HBD, were incorporated within a fibrin matrix. As above, the inventors used the Factor XIIIa-induced coupling of the $\alpha_2\text{PI}_{1-8}$ sequence to fibrin with the $\alpha_2\text{PI}_{1-8}$ -vWF HBD to functionalize the matrix. Four groups of treatment were established: fibrin only, fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ -vWF HBD, fibrin containing the GFs, and fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ -vWF HBD containing the GFs. After 7 d, histology of wounded skin was analyzed. The wounds that received fibrin matrices containing only GFs or vWF HBD did not differ from wounds treated with fibrin alone, in either amount of granulation tissue or degree of wound closure (FIG. 20C). In contrast, the combined delivery of VEGF-A165 and PDGF-BB by fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ -vWF HBD led to significantly faster wound closure due to re-epithelialization. The development of granulation tissue was maintained (FIG. 20D). The inventors next examined endothelial cells in the wounds (FIG. 20E). Co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with $\alpha_2\text{PI}_{1-8}$ -vWF HBD led to a significantly increased frequency of CD31⁺CD45⁻ endothelial cells compared to fibrin only group after 5 d of wounding. Co-delivery of VEGF-A165 and PDGF-BB in $\alpha_2\text{PI}_{1-8}$ -vWF HBD functionalized fibrin significantly increased frequency of Ki67⁺, a proliferation marker, within SMCs compared to fibrin only and $\alpha_2\text{PI}_{1-8}$ -vWF HBD functionalized fibrin only treatment groups on day 5 (FIG. 20F). These data show that treatment with $\alpha_2\text{PI}_{1-8}$ -vWF HBD and GFs incorporated within a fibrin matrix promoted wound healing via angiogenesis by sequestration and slow release of VEGF-A165 and PDGF-BB.

h. vWF HBD does not Affect Endothelial or Fibroblast Proliferation In Vitro.

The inventors next tested functions of the vWF HBD on fibroblast and endothelial cell attachment and proliferation. vWF HBD peptide coating significantly enhanced fibroblast attachment (FIG. 25A); this effect was inhibited by adding 5 mM ethylenediaminetetraacetic acid (EDTA) to the in vitro culture, suggesting that vWF HBD peptide may bind to cation-dependent cell adhesion receptors such as integrins (FIG. 25B). Coating of the vWF HBD peptide on cell culture plates did not significantly affect fibroblast proliferation in the presence of FGF-2, suggesting that the vWF HBD may

slightly enhance cell adhesion, but did not induce cell proliferation in concert with at least this GF in vitro (FIG. 25C). Similarly, vWF HBD did not affect endothelial proliferation in vitro (FIG. 25D). These data support that, in the context of wound healing and tissue repair, the vWF HBD acts as a GF reservoir rather than a cell scaffold, promoting effective wound healing and angiogenesis through its binding to the growth factors.

i. Growth Factors and Chemokines

All GFs and chemokines were purchased in their mature forms, highly pure (>95% pure), carrier-free, and lyophilized, as previously reported¹. VEGF-A121, VEGF-A165, PlGF-1, PlGF-2, PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD, FGF-1, FGF-2, FGF-6, FGF-7, FGF-18, TGF- β 1, TGF- β 3, BMP-2, BMP-7, NGF, NT-3, IGF-I, IGF-II, EGF, CXCL-11, and CXCL-12 α were purchased from PeproTech. CXCL-12 γ was purchased from R & D Systems. Except for PDGF-DD, TGF- β 1, TGF- β 3, and BMP-7, which were produced in eukaryotic cells, all GFs were produced in *Escherichia coli* and thus were not glycosylated. All GFs were reconstituted and stored according to the provider's instructions to regain full activity and prevent loss of protein.

j. Detection of vWF Binding to Recombinant GFs

ELISA tests were performed as previously reported¹. In brief, ELISA plates (med-binding, Greiner Bio-One) were coated with 50 nM GFs at 37° C. for 2 hrs. After blocking with 2% BSA solution containing PBS-T, 1 $\mu\text{g}/\text{mL}$ of plasma-derived vWF (EMD Millipore) was added. Bound vWF was detected with 1 $\mu\text{g}/\text{mL}$ of rabbit anti-human vWF antibody (Sino Biological). Then, HRP conjugated goat anti-rabbit antibody (Jackson ImmunoResearch) was added. After 60 min of incubation, 50 μL TMB substrate (Sigma-Aldrich) was added. The reaction was stopped by adding 25 μL of 2N H₂SO₄. Subsequently, the absorbance at 450 nm was measured and subtracted the absorbance at 570 nm.

k. Surface Plasmon Resonance (SPR)

SPR assays were performed as described previously². In brief, measurements were made with a Biacore X100 SPR system or Biacore 3000 SPR system (GE Healthcare). Plasma-derived vWF was immobilized via amine coupling on a C1 chip (GE Healthcare) for 2000 resonance units (RU) according to the manufacturer's instructions. Recombinant human VEGF-A165, VEGF-A121, or PDGF-BB was flowed at increasing concentrations in the running buffer at 30 $\mu\text{L}/\text{min}$. The sensor chip was regenerated with glycine at pH 2 for every cycle. Specific binding of GFs to vWF was calculated automatically using the response to a non-functionalized channel as a reference. Binding curves were fitted using BIAevaluation software (GE Healthcare). vWF-VEGF-A165 binding results were fitted with Langmuir binding kinetics (1:1 binding with drifting baseline Rmax local). vWF-PDGF-BB binding results were fitted with heterogeneous ligand-parallel reaction.

l. Inhibition of vWF-GF Binding by Heparin

ELISA plates (med-binding) were coated with 10 $\mu\text{g}/\text{mL}$ vWF. Then, wells were blocked with 2% BSA-containing PBS-T and further incubated with 1 $\mu\text{g}/\text{mL}$ each of VEGF-A, PlGF-2, or FGF-2 for 60 min at room temperature (RT) with 10 μM heparin. Next, the wells were incubated with biotinylated anti-VEGF-A, anti-PlGF, or anti-FGF-2 antibodies (R & D Systems). The antibodies were detected by streptavidin-HRP (R & D Systems). Color development and the absorbance measurement were done as described above.

m. Detection of vWF Binding to VEGF-A by Western Blotting

One mL of human serum was immunoprecipitated with 10 μ g of monoclonal rabbit anti-human vWF antibody (Sino-Biological) or control rabbit IgG (EMD Millipore) and 50 μ L of protein G-agarose (Thermo Fisher Scientific) overnight at 4° C. The resulting pellet was dissolved in Laemmli buffer and subjected to Western blot analysis. Western blot analysis was performed after SDS-PAGE (4-20% gradient gel, Bio-Rad) and transfer onto MS nitrocellulose membranes (Membrane Solutions). GFs were detected using 1 μ g/mL biotinylated antibodies for human VEGF-A (R & D Systems), followed by incubation with HRP conjugated streptavidin (R & D Systems) at 1:200 dilutions. The proteins were detected and visualized with the ECL Plus Western Blotting Detection System (GE Healthcare).

n. Detection of vWF Binding to GFs in Human Serum by ELISA

The study was approved by the ethics committees of the Hammersmith, Queen Charlotte's, and Royal Marsden hospitals; informed consent was obtained from all individuals in accordance with the Declaration of Helsinki. ELISA plates (med-binding) were coated with 10 μ g/mL rabbit monoclonal anti-human vWF antibody (clone: 111, SinoBiological). Then, wells were blocked with 2% BSA-containing PBS-T and further incubated with human serum derived from healthy donor (Sigma-Aldrich) or type 2B vWD patient for 60 min at RT. Next, the wells were incubated with biotinylated antibodies for human VEGF-A, PDGF-BB or FGF-2 (R & D Systems). The antibodies were detected by streptavidin-HRP (R & D Systems). Color development and the absorbance measurement were done as described above.

o. Expression of Recombinant vWF

The expression vector pcDNA-full length(FL)-vWF has been previously described³. R1341 residue was mutated to Glutamine (Q) using the QuikChange® XL site-directed mutagenesis kit (Stratagene). The sequences were verified and fragments containing mutations were subcloned into a vector containing full length vWF. Briefly, the 5' XhoI to KpnI fragment was digested from pGEM (XhoI-KpnI) while the 5' KpnI to AgeI fragment from pcDNA3.1-A2-CK vector, those were then cloned into pcDNA 3.1 FL-vWF-KpnI that had been digested with the same enzymes. Recombinant WT and R1341Q vWF were expressed in HEK293T cells as previously described using 10 mM polyethylenimine (PEI) as transfection reagent³. The conditioned medium was collected after 3 days, filtered and if required, concentrated or purified for further analysis. Recombinant vWF was purified using a combination of ion-exchange and heparin-Sepharose affinity chromatography as previously described^{3,4}. Briefly, filtered vWF expression medium was applied to an SK-16 chromatography column (Amersham Pharmacia, UK) previously packed with Fractogel-EMD-TMAE+ (Merck) according to manufacturers instructions. The VWF was then eluted using 20 mM Tris, 500 mM NaCl, pH 7.4 and dialysed into 20 mM Tris, 150 mM NaCl, pH 7.4 and further purified using a Heparin-Sepharose 6 fast flow column (Amersham Pharmacia, UK). The purity of vWF was assessed by SDS-PAGE gel electrophoresis and concentration determined by vWF-ELISA.

p. Detection of Recombinant GF Binding to the vWF Recombinant Protein and A1 HBD Peptide.

ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 μ g/mL of FL-vWF (WT or R1341Q), 1 μ g/mL of vWF A1 recombinant protein (U-Protein Express) or 1 μ g/mL of vWF A1 HBD peptide (sequence YIGLKDRKRPSELRRRIASQVKYA, (SEQ ID

NO:50) chemically synthesized by Genscript) at 37° C. overnight. After blocking with 2% BSA solution containing PBS-T, 1 μ g/mL of the recombinant human proteins VEGF-A121, VEGF-A165, PIGF-1, PIGF-2, PDGF-BB, FGF-2, CXCL-12 α and CXCL-12 γ were added. 1 μ g/mL of BSA served as non-binding protein control. Bound GF or chemokine was detected with biotinylated antibodies for human VEGF-A, PIGF, PDGF-BB, FGF-2, or CXCL-12 (R & D Systems). The antibodies were detected by streptavidin-HRP (R & D Systems). Color development and the absorbance measurement were done as described above.

q. Detection of vWF Binding to Recombinant VEGF-A Isoforms

ELISA was performed as previously reported¹. In brief, ELISA plates (med binding: Greiner Bio-One) were coated with 50 nM BSA (GE Healthcare), pro-peptide containing recombinant vWF (Sino Biological), plasma-derived vWF (EMD Millipore), recombinant human vWF A1 domain (U-Protein Express), recombinant human vWF A2 domain (R & D systems), recombinant human vWF A3 domain (U-Protein Express), vWF A1 HBD peptide or scrambled/mutated HBD peptide (all peptides were synthesized by Genscript). After blocking with 2% BSA solution containing PBS-T, 1 μ g/mL of recombinant human VEGF-A121 (PeproTech), recombinant human VEGF-A145 (R & D Systems), or recombinant human VEGF-A165 (PeproTech) was added. Bound VEGF-A was detected with 1 μ g/mL of mouse anti-human VEGF-A antibody (clone: 26503, R & D systems). After 60 min of incubation, horseradish peroxidase (HRP) conjugated goat anti-mouse antibody (1:2000 dilution, Dako) was added and incubated for another 60 min. Color development and the absorbance measurement were done as described above.

r. Release of GF from Fibrin Matrix

Fibrin matrices were generated with human fibrinogen as described previously^{1,5}. In brief, fibrin matrices were generated with 8 mg/mL fibrinogen, 2 U/mL human thrombin (Sigma-Aldrich), 4 U/mL factor XIIIa (Fibrogammin; Behring), 5 mM calcium chloride, 2 μ M \square 2PI1-8-vWF HBD peptide (NQEQVSPLYIGLKDRKRPSELRRRIASQVKYA (SEQ ID NO:51), chemically synthesized by Genscript), and 500 ng/mL recombinant human VEGF-A165 or PDGF-BB. Fibrin gels were polymerized at 37° C. for 1 hr and transferred into 24-well Ultra Low Cluster plates (Corning) containing 500 μ L of buffer (20 mM Tris-HCl, 150 mM NaCl, and 0.1% BSA; pH 7.4). A control well that served as a 100% released control contained only the GF in 500 μ L of buffer. Every 24 hr, buffers were removed, stored at -20° C., and replaced with fresh buffer. For the 100% released control well, 20 μ L of buffer was removed each day. After 5 d, the cumulative release of GF was quantified by ELISA (DuoSet; R&D Systems), using the 100% released control as a reference.

s. Release of GFs from Fibrin-Mimetic Matrix

Fibrin-mimetic matrices were formed from reactive PEG precursors as previously described⁶. Matrices (50 μ L) were generated in 50 mM Tris buffer (pH 7.6) to obtain 1.75% (wt/vol) PEG, 10 μ M vWF HBD-Cys (YIGLKDRKRPSELRRRIASQVKYAC (SEQ ID NO:49), chemically synthesized by Genscript), 10 U/mL factor XIIIa, 50 mM CaCl₂, 1 μ g/mL FGF-2 and 1 μ g/mL CXCL-12 γ . Fibrin-mimetic gels were polymerized at 37° C. for 1 hr and then transferred into 24-well Ultra Low Cluster plates (Corning) containing 1 mL of buffer (20 mM Tris-HCl, 150 mM NaCl, and 0.1% BSA; pH 7.4). A control well that served as 100% released control contained only the GFs in 1 mL of buffer. Every 24 hr, buffers were removed, stored at

-20° C., and replaced with fresh buffer. For the 100% released control well, 20 µL of buffer was removed each day and stored at -20° C. Cumulative release of GF was quantified by ELISA (DuoSet; R&D Systems), using the 100% released control as a reference.

t. Cell Adhesion Assay

Cell adhesion assays were performed using starved human lung fibroblasts (Lonza) in FGM-2 medium (Lonza) with or without 5 mM EDTA. Cells were plated at 3000 cells/well on 1 µg/mL vWF HBD pre-coated 96-well plates (non-tissue culture treated, Greiner Bio-one) and incubated for 30 min at 37° C. Then, the medium was removed, and wells were further washed three times with new FGM-2 medium. Cell numbers were quantified using a CyQUANT assay (Invitrogen).

u. Cell Proliferation Assay with vWF HBD

Cell proliferation assays were performed as previously reported¹. Briefly, human lung fibroblasts (Lonza) were cultured using FGM-2 medium (Lonza) (1000 cells/well) or human umbilical vein endothelial cells (HUVEC, Lonza) were cultured using EGM-2 medium (Lonza) (1000 cells/well) on 1 µg/mL vWF HBD pre-coated 96-well plates (Tissue culture treated, Falcon). Cell numbers were quantified after 72 hrs using a CyQUANT assay (Invitrogen).

TABLE 1

THE SEQUENCES OF VWF A1 HBD PEPTIDES		
SEQ ID NO	Name	Peptide sequence
49	vWF A1 HBD	YIGLKDRKRPELRRRIASQVKYAC
52	Scrambled HBD	LYCEIARGYSLKRKVPDQIRSRKA
53	Arg substituted HBD	YIGLKDSKSPSELSSIASQVKYAC
54	Naïve	YIGLKDRKRPELRRRIASQVKYA
55	R1341L	YIGLKDRKRPESELLRIASQVKYA
56	R1341P	YIGLKDRKRPELPRIASQVKYA
57	R1341Q	YIGLKDRKRPELQRIASQVKYA
58	R1341W	YIGLKDRKRPELWRIASQVKYA
59	R13415	YIGLKDRKRPELSRIASQVKYA

Although certain embodiments have been described above with a certain degree of particularity, or with reference to one or more individual embodiments, those skilled in the art could make numerous alterations to the disclosed embodiments without departing from the scope of this invention. Further, where appropriate, aspects of any of the examples described above may be combined with aspects of any of the other examples described to form further examples having comparable or different properties and addressing the same or different problems. Similarly, it will be understood that the benefits and advantages described above may relate to one embodiment or may relate to several 50 embodiments. Any reference to a patent publication or other publication is a herein a specific incorporation by reference of the disclosure of that publication. The claims are not to be interpreted as including means-plus- or step-plus-function limitations, unless such a limitation is explicitly recited in a given claim using the phrase(s) “means for” or “step for,” 65 respectively.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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Thr Arg Ser Ser His Gly Met Ile Phe Tyr Val Ser Asp Gln Glu Glu
 35 40 45

Asn Asp Phe Met Thr Leu Phe Leu Ala His Gly Arg Leu Val Tyr Met
 50 55 60

Phe Asn Val Gly His Lys Lys Leu Lys Ile Arg Ser Gln Glu Lys Tyr
 65 70 75 80

Asn Asp Gly Leu Trp His Asp Val Ile Phe Ile Arg Glu Arg Ser Ser
 85 90 95

Gly Arg Leu Val Ile Asp Gly Leu Arg Val Leu Glu Glu Ser Leu Pro
 100 105 110

Pro Thr Glu Ala Thr Trp Lys Ile Lys Gly Pro Ile Tyr Leu Gly Gly
 115 120 125

Val Ala Pro Gly Lys Ala Val Lys Asn Val Gln Ile Asn Ser Ile Tyr
 130 135 140

Ser Phe Ser Gly Cys Leu Ser Asn Leu Gln Leu Asn Gly Ala Ser Ile
 145 150 155 160

Thr Ser Ala Ser Gln Thr Phe Ser Val Thr Pro Cys
 165 170

<210> SEQ ID NO 15
 <211> LENGTH: 174
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Ser Tyr Gln Phe Gly Gly Ser Leu Ser Ser His Leu Glu Phe Val Gly
 1 5 10 15

Ile Leu Ala Arg His Arg Asn Trp Pro Ser Leu Ser Met His Val Leu
 20 25 30

Pro Arg Ser Ser Arg Gly Leu Leu Leu Phe Thr Ala Arg Leu Arg Pro
 35 40 45

Gly Ser Pro Ser Leu Ala Leu Phe Leu Ser Asn Gly His Phe Val Ala
 50 55 60

Gln Met Glu Gly Leu Gly Thr Arg Leu Arg Ala Gln Ser Arg Gln Arg
 65 70 75 80

Ser Arg Pro Gly Arg Trp His Lys Val Ser Val Arg Trp Glu Lys Asn
 85 90 95

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

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

Phe Val Gly Gly Leu Pro Ala Ser Ser His Ser Ser Lys Leu Pro Val
 130 135 140

Thr Val Gly Phe Ser Gly Cys Val Lys Arg Leu Arg Leu His Gly Arg
 145 150 155 160

Pro Leu Gly Ala Pro Thr Arg Met Ala Gly Val Thr Pro Cys
 165 170

<210> SEQ ID NO 16
 <211> LENGTH: 177
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 16

Asn Gln Glu Gln Val Ser Pro Leu Gly Gly Ser Gly Ala Leu Gln Phe
 1 5 10 15

Gly Asp Ile Pro Thr Ser His Leu Leu Phe Lys Leu Pro Gln Glu Leu
 20 25 30

Leu Lys Pro Arg Ser Gln Phe Ala Val Asp Met Gln Thr Thr Ser Ser
 35 40 45

Arg Gly Leu Val Phe His Thr Gly Thr Lys Asn Ser Phe Met Ala Leu
 50 55 60

Tyr Leu Ser Lys Gly Arg Leu Val Phe Ala Leu Gly Thr Asp Gly Lys
 65 70 75 80

Lys Leu Arg Ile Lys Ser Lys Glu Lys Cys Asn Asp Gly Lys Trp His
 85 90 95

Thr Val Val Phe Gly His Asp Gly Glu Lys Gly Arg Leu Val Val Asp
 100 105 110

Gly Leu Arg Ala Arg Glu Gly Ser Leu Pro Gly Asn Ser Thr Ile Ser
 115 120 125

Ile Arg Ala Pro Val Tyr Leu Gly Ser Pro Pro Ser Gly Lys Pro Lys
 130 135 140

Ser Leu Pro Thr Asn Ser Phe Val Gly Cys Leu Lys Asn Phe Gln Leu
 145 150 155 160

Asp Ser Lys Pro Leu Tyr Thr Pro Ser Ser Ser Phe Gly Val Ser Ser
 165 170 175

Cys

<210> SEQ ID NO 17
 <211> LENGTH: 184
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 17

Asn Gln Glu Gln Val Ser Pro Leu Gly Gly Ser Gly Ala Tyr Gln Tyr
 1 5 10 15

Gly Gly Thr Ala Asn Ser Arg Gln Glu Phe Glu His Leu Lys Gly Asp
 20 25 30

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

<210> SEQ ID NO 18
 <211> LENGTH: 186
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 18
 Asn Gln Glu Gln Val Ser Pro Leu Gly Gly Ser Gly Ser Tyr Gln Phe
 1 5 10 15
 Gly Gly Ser Leu Ser Ser His Leu Glu Phe Val Gly Ile Leu Ala Arg
 20 25 30
 His Arg Asn Trp Pro Ser Leu Ser Met His Val Leu Pro Arg Ser Ser
 35 40 45
 Arg Gly Leu Leu Leu Phe Thr Ala Arg Leu Arg Pro Gly Ser Pro Ser
 50 55 60
 Leu Ala Leu Phe Leu Ser Asn Gly His Phe Val Ala Gln Met Glu Gly
 65 70 75 80
 Leu Gly Thr Arg Leu Arg Ala Gln Ser Arg Gln Arg Ser Arg Pro Gly
 85 90 95
 Arg Trp His Lys Val Ser Val Arg Trp Glu Lys Asn Arg Ile Leu Leu
 100 105 110
 Val Thr Asp Gly Ala Arg Ala Trp Ser Gln Glu Gly Pro His Arg Gln
 115 120 125
 His Gln Gly Ala Glu His Pro Gln Pro His Thr Leu Phe Val Gly Gly
 130 135 140
 Leu Pro Ala Ser Ser His Ser Ser Lys Leu Pro Val Thr Val Gly Phe
 145 150 155 160
 Ser Gly Cys Val Lys Arg Leu Arg Leu His Gly Arg Pro Leu Gly Ala
 165 170 175
 Pro Thr Arg Met Ala Gly Val Thr Pro Cys
 180 185

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<210> SEQ ID NO 19
 <211> LENGTH: 495
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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gccctccagt ttggggacat tcccaccagc cacttgetat tcaagcttcc tcaggagctg   60
ctgaaaccca ggtcacagtt tgctgtggac atgcagacaa catcctccag aggactggtg   120
tttcacacgg gcactaagaa ctcttttatg gctctttatc tttcaaaagg acgtctggtc   180
tttgactggt ggacagatgg gaaaaaattg aggatcaaaa gcaaggagaa atgcaatgat   240
gggaaatggc acacgggtgt gtttggccat gatggggaaa aggggcgctt ggttgtggat   300
ggactgaggg cccgggaggg aagtttgctt ggaaactcca ccacagcat cagagcgcca   360
gtttacctgg gatcacctcc atcagggaaa ccaaagagcc tccccacaaa cagctttgtg   420
ggatgcctga agaactttca gctggattca aaacccttgt atacccttc tcaagcttc   480
ggggtgtctt cctgc                                         495

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<210> SEQ ID NO 20
 <211> LENGTH: 516
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

```

gcctatcaat atggaggaac agccaacagc cgccaagagt ttgaacctt aaaaggagat   60
tttggtgcca aatctcagtt ttccattcgt ctgagaactc gttcctcca tggcatgatc   120
ttctatgtct cagatcaaga agagaatgac ttcattgactc ttttttggc ccatggccgc   180
ttggtttaca tgtttaatgt tggtcacaaa aaactgaaga ttagaagcca ggagaaatac   240
aatgatggcc tgtggcatga tgtgatattt attcgagaaa ggagcagtgg ccgactggta   300
attgatggtc tccagatcct agaagaaagt cttcctccta ctgaagctac ctggaaaatc   360
aagggtccca tttatttggg aggtgtggct cctggaaagg ctgtgaaaaa tgttcagatt   420
aactccatct acagttttag tggctgtctc agcaatctcc agctcaatgg ggctccatc   480
acctctgctt ctcagacatt cagtgtgacc cettgc                                         516

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<210> SEQ ID NO 21
 <211> LENGTH: 522
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

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tcctaccagt ttgggggttc cctgtccagt cacctggagt ttgtgggcat cctggcccga   60
cataggaact ggcccagctc ctccatgcac gtctcccgc gaagctcccg aggcctcctc   120
ctcttcaactg cccgtctgag gcccggcagc cctccctggc cgtcttctc gagcaatggc   180
cacttcgttg cacagatgga aggcctcggg actcggtccc gcgccagag ccgccagcgc   240
tccccgcctg gccgctggca caaggctccc gtgcgctggg agaagaaccg gatcctgctg   300
gtgacggacg gggccccggc ctggagccag gaggggccgc accggcagca ccagggggca   360
gagcaccccc agccccacac cctctttgtg ggcggcctcc cggccagcag ccacagctcc   420
aaacttccgg tgaccgtcgg gttcagcggc tgtgtgaaga gactgaggct gcacgggagg   480
cccctggggg cccccacag gatggcaggg gtcacaccct gc                                         522

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<210> SEQ ID NO 22
<211> LENGTH: 531
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
        Synthetic polynucleotide"

<400> SEQUENCE: 22

aaccaggagc aggtgtcccc acttggtgga tccggcgccc tccagtttgg ggacattccc      60
accagccact tgctattcaa gcttcctcag gagctgctga aaccagggtc acagtttgct      120
gtggacatgc agacaacatc ctccagagga ctgggttttc acacgggcac taagaactcc      180
tttatggctc tttatcttcc aaaaggacgt ctggcttttg cactggggac agatgggaaa      240
aaattgagga tcaaaagcaa ggagaaatgc aatgatggga aatggcacac ggtggtgttt      300
ggccatgatg gggaaaaggg gcgcttggtt gtggatggac tgagggcccg ggagggaaagt      360
ttgcctggaa actccaccat cagcatcaga ggccagttt acctgggatc acctccatca      420
gggaaaccaa agagcctccc cacaacagc tttgtgggat gctgaagaa ctttcagctg      480
gattcaaac cctgtatata ccctcttca agcttcgggg tgtcttctcg c              531

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<210> SEQ ID NO 23
<211> LENGTH: 552
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
        Synthetic polynucleotide"

<400> SEQUENCE: 23

aaccaggagc aggtgtcccc acttggtgga tccggcgccc atcaatatgg aggaacagcc      60
aacagccgcc aagagtttga acacttaaaa ggagattttg gtgccaaatc tcagttttcc      120
attcgtctga gaactcgttc ctcccatggc atgatcttct atgtctcaga tcaagaagag      180
aatgacttca tgactctatt tttggcccat ggccgcttgg tttacatggt taatgttggt      240
cacaaaaaac tgaagattag aagccaggag aaatacaatg atggcctgtg gcatgatgtg      300
atatttattc gagaaaggag cagtggccga ctggtaattg atggtctccg agtcctagaa      360
gaaagtcttc ctctactga agctacctgg aaaatcaagg gtcccattta tttgggaggt      420
gtggctctcg gaaaggctgt gaaaaatggt cagattaact ccactacag ttttagtggc      480
tgtctcagca atctccagct caatggggcc tccatcacct ctgcttctca gacattcagt      540
gtgaccctt gc              552

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<210> SEQ ID NO 24
<211> LENGTH: 558
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
        Synthetic polynucleotide"

<400> SEQUENCE: 24

aaccaggagc aggtgtcccc acttggtgga tccggctcct accagtttgg gggttccctg      60
tccagtcacc tggagtttgt gggcatcctg gcccgacata ggaactggcc cagtctctcc      120
atgcacgtcc tcccgcgaag ctcccgaggc ctctctctct tcaactgccg tctgaggccc      180

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ggcagccct cctggcgct cttctgagc aatggccact tegtgcaca gatggaaggc 240
ctcgggactc ggtccgcgc ccagagccgc cagcgtccc ggctggccg ctggcacaag 300
gtctccgtgc gctgggagaa gaaccggatc ctgctggtga cggacggggc cggggcctgg 360
agccaggagg ggcgcaccg gcagcaccag ggggcagagc acccccagcc ccacaccctc 420
tttgtgggcg gctcccggc cagcagccac agctccaaac ttccggtgac cgtcgggttc 480
agcggctgtg tgaagagact gaggctgcac gggaggcccc tgggggcccc cacacggatg 540
gcaggggtca caccctgc 558
    
```

```

<210> SEQ ID NO 25
<211> LENGTH: 3075
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
    
```

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<400> SEQUENCE: 25
    
```

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Met Arg Gly Gly Val Leu Leu Val Leu Leu Leu Cys Val Ala Ala Gln
1          5          10          15
Cys Arg Gln Arg Gly Leu Phe Pro Ala Ile Leu Asn Leu Ala Ser Asn
20          25          30
Ala His Ile Ser Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met
35          40          45
Phe Cys Lys Leu Val Glu His Val Pro Gly Arg Pro Val Arg Asn Pro
50          55          60
Gln Cys Arg Ile Cys Asp Gly Asn Ser Ala Asn Pro Arg Glu Arg His
65          70          75          80
Pro Ile Ser His Ala Ile Asp Gly Thr Asn Asn Trp Trp Gln Ser Pro
85          90          95
Ser Ile Gln Asn Gly Arg Glu Tyr His Trp Val Thr Ile Thr Leu Asp
100         105         110
Leu Arg Gln Val Phe Gln Val Ala Tyr Val Ile Ile Lys Ala Ala Asn
115         120         125
Ala Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Gly Thr
130         135         140
Thr Phe Ser Pro Trp Gln Tyr Tyr Ala Val Ser Asp Ser Glu Cys Leu
145         150         155         160
Ser Arg Tyr Asn Ile Thr Pro Arg Arg Gly Pro Pro Thr Tyr Arg Ala
165         170         175
Asp Asp Glu Val Ile Cys Thr Ser Tyr Tyr Ser Arg Leu Val Pro Leu
180         185         190
Glu His Gly Glu Ile His Thr Ser Leu Ile Asn Gly Arg Pro Ser Ala
195         200         205
Asp Asp Leu Ser Pro Lys Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile
210         215         220
Arg Leu Arg Leu Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Thr
225         230         235         240
Leu Ser His Arg Glu Pro Lys Glu Leu Asp Pro Ile Val Thr Arg Arg
245         250         255
Tyr Tyr Tyr Ser Ile Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys
260         265         270
Tyr Gly His Ala Ser Ser Cys Pro Trp Asp Glu Thr Thr Lys Lys Leu
275         280         285
Gln Cys Gln Cys Glu His Asn Thr Cys Gly Glu Ser Cys Asn Arg Cys
290         295         300
    
```

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Cys Pro Gly Tyr His Gln Gln Pro Trp Arg Pro Gly Thr Val Ser Ser
 305 310 315 320
 Gly Asn Thr Cys Glu Ala Cys Asn Cys His Asn Lys Ala Lys Asp Cys
 325 330 335
 Tyr Tyr Asp Glu Ser Val Ala Lys Gln Lys Lys Ser Leu Asn Thr Ala
 340 345 350
 Gly Gln Phe Arg Gly Gly Gly Val Cys Ile Asn Cys Leu Gln Asn Thr
 355 360 365
 Met Gly Ile Asn Cys Glu Thr Cys Ile Asp Gly Tyr Tyr Arg Pro His
 370 375 380
 Lys Val Ser Pro Tyr Glu Asp Glu Pro Cys Arg Pro Cys Asn Cys Asp
 385 390 395 400
 Pro Val Gly Ser Leu Ser Ser Val Cys Ile Lys Asp Asp Leu His Ser
 405 410 415
 Asp Leu His Asn Gly Lys Gln Pro Gly Gln Cys Pro Cys Lys Glu Gly
 420 425 430
 Tyr Thr Gly Glu Lys Cys Asp Arg Cys Gln Leu Gly Tyr Lys Asp Tyr
 435 440 445
 Pro Thr Cys Val Ser Cys Gly Cys Asn Pro Val Gly Ser Ala Ser Asp
 450 455 460
 Glu Pro Cys Thr Gly Pro Cys Val Cys Lys Glu Asn Val Glu Gly Lys
 465 470 475 480
 Ala Cys Asp Arg Cys Lys Pro Gly Phe Tyr Asn Leu Lys Glu Lys Asn
 485 490 495
 Pro Arg Gly Cys Ser Glu Cys Phe Cys Phe Gly Val Ser Asp Val Cys
 500 505 510
 Ser Ser Leu Ser Trp Pro Val Gly Gln Val Asn Ser Met Ser Gly Trp
 515 520 525
 Leu Val Thr Asp Leu Ile Ser Pro Arg Lys Ile Pro Ser Gln Gln Asp
 530 535 540
 Ala Leu Gly Gly Arg His Gln Val Ser Ile Asn Asn Thr Ala Val Met
 545 550 555 560
 Gln Arg Leu Ala Pro Lys Tyr Tyr Trp Ala Ala Pro Glu Ala Tyr Leu
 565 570 575
 Gly Asn Lys Leu Thr Ala Phe Gly Gly Phe Leu Lys Tyr Thr Val Ser
 580 585 590
 Tyr Asp Ile Pro Val Glu Thr Val Asp Ser Asn Leu Met Ser His Ala
 595 600 605
 Asp Val Ile Ile Lys Gly Asn Gly Leu Thr Leu Ser Thr Gln Ala Glu
 610 615 620
 Gly Leu Ser Leu Gln Pro Tyr Glu Glu Tyr Leu Asn Val Val Arg Leu
 625 630 635 640
 Val Pro Glu Asn Phe Gln Asp Phe His Ser Lys Arg Gln Ile Asp Arg
 645 650 655
 Asp Gln Leu Met Thr Val Leu Ala Asn Val Thr His Leu Leu Ile Arg
 660 665 670
 Ala Asn Tyr Asn Ser Ala Lys Met Ala Leu Tyr Arg Leu Glu Ser Val
 675 680 685
 Ser Leu Asp Ile Ala Ser Ser Asn Ala Ile Asp Leu Val Val Ala Ala
 690 695 700
 Asp Val Glu His Cys Glu Cys Pro Gln Gly Tyr Thr Gly Thr Ser Cys
 705 710 715 720
 Glu Ser Cys Leu Ser Gly Tyr Tyr Arg Val Asp Gly Ile Leu Phe Gly

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725					730					735					
Gly	Ile	Cys	Gln	Pro	Cys	Glu	Cys	His	Gly	His	Ala	Ala	Glu	Cys	Asn
			740					745					750		
Val	His	Gly	Val	Cys	Ile	Ala	Cys	Ala	His	Asn	Thr	Thr	Gly	Val	His
		755					760						765		
Cys	Glu	Gln	Cys	Leu	Pro	Gly	Phe	Tyr	Gly	Glu	Pro	Ser	Arg	Gly	Thr
	770					775					780				
Pro	Gly	Asp	Cys	Gln	Pro	Cys	Ala	Cys	Pro	Leu	Thr	Ile	Ala	Ser	Asn
	785					790					795				800
Asn	Phe	Ser	Pro	Thr	Cys	His	Leu	Asn	Asp	Gly	Asp	Glu	Val	Val	Cys
				805					810					815	
Asp	Trp	Cys	Ala	Pro	Gly	Tyr	Ser	Gly	Ala	Trp	Cys	Glu	Arg	Cys	Ala
			820					825					830		
Asp	Gly	Tyr	Tyr	Gly	Asn	Pro	Thr	Val	Pro	Gly	Glu	Ser	Cys	Val	Pro
		835					840					845			
Cys	Asp	Cys	Ser	Gly	Asn	Val	Asp	Pro	Ser	Glu	Ala	Gly	His	Cys	Asp
	850					855					860				
Ser	Val	Thr	Gly	Glu	Cys	Leu	Lys	Cys	Leu	Gly	Asn	Thr	Asp	Gly	Ala
	865					870					875				880
His	Cys	Glu	Arg	Cys	Ala	Asp	Gly	Phe	Tyr	Gly	Asp	Ala	Val	Thr	Ala
			885					890						895	
Lys	Asn	Cys	Arg	Ala	Cys	Glu	Cys	His	Val	Lys	Gly	Ser	His	Ser	Ala
			900					905					910		
Val	Cys	His	Leu	Glu	Thr	Gly	Leu	Cys	Asp	Cys	Lys	Pro	Asn	Val	Thr
	915						920					925			
Gly	Gln	Gln	Cys	Asp	Gln	Cys	Leu	His	Gly	Tyr	Tyr	Gly	Leu	Asp	Ser
	930					935						940			
Gly	His	Gly	Cys	Arg	Pro	Cys	Asn	Cys	Ser	Val	Ala	Gly	Ser	Val	Ser
	945					950					955				960
Asp	Gly	Cys	Thr	Asp	Glu	Gly	Gln	Cys	His	Cys	Val	Pro	Gly	Val	Ala
			965					970						975	
Gly	Lys	Arg	Cys	Asp	Arg	Cys	Ala	His	Gly	Phe	Tyr	Ala	Tyr	Gln	Asp
			980					985						990	
Gly	Ser	Cys	Thr	Pro	Cys	Asp	Cys	Pro	His	Thr	Gln	Asn	Thr	Cys	Asp
		995					1000					1005			
Pro	Glu	Thr	Gly	Glu	Cys	Val	Cys	Pro	Pro	His	Thr	Gln	Gly	Val	
	1010					1015					1020				
Lys	Cys	Glu	Glu	Cys	Glu	Asp	Gly	His	Trp	Gly	Tyr	Asp	Ala	Glu	
	1025					1030					1035				
Val	Gly	Cys	Gln	Ala	Cys	Asn	Cys	Ser	Leu	Val	Gly	Ser	Thr	His	
	1040					1045					1050				
His	Arg	Cys	Asp	Val	Val	Thr	Gly	His	Cys	Gln	Cys	Lys	Ser	Lys	
	1055					1060					1065				
Phe	Gly	Gly	Arg	Ala	Cys	Asp	Gln	Cys	Ser	Leu	Gly	Tyr	Arg	Asp	
	1070					1075					1080				
Phe	Pro	Asp	Cys	Val	Pro	Cys	Asp	Cys	Asp	Leu	Arg	Gly	Thr	Ser	
	1085					1090					1095				
Gly	Asp	Ala	Cys	Asn	Leu	Glu	Gln	Gly	Leu	Cys	Gly	Cys	Val	Glu	
	1100					1105					1110				
Glu	Thr	Gly	Ala	Cys	Pro	Cys	Lys	Glu	Asn	Val	Phe	Gly	Pro	Gln	
	1115					1120					1125				
Cys	Asn	Glu	Cys	Arg	Glu	Gly	Thr	Phe	Ala	Leu	Arg	Ala	Asp	Asn	
	1130					1135					1140				

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Pro	Leu	Gly	Cys	Ser	Pro	Cys	Phe	Cys	Ser	Gly	Leu	Ser	His	Leu
1145						1150					1155			
Cys	Ser	Glu	Leu	Glu	Asp	Tyr	Val	Arg	Thr	Pro	Val	Thr	Leu	Gly
1160						1165					1170			
Ser	Asp	Gln	Pro	Leu	Leu	Arg	Val	Val	Ser	Gln	Ser	Asn	Leu	Arg
1175						1180					1185			
Gly	Thr	Thr	Glu	Gly	Val	Tyr	Tyr	Gln	Ala	Pro	Asp	Phe	Leu	Leu
1190						1195					1200			
Asp	Ala	Ala	Thr	Val	Arg	Gln	His	Ile	Arg	Ala	Glu	Pro	Phe	Tyr
1205						1210					1215			
Trp	Arg	Leu	Pro	Gln	Gln	Phe	Gln	Gly	Asp	Gln	Leu	Met	Ala	Tyr
1220						1225					1230			
Gly	Gly	Lys	Leu	Lys	Tyr	Ser	Val	Ala	Phe	Tyr	Ser	Leu	Asp	Gly
1235						1240					1245			
Val	Gly	Thr	Ser	Asn	Phe	Glu	Pro	Gln	Val	Leu	Ile	Lys	Gly	Gly
1250						1255					1260			
Arg	Ile	Arg	Lys	Gln	Val	Ile	Tyr	Met	Asp	Ala	Pro	Ala	Pro	Glu
1265						1270					1275			
Asn	Gly	Val	Arg	Gln	Glu	Gln	Glu	Val	Ala	Met	Arg	Glu	Asn	Phe
1280						1285					1290			
Trp	Lys	Tyr	Phe	Asn	Ser	Val	Ser	Glu	Lys	Pro	Val	Thr	Arg	Glu
1295						1300					1305			
Asp	Phe	Met	Ser	Val	Leu	Ser	Asp	Ile	Glu	Tyr	Ile	Leu	Ile	Lys
1310						1315					1320			
Ala	Ser	Tyr	Gly	Gln	Gly	Leu	Gln	Gln	Ser	Arg	Ile	Ser	Asp	Ile
1325						1330					1335			
Ser	Met	Glu	Val	Gly	Arg	Lys	Ala	Glu	Lys	Leu	His	Pro	Glu	Glu
1340						1345					1350			
Glu	Val	Ala	Ser	Leu	Leu	Glu	Asn	Cys	Val	Cys	Pro	Pro	Gly	Thr
1355						1360					1365			
Val	Gly	Phe	Ser	Cys	Gln	Asp	Cys	Ala	Pro	Gly	Tyr	His	Arg	Gly
1370						1375					1380			
Lys	Leu	Pro	Ala	Gly	Ser	Asp	Arg	Gly	Pro	Arg	Pro	Leu	Val	Ala
1385						1390					1395			
Pro	Cys	Val	Pro	Cys	Ser	Cys	Asn	Asn	His	Ser	Asp	Thr	Cys	Asp
1400						1405					1410			
Pro	Asn	Thr	Gly	Lys	Cys	Leu	Asn	Cys	Gly	Asp	Asn	Thr	Ala	Gly
1415						1420					1425			
Asp	His	Cys	Asp	Val	Cys	Thr	Ser	Gly	Tyr	Tyr	Gly	Lys	Val	Thr
1430						1435					1440			
Gly	Ser	Ala	Ser	Asp	Cys	Ala	Leu	Cys	Ala	Cys	Pro	His	Ser	Pro
1445						1450					1455			
Pro	Ala	Ser	Phe	Ser	Pro	Thr	Cys	Val	Leu	Glu	Gly	Asp	His	Asp
1460						1465					1470			
Phe	Arg	Cys	Asp	Ala	Cys	Leu	Leu	Gly	Tyr	Glu	Gly	Lys	His	Cys
1475						1480					1485			
Glu	Arg	Cys	Ser	Ser	Ser	Tyr	Tyr	Gly	Asn	Pro	Gln	Thr	Pro	Gly
1490						1495					1500			
Gly	Ser	Cys	Gln	Lys	Cys	Asp	Cys	Asn	Pro	His	Gly	Ser	Val	His
1505						1510					1515			
Gly	Asp	Cys	Asp	Arg	Thr	Ser	Gly	Gln	Cys	Val	Cys	Arg	Leu	Gly
1520						1525					1530			

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Ala	Ser	Gly	Leu	Arg	Cys	Asp	Glu	Cys	Glu	Pro	Arg	His	Ile	Leu
1535						1540					1545			
Met	Glu	Thr	Asp	Cys	Val	Ser	Cys	Asp	Asp	Glu	Cys	Val	Gly	Val
1550						1555					1560			
Leu	Leu	Asn	Asp	Leu	Asp	Glu	Ile	Gly	Asp	Ala	Val	Leu	Ser	Leu
1565						1570					1575			
Asn	Leu	Thr	Gly	Ile	Ile	Pro	Val	Pro	Tyr	Gly	Ile	Leu	Ser	Asn
1580						1585					1590			
Leu	Glu	Asn	Thr	Thr	Lys	Tyr	Leu	Gln	Glu	Ser	Leu	Leu	Lys	Glu
1595						1600					1605			
Asn	Met	Gln	Lys	Asp	Leu	Gly	Lys	Ile	Lys	Leu	Glu	Gly	Val	Ala
1610						1615					1620			
Glu	Glu	Thr	Asp	Asn	Leu	Gln	Lys	Lys	Leu	Thr	Arg	Met	Leu	Ala
1625						1630					1635			
Ser	Thr	Gln	Lys	Val	Asn	Arg	Ala	Thr	Glu	Arg	Ile	Phe	Lys	Glu
1640						1645					1650			
Ser	Gln	Asp	Leu	Ala	Ile	Ala	Ile	Glu	Arg	Leu	Gln	Met	Ser	Ile
1655						1660					1665			
Thr	Glu	Ile	Met	Glu	Lys	Thr	Thr	Leu	Asn	Gln	Thr	Leu	Asp	Glu
1670						1675					1680			
Asp	Phe	Leu	Leu	Pro	Asn	Ser	Thr	Leu	Gln	Asn	Met	Gln	Gln	Asn
1685						1690					1695			
Gly	Thr	Ser	Leu	Leu	Glu	Ile	Met	Gln	Ile	Arg	Asp	Phe	Thr	Gln
1700						1705					1710			
Leu	His	Gln	Asn	Ala	Thr	Leu	Glu	Leu	Lys	Ala	Ala	Glu	Asp	Leu
1715						1720					1725			
Leu	Ser	Gln	Ile	Gln	Glu	Asn	Tyr	Gln	Lys	Pro	Leu	Glu	Glu	Leu
1730						1735					1740			
Glu	Val	Leu	Lys	Glu	Ala	Ala	Ser	His	Val	Leu	Ser	Lys	His	Asn
1745						1750					1755			
Asn	Glu	Leu	Lys	Ala	Ala	Glu	Ala	Leu	Val	Arg	Glu	Ala	Glu	Ala
1760						1765					1770			
Lys	Met	Gln	Glu	Ser	Asn	His	Leu	Leu	Leu	Met	Val	Asn	Ala	Asn
1775						1780					1785			
Leu	Arg	Glu	Phe	Ser	Asp	Lys	Lys	Leu	His	Val	Gln	Glu	Glu	Gln
1790						1795					1800			
Asn	Leu	Thr	Ser	Glu	Leu	Ile	Val	Gln	Gly	Arg	Gly	Leu	Ile	Asp
1805						1810					1815			
Ala	Ala	Ala	Ala	Gln	Thr	Asp	Ala	Val	Gln	Asp	Ala	Leu	Glu	His
1820						1825					1830			
Leu	Glu	Asp	His	Gln	Asp	Lys	Leu	Leu	Leu	Trp	Ser	Ala	Lys	Ile
1835						1840					1845			
Arg	His	His	Ile	Asp	Asp	Leu	Val	Met	His	Met	Ser	Gln	Arg	Asn
1850						1855					1860			
Ala	Val	Asp	Leu	Val	Tyr	Arg	Ala	Glu	Asp	His	Ala	Ala	Glu	Phe
1865						1870					1875			
Gln	Arg	Leu	Ala	Asp	Val	Leu	Tyr	Ser	Gly	Leu	Glu	Asn	Ile	Arg
1880						1885					1890			
Asn	Val	Ser	Leu	Asn	Ala	Thr	Ser	Ala	Ala	Tyr	Val	His	Tyr	Asn
1895						1900					1905			
Ile	Gln	Ser	Leu	Ile	Glu	Glu	Ser	Glu	Glu	Leu	Ala	Arg	Asp	Ala
1910						1915					1920			
His	Arg	Thr	Val	Thr	Glu	Thr	Ser	Leu	Leu	Ser	Glu	Ser	Leu	Val

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1925	1930	1935
Ser Asn Gly Lys Ala Ala 1940	Val Gln Arg Ser Ser Arg 1945	Phe Leu Lys 1950
Glu Gly Asn Asn Leu Ser 1955	Arg Lys Leu Pro Gly Ile 1960	Ala Leu Glu 1965
Leu Ser Glu Leu Arg Asn 1970	Lys Thr Asn Arg Phe Gln 1975	Glu Asn Ala 1980
Val Glu Ile Thr Arg Gln 1985	Thr Asn Glu Ser Leu Leu 1990	Ile Leu Arg 1995
Ala Ile Pro Lys Gly Ile 2000	Arg Asp Lys Gly Ala Lys 2005	Thr Lys Glu 2010
Leu Ala Thr Ser Ala Ser 2015	Gln Ser Ala Val Ser Thr 2020	Leu Arg Asp 2025
Val Ala Gly Leu Ser Gln 2030	Glu Leu Leu Asn Thr Ser 2035	Ala Ser Leu 2040
Ser Arg Val Asn Thr Thr 2045	Leu Arg Glu Thr His Gln 2050	Leu Leu Gln 2055
Asp Ser Thr Met Ala Thr 2060	Leu Leu Ala Gly Arg Lys 2065	Val Lys Asp 2070
Val Glu Ile Gln Ala Asn 2075	Leu Leu Phe Asp Arg Leu 2080	Lys Pro Leu 2085
Lys Met Leu Glu Glu Asn 2090	Leu Ser Arg Asn Leu Ser 2095	Glu Ile Lys 2100
Leu Leu Ile Ser Gln Ala 2105	Arg Lys Gln Ala Ala Ser 2110	Ile Lys Val 2115
Ala Val Ser Ala Asp Arg 2120	Asp Cys Ile Arg Ala Tyr 2125	Gln Pro Gln 2130
Ile Ser Ser Thr Asn Tyr 2135	Asn Thr Leu Thr Leu Asn 2140	Val Lys Thr 2145
Gln Glu Pro Asp Asn Leu 2150	Leu Phe Tyr Leu Gly Ser 2155	Ser Thr Ala 2160
Ser Asp Phe Leu Ala Val 2165	Glu Met Arg Arg Gly Arg 2170	Val Ala Phe 2175
Leu Trp Asp Leu Gly Ser 2180	Gly Ser Thr Arg Leu Glu 2185	Phe Pro Asp 2190
Phe Pro Ile Asp Asp Asn 2195	Arg Trp His Ser Ile His 2200	Val Ala Arg 2205
Phe Gly Asn Ile Gly Ser 2210	Leu Ser Val Lys Glu Met 2215	Ser Ser Asn 2220
Gln Lys Ser Pro Thr Lys 2225	Thr Ser Lys Ser Pro Gly 2230	Thr Ala Asn 2235
Val Leu Asp Val Asn Asn 2240	Ser Thr Leu Met Phe Val 2245	Gly Gly Leu 2250
Gly Gly Gln Ile Lys Lys 2255	Ser Pro Ala Val Lys Val 2260	Thr His Phe 2265
Lys Gly Cys Leu Gly Glu 2270	Ala Phe Leu Asn Gly Lys 2275	Ser Ile Gly 2280
Leu Trp Asn Tyr Ile Glu 2285	Arg Glu Gly Lys Cys Arg 2290	Gly Cys Phe 2295
Gly Ser Ser Gln Asn Glu 2300	Asp Pro Ser Phe His Phe 2305	Asp Gly Ser 2310
Gly Tyr Ser Val Val Glu 2315	Lys Ser Leu Pro Ala Thr 2320	Val Thr Gln 2325

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Ile	Ile	Met	Leu	Phe	Asn	Thr	Phe	Ser	Pro	Asn	Gly	Leu	Leu	Leu
2330						2335					2340			
Tyr	Leu	Gly	Ser	Tyr	Gly	Thr	Lys	Asp	Phe	Leu	Ser	Ile	Glu	Leu
2345						2350					2355			
Phe	Arg	Gly	Arg	Val	Lys	Val	Met	Thr	Asp	Leu	Gly	Ser	Gly	Pro
2360						2365					2370			
Ile	Thr	Leu	Leu	Thr	Asp	Arg	Arg	Tyr	Asn	Asn	Gly	Thr	Trp	Tyr
2375						2380					2385			
Lys	Ile	Ala	Phe	Gln	Arg	Asn	Arg	Lys	Gln	Gly	Val	Leu	Ala	Val
2390						2395					2400			
Ile	Asp	Ala	Tyr	Asn	Thr	Ser	Asn	Lys	Glu	Thr	Lys	Gln	Gly	Glu
2405						2410					2415			
Thr	Pro	Gly	Ala	Ser	Ser	Asp	Leu	Asn	Arg	Leu	Asp	Lys	Asp	Pro
2420						2425					2430			
Ile	Tyr	Val	Gly	Gly	Leu	Pro	Arg	Ser	Arg	Val	Val	Arg	Arg	Gly
2435						2440					2445			
Val	Thr	Thr	Lys	Ser	Phe	Val	Gly	Cys	Ile	Lys	Asn	Leu	Glu	Ile
2450						2455					2460			
Ser	Arg	Ser	Thr	Phe	Asp	Leu	Leu	Arg	Asn	Ser	Tyr	Gly	Val	Arg
2465						2470					2475			
Lys	Gly	Cys	Leu	Leu	Glu	Pro	Ile	Arg	Ser	Val	Ser	Phe	Leu	Lys
2480						2485					2490			
Gly	Gly	Tyr	Ile	Glu	Leu	Pro	Pro	Lys	Ser	Leu	Ser	Pro	Glu	Ser
2495						2500					2505			
Glu	Trp	Leu	Val	Thr	Phe	Ala	Thr	Thr	Asn	Ser	Ser	Gly	Ile	Ile
2510						2515					2520			
Leu	Ala	Ala	Leu	Gly	Gly	Asp	Val	Glu	Lys	Arg	Gly	Asp	Arg	Glu
2525						2530					2535			
Glu	Ala	His	Val	Pro	Phe	Phe	Ser	Val	Met	Leu	Ile	Gly	Gly	Asn
2540						2545					2550			
Ile	Glu	Val	His	Val	Asn	Pro	Gly	Asp	Gly	Thr	Gly	Leu	Arg	Lys
2555						2560					2565			
Ala	Leu	Leu	His	Ala	Pro	Thr	Gly	Thr	Cys	Ser	Asp	Gly	Gln	Ala
2570						2575					2580			
His	Ser	Ile	Ser	Leu	Val	Arg	Asn	Arg	Arg	Ile	Ile	Thr	Val	Gln
2585						2590					2595			
Leu	Asp	Glu	Asn	Asn	Pro	Val	Glu	Met	Lys	Leu	Gly	Thr	Leu	Val
2600						2605					2610			
Glu	Ser	Arg	Thr	Ile	Asn	Val	Ser	Asn	Leu	Tyr	Val	Gly	Gly	Ile
2615						2620					2625			
Pro	Glu	Gly	Glu	Gly	Thr	Ser	Leu	Leu	Thr	Met	Arg	Arg	Ser	Phe
2630						2635					2640			
His	Gly	Cys	Ile	Lys	Asn	Leu	Ile	Phe	Asn	Leu	Glu	Leu	Leu	Asp
2645						2650					2655			
Phe	Asn	Ser	Ala	Val	Gly	His	Glu	Gln	Val	Asp	Leu	Asp	Thr	Cys
2660						2665					2670			
Trp	Leu	Ser	Glu	Arg	Pro	Lys	Leu	Ala	Pro	Asp	Ala	Glu	Asp	Ser
2675						2680					2685			
Lys	Leu	Leu	Pro	Glu	Pro	Arg	Ala	Phe	Pro	Glu	Gln	Cys	Val	Val
2690						2695					2700			
Asp	Ala	Ala	Leu	Glu	Tyr	Val	Pro	Gly	Ala	His	Gln	Phe	Gly	Leu
2705						2710					2715			

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Thr	Gln	Asn	Ser	His	Phe	Ile	Leu	Pro	Phe	Asn	Gln	Ser	Ala	Val
2720						2725					2730			
Arg	Lys	Lys	Leu	Ser	Val	Glu	Leu	Ser	Ile	Arg	Thr	Phe	Ala	Ser
2735						2740					2745			
Ser	Gly	Leu	Ile	Tyr	Tyr	Met	Ala	His	Gln	Asn	Gln	Ala	Asp	Tyr
2750						2755					2760			
Ala	Val	Leu	Gln	Leu	His	Gly	Gly	Arg	Leu	His	Phe	Met	Phe	Asp
2765						2770					2775			
Leu	Gly	Lys	Gly	Arg	Thr	Lys	Val	Ser	His	Pro	Ala	Leu	Leu	Ser
2780						2785					2790			
Asp	Gly	Lys	Trp	His	Thr	Val	Lys	Thr	Asp	Tyr	Val	Lys	Arg	Lys
2795						2800					2805			
Gly	Phe	Ile	Thr	Val	Asp	Gly	Arg	Glu	Ser	Pro	Met	Val	Thr	Val
2810						2815					2820			
Val	Gly	Asp	Gly	Thr	Met	Leu	Asp	Val	Glu	Gly	Leu	Phe	Tyr	Leu
2825						2830					2835			
Gly	Gly	Leu	Pro	Ser	Gln	Tyr	Gln	Ala	Arg	Lys	Ile	Gly	Asn	Ile
2840						2845					2850			
Thr	His	Ser	Ile	Pro	Ala	Cys	Ile	Gly	Asp	Val	Thr	Val	Asn	Ser
2855						2860					2865			
Lys	Gln	Leu	Asp	Lys	Asp	Ser	Pro	Val	Ser	Ala	Phe	Thr	Val	Asn
2870						2875					2880			
Arg	Cys	Tyr	Ala	Val	Ala	Gln	Glu	Gly	Thr	Tyr	Phe	Asp	Gly	Ser
2885						2890					2895			
Gly	Tyr	Ala	Ala	Leu	Val	Lys	Glu	Gly	Tyr	Lys	Val	Gln	Ser	Asp
2900						2905					2910			
Val	Asn	Ile	Thr	Leu	Glu	Phe	Arg	Thr	Ser	Ser	Gln	Asn	Gly	Val
2915						2920					2925			
Leu	Leu	Gly	Ile	Ser	Thr	Ala	Lys	Val	Asp	Ala	Ile	Gly	Leu	Glu
2930						2935					2940			
Leu	Val	Asp	Gly	Lys	Val	Leu	Phe	His	Val	Asn	Asn	Gly	Ala	Gly
2945						2950					2955			
Arg	Ile	Thr	Ala	Ala	Tyr	Glu	Pro	Lys	Thr	Ala	Thr	Val	Leu	Cys
2960						2965					2970			
Asp	Gly	Lys	Trp	His	Thr	Leu	Gln	Ala	Asn	Lys	Ser	Lys	His	Arg
2975						2980					2985			
Ile	Thr	Leu	Ile	Val	Asp	Gly	Asn	Ala	Val	Gly	Ala	Glu	Ser	Pro
2990						2995					3000			
His	Thr	Gln	Ser	Thr	Ser	Val	Asp	Thr	Asn	Asn	Pro	Ile	Tyr	Val
3005						3010					3015			
Gly	Gly	Tyr	Pro	Ala	Gly	Val	Lys	Gln	Lys	Cys	Leu	Arg	Ser	Gln
3020						3025					3030			
Thr	Ser	Phe	Arg	Gly	Cys	Leu	Arg	Lys	Leu	Ala	Leu	Ile	Lys	Ser
3035						3040					3045			
Pro	Gln	Val	Gln	Ser	Phe	Asp	Phe	Ser	Arg	Ala	Phe	Glu	Leu	His
3050						3055					3060			
Gly	Val	Phe	Leu	His	Ser	Cys	Pro	Gly	Thr	Glu	Ser			
3065						3070					3075			

<210> SEQ ID NO 26

<211> LENGTH: 3122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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Met Pro Gly Ala Ala Gly Val Leu Leu Leu Leu Leu Leu Ser Gly Gly
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Leu Gly Gly Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln
 20 25 30

Ala His Gln Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser
 35 40 45

Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu
 50 55 60

Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn
 65 70 75 80

Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg
 85 90 95

His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser
 100 105 110

Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu
 115 120 125

Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala
 130 135 140

Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp
 145 150 155 160

Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys
 165 170 175

Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala
 180 185 190

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

Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser
 210 215 220

Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr
 225 230 235 240

Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met
 245 250 255

Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg
 260 265 270

Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile
 275 280 285

Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys
 290 295 300

Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln
 305 310 315 320

Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu
 325 330 335

Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu
 340 345 350

Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile
 355 360 365

Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn
 370 375 380

Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro
 385 390 395 400

Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys
 405 410 415

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Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His
 420 425 430
 Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe
 435 440 445
 Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro
 450 455 460
 Asp Cys Lys Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp
 465 470 475 480
 Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp
 485 490 495
 Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp
 500 505 510
 Lys Gly Cys Asp Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln
 515 520 525
 Ser Ser Tyr Trp Thr Tyr Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr
 530 535 540
 Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Gln Asp Asp
 545 550 555 560
 Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln
 565 570 575
 Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly
 580 585 590
 Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr
 595 600 605
 Asp Leu Glu Glu Glu Glu Asp Thr Glu Arg Val Leu Gln Leu Met
 610 615 620
 Ile Ile Leu Glu Gly Asn Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu
 625 630 635 640
 Val Tyr Leu His Pro Ser Glu Glu His Thr Asn Val Leu Leu Leu Lys
 645 650 655
 Glu Glu Ser Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys
 660 665 670
 Glu Phe Met Thr Val Leu Ala Asn Leu Lys Arg Val Leu Leu Gln Ile
 675 680 685
 Thr Tyr Ser Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn
 690 695 700
 Leu Glu Ser Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala
 705 710 715 720
 Val Glu Val Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu
 725 730 735
 Ser Cys Trp Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly
 740 745 750
 Ile Cys Glu Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp
 755 760 765
 Val Thr Gly Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr
 770 775 780
 Cys Asp Lys Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr
 785 790 795 800
 Ser Glu Asp Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn
 805 810 815
 Asn Phe Ser Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys
 820 825 830
 Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala

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835					840					845					
Glu	Gly	Tyr	Phe	Gly	Gln	Pro	Ser	Val	Pro	Gly	Gly	Ser	Cys	Gln	Pro
850					855					860					
Cys	Gln	Cys	Asn	Asp	Asn	Leu	Asp	Phe	Ser	Ile	Pro	Gly	Ser	Cys	Asp
865					870					875					880
Ser	Leu	Ser	Gly	Ser	Cys	Leu	Ile	Cys	Lys	Pro	Gly	Thr	Thr	Gly	Arg
					885					890					895
Tyr	Cys	Glu	Leu	Cys	Ala	Asp	Gly	Tyr	Phe	Gly	Asp	Ala	Val	Asp	Ala
					900					905					910
Lys	Asn	Cys	Gln	Pro	Cys	Arg	Cys	Asn	Ala	Gly	Gly	Ser	Phe	Ser	Glu
					915					920					925
Val	Cys	His	Ser	Gln	Thr	Gly	Gln	Cys	Glu	Cys	Arg	Ala	Asn	Val	Gln
					930					935					940
Gly	Gln	Arg	Cys	Asp	Lys	Cys	Lys	Ala	Gly	Thr	Phe	Gly	Leu	Gln	Ser
945					950					955					960
Ala	Arg	Gly	Cys	Val	Pro	Cys	Asn	Cys	Asn	Ser	Phe	Gly	Ser	Lys	Ser
					965					970					975
Phe	Asp	Cys	Glu	Glu	Ser	Gly	Gln	Cys	Trp	Cys	Gln	Pro	Gly	Val	Thr
					980					985					990
Gly	Lys	Lys	Cys	Asp	Arg	Cys	Ala	His	Gly	Tyr	Phe	Asn	Phe	Gln	Glu
					995					1000					1005
Gly	Gly	Cys	Thr	Ala	Cys	Glu	Cys	Ser	His	Leu	Gly	Asn	Asn	Cys	
					1010					1015					1020
Asp	Pro	Lys	Thr	Gly	Arg	Cys	Ile	Cys	Pro	Pro	Asn	Thr	Ile	Gly	
					1025					1030					1035
Glu	Lys	Cys	Ser	Lys	Cys	Ala	Pro	Asn	Thr	Trp	Gly	His	Ser	Ile	
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Thr	Thr	Gly	Cys	Lys	Ala	Cys	Asn	Cys	Ser	Thr	Val	Gly	Ser	Leu	
					1055					1060					1065
Asp	Phe	Gln	Cys	Asn	Val	Asn	Thr	Gly	Gln	Cys	Asn	Cys	His	Pro	
					1070					1075					1080
Lys	Phe	Ser	Gly	Ala	Lys	Cys	Thr	Glu	Cys	Ser	Arg	Gly	His	Trp	
					1085					1090					1095
Asn	Tyr	Pro	Arg	Cys	Asn	Leu	Cys	Asp	Cys	Phe	Leu	Pro	Gly	Thr	
					1100					1105					1110
Asp	Ala	Thr	Thr	Cys	Asp	Ser	Glu	Thr	Lys	Lys	Cys	Ser	Cys	Ser	
					1115					1120					1125
Asp	Gln	Thr	Gly	Gln	Cys	Thr	Cys	Lys	Val	Asn	Val	Glu	Gly	Ile	
					1130					1135					1140
His	Cys	Asp	Arg	Cys	Arg	Pro	Gly	Lys	Phe	Gly	Leu	Asp	Ala	Lys	
					1145					1150					1155
Asn	Pro	Leu	Gly	Cys	Ser	Ser	Cys	Tyr	Cys	Phe	Gly	Thr	Thr	Thr	
					1160					1165					1170
Gln	Cys	Ser	Glu	Ala	Lys	Gly	Leu	Ile	Arg	Thr	Trp	Val	Thr	Leu	
					1175					1180					1185
Lys	Ala	Glu	Gln	Thr	Ile	Leu	Pro	Leu	Val	Asp	Glu	Ala	Leu	Gln	
					1190					1195					1200
His	Thr	Thr	Thr	Lys	Gly	Ile	Val	Phe	Gln	His	Pro	Glu	Ile	Val	
					1205					1210					1215
Ala	His	Met	Asp	Leu	Met	Arg	Glu	Asp	Leu	His	Leu	Glu	Pro	Phe	
					1220					1225					1230
Tyr	Trp	Lys	Leu	Pro	Glu	Gln	Phe	Glu	Gly	Lys	Lys	Leu	Met	Ala	
					1235					1240					1245

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Tyr	Gly	Gly	Lys	Leu	Lys	Tyr	Ala	Ile	Tyr	Phe	Glu	Ala	Arg	Glu
1250						1255					1260			
Glu	Thr	Gly	Phe	Ser	Thr	Tyr	Asn	Pro	Gln	Val	Ile	Ile	Arg	Gly
1265						1270					1275			
Gly	Thr	Pro	Thr	His	Ala	Arg	Ile	Ile	Val	Arg	His	Met	Ala	Ala
1280						1285					1290			
Pro	Leu	Ile	Gly	Gln	Leu	Thr	Arg	His	Glu	Ile	Glu	Met	Thr	Glu
1295						1300					1305			
Lys	Glu	Trp	Lys	Tyr	Tyr	Gly	Asp	Asp	Pro	Arg	Val	His	Arg	Thr
1310						1315					1320			
Val	Thr	Arg	Glu	Asp	Phe	Leu	Asp	Ile	Leu	Tyr	Asp	Ile	His	Tyr
1325						1330					1335			
Ile	Leu	Ile	Lys	Ala	Thr	Tyr	Gly	Asn	Phe	Met	Arg	Gln	Ser	Arg
1340						1345					1350			
Ile	Ser	Glu	Ile	Ser	Met	Glu	Val	Ala	Glu	Gln	Gly	Arg	Gly	Thr
1355						1360					1365			
Thr	Met	Thr	Pro	Pro	Ala	Asp	Leu	Ile	Glu	Lys	Cys	Asp	Cys	Pro
1370						1375					1380			
Leu	Gly	Tyr	Ser	Gly	Leu	Ser	Cys	Glu	Ala	Cys	Leu	Pro	Gly	Phe
1385						1390					1395			
Tyr	Arg	Leu	Arg	Ser	Gln	Pro	Gly	Gly	Arg	Thr	Pro	Gly	Pro	Thr
1400						1405					1410			
Leu	Gly	Thr	Cys	Val	Pro	Cys	Gln	Cys	Asn	Gly	His	Ser	Ser	Leu
1415						1420					1425			
Cys	Asp	Pro	Glu	Thr	Ser	Ile	Cys	Gln	Asn	Cys	Gln	His	His	Thr
1430						1435					1440			
Ala	Gly	Asp	Phe	Cys	Glu	Arg	Cys	Ala	Leu	Gly	Tyr	Tyr	Gly	Ile
1445						1450					1455			
Val	Lys	Gly	Leu	Pro	Asn	Asp	Cys	Gln	Gln	Cys	Ala	Cys	Pro	Leu
1460						1465					1470			
Ile	Ser	Ser	Ser	Asn	Asn	Phe	Ser	Pro	Ser	Cys	Val	Ala	Glu	Gly
1475						1480					1485			
Leu	Asp	Asp	Tyr	Arg	Cys	Thr	Ala	Cys	Pro	Arg	Gly	Tyr	Glu	Gly
1490						1495					1500			
Gln	Tyr	Cys	Glu	Arg	Cys	Ala	Pro	Gly	Tyr	Thr	Gly	Ser	Pro	Gly
1505						1510					1515			
Asn	Pro	Gly	Gly	Ser	Cys	Gln	Glu	Cys	Glu	Cys	Asp	Pro	Tyr	Gly
1520						1525					1530			
Ser	Leu	Pro	Val	Pro	Cys	Asp	Pro	Val	Thr	Gly	Phe	Cys	Thr	Cys
1535						1540					1545			
Arg	Pro	Gly	Ala	Thr	Gly	Arg	Lys	Cys	Asp	Gly	Cys	Lys	His	Trp
1550						1555					1560			
His	Ala	Arg	Glu	Gly	Trp	Glu	Cys	Val	Phe	Cys	Gly	Asp	Glu	Cys
1565						1570					1575			
Thr	Gly	Leu	Leu	Leu	Gly	Asp	Leu	Ala	Arg	Leu	Glu	Gln	Met	Val
1580						1585					1590			
Met	Ser	Ile	Asn	Leu	Thr	Gly	Pro	Leu	Pro	Ala	Pro	Tyr	Lys	Met
1595						1600					1605			
Leu	Tyr	Gly	Leu	Glu	Asn	Met	Thr	Gln	Glu	Leu	Lys	His	Leu	Leu
1610						1615					1620			
Ser	Pro	Gln	Arg	Ala	Pro	Glu	Arg	Leu	Ile	Gln	Leu	Ala	Glu	Gly
1625						1630					1635			

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Asn 1640	Leu	Asn Thr	Leu Val	Thr	Glu Met	Asn	Glu	Leu	Leu Thr	Arg
				1645				1650		
Ala 1655	Thr	Lys Val	Thr Ala	Asp	Gly Glu	Gln	Thr	Gly	Gln Asp	Ala
				1660				1665		
Glu 1670	Arg	Thr Asn	Thr Arg	Ala	Lys Ser	Leu	Gly	Glu	Phe Ile	Lys
				1675				1680		
Glu 1685	Leu	Ala Arg	Asp Ala	Glu	Ala Val	Asn	Glu	Lys	Ala Ile	Lys
				1690				1695		
Leu 1700	Asn	Glu Thr	Leu Gly	Thr	Arg Asp	Glu	Ala	Phe	Glu Arg	Asn
				1705				1710		
Leu 1715	Glu	Gly Leu	Gln Lys	Glu	Ile Asp	Gln	Met	Ile	Lys Glu	Leu
				1720				1725		
Arg 1730	Arg	Lys Asn	Leu Glu	Thr	Gln Lys	Glu	Ile	Ala	Glu Asp	Glu
				1735				1740		
Leu 1745	Val	Ala Ala	Glu Ala	Leu	Leu Lys	Lys	Val	Lys	Lys Leu	Phe
				1750				1755		
Gly 1760	Glu	Ser Arg	Gly Glu	Asn	Glu Glu	Met	Glu	Lys	Asp Leu	Arg
				1765				1770		
Glu 1775	Lys	Leu Ala	Asp Tyr	Lys	Asn Lys	Val	Asp	Asp	Ala Trp	Asp
				1780				1785		
Leu 1790	Leu	Arg Glu	Ala Thr	Asp	Lys Ile	Arg	Glu	Ala	Asn Arg	Leu
				1795				1800		
Phe 1805	Ala	Val Asn	Gln Lys	Asn	Met Thr	Ala	Leu	Glu	Lys Lys	Lys
				1810				1815		
Glu 1820	Ala	Val Glu	Ser Gly	Lys	Arg Gln	Ile	Glu	Asn	Thr Leu	Lys
				1825				1830		
Glu 1835	Gly	Asn Asp	Ile Leu	Asp	Glu Ala	Asn	Arg	Leu	Ala Asp	Glu
				1840				1845		
Ile 1850	Asn	Ser Ile	Ile Asp	Tyr	Val Glu	Asp	Ile	Gln	Thr Lys	Leu
				1855				1860		
Pro 1865	Pro	Met Ser	Glu Glu	Leu	Asn Asp	Lys	Ile	Asp	Asp Leu	Ser
				1870				1875		
Gln 1880	Glu	Ile Lys	Asp Arg	Lys	Leu Ala	Glu	Lys	Val	Ser Gln	Ala
				1885				1890		
Glu 1895	Ser	His Ala	Ala Gln	Leu	Asn Asp	Ser	Ser	Ala	Val Leu	Asp
				1900				1905		
Gly 1910	Ile	Leu Asp	Glu Ala	Lys	Asn Ile	Ser	Phe	Asn	Ala Thr	Ala
				1915				1920		
Ala 1925	Phe	Lys Ala	Tyr Ser	Asn	Ile Lys	Asp	Tyr	Ile	Asp Glu	Ala
				1930				1935		
Glu 1940	Lys	Val Ala	Lys Glu	Ala	Lys Asp	Leu	Ala	His	Glu Ala	Thr
				1945				1950		
Lys 1955	Leu	Ala Thr	Gly Pro	Arg	Gly Leu	Leu	Lys	Glu	Asp Ala	Lys
				1960				1965		
Gly 1970	Cys	Leu Gln	Lys Ser	Phe	Arg Ile	Leu	Asn	Glu	Ala Lys	Lys
				1975				1980		
Leu 1985	Ala	Asn Asp	Val Lys	Glu	Asn Glu	Asp	His	Leu	Asn Gly	Leu
				1990				1995		
Lys 2000	Thr	Arg Ile	Glu Asn	Ala	Asp Ala	Arg	Asn	Gly	Asp Leu	Leu
				2005				2010		
Arg 2015	Thr	Leu Asn	Asp Thr	Leu	Gly Lys	Leu	Ser	Ala	Ile Pro	Asn
				2020				2025		
Asp 2030	Thr	Ala Ala	Lys Leu	Gln	Ala Val	Lys	Asp	Lys	Ala Arg	Gln

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2030	2035	2040
Ala Asn Asp Thr Ala Lys Asp 2045	Val Leu Ala Gln Ile Thr Glu Leu 2050	
His Gln Asn Leu Asp Gly Leu 2060	Lys Lys Asn Tyr Asn Lys Leu Ala 2065	
Asp Ser Val Ala Lys Thr Asn 2075	Ala Val Val Lys Asp Pro Ser Lys 2080	
Asn Lys Ile Ile Ala Asp Ala 2090	Asp Ala Thr Val Lys Asn Leu Glu 2095	
Gln Glu Ala Asp Arg Leu Ile 2105	Asp Lys Leu Lys Pro Ile Lys Glu 2110	
Leu Glu Asp Asn Leu Lys Lys 2120	Asn Ile Ser Glu Ile Lys Glu Leu 2125	
Ile Asn Gln Ala Arg Lys Gln 2135	Ala Asn Ser Ile Lys Val Ser Val 2140	
Ser Ser Gly Gly Asp Cys Ile 2150	Arg Thr Tyr Lys Pro Glu Ile Lys 2155	
Lys Gly Ser Tyr Asn Asn Ile 2165	Val Val Asn Val Lys Thr Ala Val 2170	
Ala Asp Asn Leu Leu Phe Tyr 2180	Leu Gly Ser Ala Lys Phe Ile Asp 2185	
Phe Leu Ala Ile Glu Met Arg 2195	Lys Gly Lys Val Ser Phe Leu Trp 2200	
Asp Val Gly Ser Gly Val Gly 2210	Arg Val Glu Tyr Pro Asp Leu Thr 2215	
Ile Asp Asp Ser Tyr Trp Tyr 2225	Arg Ile Val Ala Ser Arg Thr Gly 2230	
Arg Asn Gly Thr Ile Ser Val 2240	Arg Ala Leu Asp Gly Pro Lys Ala 2245	
Ser Ile Val Pro Ser Thr His 2255	His Ser Thr Ser Pro Pro Gly Tyr 2260	
Thr Ile Leu Asp Val Asp Ala 2270	Asn Ala Met Leu Phe Val Gly Gly 2275	
Leu Thr Gly Lys Leu Lys Lys 2285	Ala Asp Ala Val Arg Val Ile Thr 2290	
Phe Thr Gly Cys Met Gly Glu 2300	Thr Tyr Phe Asp Asn Lys Pro Ile 2305	
Gly Leu Trp Asn Phe Arg Glu 2315	Lys Glu Gly Asp Cys Lys Gly Cys 2320	
Thr Val Ser Pro Gln Val Glu 2330	Asp Ser Glu Gly Thr Ile Gln Phe 2335	
Asp Gly Glu Gly Tyr Ala Leu 2345	Val Ser Arg Pro Ile Arg Trp Tyr 2350	
Pro Asn Ile Ser Thr Val Met 2360	Phe Lys Phe Arg Thr Phe Ser Ser 2365	
Ser Ala Leu Leu Met Tyr Leu 2375	Ala Thr Arg Asp Leu Arg Asp Phe 2380	
Met Ser Val Glu Leu Thr Asp 2390	Gly His Ile Lys Val Ser Tyr Asp 2395	
Leu Gly Ser Gly Met Ala Ser 2405	Val Val Ser Asn Gln Asn His Asn 2410	
Asp Gly Lys Trp Lys Ser Phe 2420	Thr Leu Ser Arg Ile Gln Lys Gln 2425	

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Ala	Asn	Ile	Ser	Ile	Val	Asp	Ile	Asp	Thr	Asn	Gln	Glu	Glu	Asn
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Ile	Ala	Thr	Ser	Ser	Ser	Gly	Asn	Asn	Phe	Gly	Leu	Asp	Leu	Lys
2450						2455					2460			
Ala	Asp	Asp	Lys	Ile	Tyr	Phe	Gly	Gly	Leu	Pro	Thr	Leu	Arg	Asn
2465						2470					2475			
Leu	Ser	Met	Lys	Ala	Arg	Pro	Glu	Val	Asn	Leu	Lys	Lys	Tyr	Ser
2480						2485					2490			
Gly	Cys	Leu	Lys	Asp	Ile	Glu	Ile	Ser	Arg	Thr	Pro	Tyr	Asn	Ile
2495						2500					2505			
Leu	Ser	Ser	Pro	Asp	Tyr	Val	Gly	Val	Thr	Lys	Gly	Cys	Ser	Leu
2510						2515					2520			
Glu	Asn	Val	Tyr	Thr	Val	Ser	Phe	Pro	Lys	Pro	Gly	Phe	Val	Glu
2525						2530					2535			
Leu	Ser	Pro	Val	Pro	Ile	Asp	Val	Gly	Thr	Glu	Ile	Asn	Leu	Ser
2540						2545					2550			
Phe	Ser	Thr	Lys	Asn	Glu	Ser	Gly	Ile	Ile	Leu	Leu	Gly	Ser	Gly
2555						2560					2565			
Gly	Thr	Pro	Ala	Pro	Pro	Arg	Arg	Lys	Arg	Arg	Gln	Thr	Gly	Gln
2570						2575					2580			
Ala	Tyr	Tyr	Val	Ile	Leu	Leu	Asn	Arg	Gly	Arg	Leu	Glu	Val	His
2585						2590					2595			
Leu	Ser	Thr	Gly	Ala	Arg	Thr	Met	Arg	Lys	Ile	Val	Ile	Arg	Pro
2600						2605					2610			
Glu	Pro	Asn	Leu	Phe	His	Asp	Gly	Arg	Glu	His	Ser	Val	His	Val
2615						2620					2625			
Glu	Arg	Thr	Arg	Gly	Ile	Phe	Thr	Val	Gln	Val	Asp	Glu	Asn	Arg
2630						2635					2640			
Arg	Tyr	Met	Gln	Asn	Leu	Thr	Val	Glu	Gln	Pro	Ile	Glu	Val	Lys
2645						2650					2655			
Lys	Leu	Phe	Val	Gly	Gly	Ala	Pro	Pro	Glu	Phe	Gln	Pro	Ser	Pro
2660						2665					2670			
Leu	Arg	Asn	Ile	Pro	Pro	Phe	Glu	Gly	Cys	Ile	Trp	Asn	Leu	Val
2675						2680					2685			
Ile	Asn	Ser	Val	Pro	Met	Asp	Phe	Ala	Arg	Pro	Val	Ser	Phe	Lys
2690						2695					2700			
Asn	Ala	Asp	Ile	Gly	Arg	Cys	Ala	His	Gln	Lys	Leu	Arg	Glu	Asp
2705						2710					2715			
Glu	Asp	Gly	Ala	Ala	Pro	Ala	Glu	Ile	Val	Ile	Gln	Pro	Glu	Pro
2720						2725					2730			
Val	Pro	Thr	Pro	Ala	Phe	Pro	Thr	Pro	Thr	Pro	Val	Leu	Thr	His
2735						2740					2745			
Gly	Pro	Cys	Ala	Ala	Glu	Ser	Glu	Pro	Ala	Leu	Leu	Ile	Gly	Ser
2750						2755					2760			
Lys	Gln	Phe	Gly	Leu	Ser	Arg	Asn	Ser	His	Ile	Ala	Ile	Ala	Phe
2765						2770					2775			
Asp	Asp	Thr	Lys	Val	Lys	Asn	Arg	Leu	Thr	Ile	Glu	Leu	Glu	Val
2780						2785					2790			
Arg	Thr	Glu	Ala	Glu	Ser	Gly	Leu	Leu	Phe	Tyr	Met	Ala	Arg	Ile
2795						2800					2805			
Asn	His	Ala	Asp	Phe	Ala	Thr	Val	Gln	Leu	Arg	Asn	Gly	Leu	Pro
2810						2815					2820			

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Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His Thr Met Ile
 2825 2830 2835

Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met
 2840 2845 2850

Arg Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser Asn
 2855 2860 2865

Arg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly
 2870 2875 2880

Met Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg
 2885 2890 2895

Ile Gly Pro Val Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu
 2900 2905 2910

His Met Ala Glu Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser
 2915 2920 2925

Phe His Val Gly Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr
 2930 2935 2940

Phe Asp Gly Thr Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val
 2945 2950 2955

Gly Leu Asp Leu Leu Val Glu Phe Glu Phe Arg Thr Thr Thr Thr
 2960 2965 2970

Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met
 2975 2980 2985

Gly Ile Glu Met Ile Asp Glu Lys Leu Met Phe His Val Asp Asn
 2990 2995 3000

Gly Ala Gly Arg Phe Thr Ala Val Tyr Asp Ala Gly Val Pro Gly
 3005 3010 3015

His Leu Cys Asp Gly Gln Trp His Lys Val Thr Ala Asn Lys Ile
 3020 3025 3030

Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val Glu Ala
 3035 3040 3045

Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp Pro
 3050 3055 3060

Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu
 3065 3070 3075

Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu
 3080 3085 3090

Thr Lys Gly Thr Gly Lys Pro Leu Glu Val Asn Phe Ala Lys Ala
 3095 3100 3105

Leu Glu Leu Arg Gly Val Gln Pro Val Ser Cys Pro Ala Asn
 3110 3115 3120

<210> SEQ ID NO 27
 <211> LENGTH: 3118
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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Leu Gly Gly Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln
 20 25 30

Ala His Gln Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser
 35 40 45

Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu
 50 55 60

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Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn
 65 70 75 80
 Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg
 85 90 95
 His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser
 100 105 110
 Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu
 115 120 125
 Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala
 130 135 140
 Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp
 145 150 155 160
 Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys
 165 170 175
 Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala
 180 185 190
 Lys Asp Asp Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro
 195 200 205
 Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser
 210 215 220
 Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr
 225 230 235 240
 Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met
 245 250 255
 Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg
 260 265 270
 Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile
 275 280 285
 Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys
 290 295 300
 Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln
 305 310 315 320
 Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu
 325 330 335
 Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu
 340 345 350
 Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile
 355 360 365
 Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn
 370 375 380
 Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro
 385 390 395 400
 Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys
 405 410 415
 Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His
 420 425 430
 Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe
 435 440 445
 Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro
 450 455 460
 Asp Cys Lys Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp
 465 470 475 480

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Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp
 485 490 495
 Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp
 500 505 510
 Lys Gly Cys Asp Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln
 515 520 525
 Ser Ser Tyr Trp Thr Tyr Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr
 530 535 540
 Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Gln Asp Asp
 545 550 555 560
 Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln
 565 570 575
 Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly
 580 585 590
 Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr
 595 600 605
 Asp Leu Glu Glu Glu Glu Glu Asp Thr Glu Arg Val Leu Gln Leu Met
 610 615 620
 Ile Ile Leu Glu Gly Asn Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu
 625 630 635
 Val Tyr Leu His Pro Ser Glu Glu His Thr Asn Val Leu Leu Leu Lys
 645 650 655
 Glu Glu Ser Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys
 660 665 670
 Glu Phe Met Thr Val Leu Ala Asn Leu Lys Arg Val Leu Leu Gln Ile
 675 680 685
 Thr Tyr Ser Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn
 690 695 700
 Leu Glu Ser Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala
 705 710 715 720
 Val Glu Val Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu
 725 730 735
 Ser Cys Trp Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly
 740 745 750
 Ile Cys Glu Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp
 755 760 765
 Val Thr Gly Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr
 770 775 780
 Cys Asp Lys Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr
 785 790 795 800
 Ser Glu Asp Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn
 805 810 815
 Asn Phe Ser Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys
 820 825 830
 Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala
 835 840 845
 Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro
 850 855 860
 Cys Gln Cys Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp
 865 870 875 880
 Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg
 885 890 895
 Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala

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900					905					910					
Lys	Asn	Cys	Gln	Pro	Cys	Arg	Cys	Asn	Ala	Gly	Gly	Ser	Phe	Ser	Glu
	915						920					925			
Val	Cys	His	Ser	Gln	Thr	Gly	Gln	Cys	Glu	Cys	Arg	Ala	Asn	Val	Gln
	930				935						940				
Gly	Gln	Arg	Cys	Asp	Lys	Cys	Lys	Ala	Gly	Thr	Phe	Gly	Leu	Gln	Ser
945					950					955					960
Ala	Arg	Gly	Cys	Val	Pro	Cys	Asn	Cys	Asn	Ser	Phe	Gly	Ser	Lys	Ser
				965					970					975	
Phe	Asp	Cys	Glu	Glu	Ser	Gly	Gln	Cys	Trp	Cys	Gln	Pro	Gly	Val	Thr
			980					985					990		
Gly	Lys	Lys	Cys	Asp	Arg	Cys	Ala	His	Gly	Tyr	Phe	Asn	Phe	Gln	Glu
	995						1000					1005			
Gly	Gly	Cys	Thr	Ala	Cys	Glu	Cys	Ser	His	Leu	Gly	Asn	Asn	Cys	
	1010					1015					1020				
Asp	Pro	Lys	Thr	Gly	Arg	Cys	Ile	Cys	Pro	Pro	Asn	Thr	Ile	Gly	
	1025					1030					1035				
Glu	Lys	Cys	Ser	Lys	Cys	Ala	Pro	Asn	Thr	Trp	Gly	His	Ser	Ile	
	1040					1045					1050				
Thr	Thr	Gly	Cys	Lys	Ala	Cys	Asn	Cys	Ser	Thr	Val	Gly	Ser	Leu	
	1055					1060					1065				
Asp	Phe	Gln	Cys	Asn	Val	Asn	Thr	Gly	Gln	Cys	Asn	Cys	His	Pro	
	1070					1075					1080				
Lys	Phe	Ser	Gly	Ala	Lys	Cys	Thr	Glu	Cys	Ser	Arg	Gly	His	Trp	
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Asn	Tyr	Pro	Arg	Cys	Asn	Leu	Cys	Asp	Cys	Phe	Leu	Pro	Gly	Thr	
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Asp	Ala	Thr	Thr	Cys	Asp	Ser	Glu	Thr	Lys	Lys	Cys	Ser	Cys	Ser	
	1115					1120					1125				
Asp	Gln	Thr	Gly	Gln	Cys	Thr	Cys	Lys	Val	Asn	Val	Glu	Gly	Ile	
	1130					1135					1140				
His	Cys	Asp	Arg	Cys	Arg	Pro	Gly	Lys	Phe	Gly	Leu	Asp	Ala	Lys	
	1145					1150					1155				
Asn	Pro	Leu	Gly	Cys	Ser	Ser	Cys	Tyr	Cys	Phe	Gly	Thr	Thr	Thr	
	1160					1165					1170				
Gln	Cys	Ser	Glu	Ala	Lys	Gly	Leu	Ile	Arg	Thr	Trp	Val	Thr	Leu	
	1175					1180					1185				
Lys	Ala	Glu	Gln	Thr	Ile	Leu	Pro	Leu	Val	Asp	Glu	Ala	Leu	Gln	
	1190					1195					1200				
His	Thr	Thr	Thr	Lys	Gly	Ile	Val	Phe	Gln	His	Pro	Glu	Ile	Val	
	1205					1210					1215				
Ala	His	Met	Asp	Leu	Met	Arg	Glu	Asp	Leu	His	Leu	Glu	Pro	Phe	
	1220					1225					1230				
Tyr	Trp	Lys	Leu	Pro	Glu	Gln	Phe	Glu	Gly	Lys	Lys	Leu	Met	Ala	
	1235					1240					1245				
Tyr	Gly	Gly	Lys	Leu	Lys	Tyr	Ala	Ile	Tyr	Phe	Glu	Ala	Arg	Glu	
	1250					1255					1260				
Glu	Thr	Gly	Phe	Ser	Thr	Tyr	Asn	Pro	Gln	Val	Ile	Ile	Arg	Gly	
	1265					1270					1275				
Gly	Thr	Pro	Thr	His	Ala	Arg	Ile	Ile	Val	Arg	His	Met	Ala	Ala	
	1280					1285					1290				
Pro	Leu	Ile	Gly	Gln	Leu	Thr	Arg	His	Glu	Ile	Glu	Met	Thr	Glu	
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Lys	Glu	Trp	Lys	Tyr	Tyr	Gly	Asp	Asp	Pro	Arg	Val	His	Arg	Thr
1310						1315					1320			
Val	Thr	Arg	Glu	Asp	Phe	Leu	Asp	Ile	Leu	Tyr	Asp	Ile	His	Tyr
1325						1330					1335			
Ile	Leu	Ile	Lys	Ala	Thr	Tyr	Gly	Asn	Phe	Met	Arg	Gln	Ser	Arg
1340						1345					1350			
Ile	Ser	Glu	Ile	Ser	Met	Glu	Val	Ala	Glu	Gln	Gly	Arg	Gly	Thr
1355						1360					1365			
Thr	Met	Thr	Pro	Pro	Ala	Asp	Leu	Ile	Glu	Lys	Cys	Asp	Cys	Pro
1370						1375					1380			
Leu	Gly	Tyr	Ser	Gly	Leu	Ser	Cys	Glu	Ala	Cys	Leu	Pro	Gly	Phe
1385						1390					1395			
Tyr	Arg	Leu	Arg	Ser	Gln	Pro	Gly	Gly	Arg	Thr	Pro	Gly	Pro	Thr
1400						1405					1410			
Leu	Gly	Thr	Cys	Val	Pro	Cys	Gln	Cys	Asn	Gly	His	Ser	Ser	Leu
1415						1420					1425			
Cys	Asp	Pro	Glu	Thr	Ser	Ile	Cys	Gln	Asn	Cys	Gln	His	His	Thr
1430						1435					1440			
Ala	Gly	Asp	Phe	Cys	Glu	Arg	Cys	Ala	Leu	Gly	Tyr	Tyr	Gly	Ile
1445						1450					1455			
Val	Lys	Gly	Leu	Pro	Asn	Asp	Cys	Gln	Gln	Cys	Ala	Cys	Pro	Leu
1460						1465					1470			
Ile	Ser	Ser	Ser	Asn	Asn	Phe	Ser	Pro	Ser	Cys	Val	Ala	Glu	Gly
1475						1480					1485			
Leu	Asp	Asp	Tyr	Arg	Cys	Thr	Ala	Cys	Pro	Arg	Gly	Tyr	Glu	Gly
1490						1495					1500			
Gln	Tyr	Cys	Glu	Arg	Cys	Ala	Pro	Gly	Tyr	Thr	Gly	Ser	Pro	Gly
1505						1510					1515			
Asn	Pro	Gly	Gly	Ser	Cys	Gln	Glu	Cys	Glu	Cys	Asp	Pro	Tyr	Gly
1520						1525					1530			
Ser	Leu	Pro	Val	Pro	Cys	Asp	Pro	Val	Thr	Gly	Phe	Cys	Thr	Cys
1535						1540					1545			
Arg	Pro	Gly	Ala	Thr	Gly	Arg	Lys	Cys	Asp	Gly	Cys	Lys	His	Trp
1550						1555					1560			
His	Ala	Arg	Glu	Gly	Trp	Glu	Cys	Val	Phe	Cys	Gly	Asp	Glu	Cys
1565						1570					1575			
Thr	Gly	Leu	Leu	Leu	Gly	Asp	Leu	Ala	Arg	Leu	Glu	Gln	Met	Val
1580						1585					1590			
Met	Ser	Ile	Asn	Leu	Thr	Gly	Pro	Leu	Pro	Ala	Pro	Tyr	Lys	Met
1595						1600					1605			
Leu	Tyr	Gly	Leu	Glu	Asn	Met	Thr	Gln	Glu	Leu	Lys	His	Leu	Leu
1610						1615					1620			
Ser	Pro	Gln	Arg	Ala	Pro	Glu	Arg	Leu	Ile	Gln	Leu	Ala	Glu	Gly
1625						1630					1635			
Asn	Leu	Asn	Thr	Leu	Val	Thr	Glu	Met	Asn	Glu	Leu	Leu	Thr	Arg
1640						1645					1650			
Ala	Thr	Lys	Val	Thr	Ala	Asp	Gly	Glu	Gln	Thr	Gly	Gln	Asp	Ala
1655						1660					1665			
Glu	Arg	Thr	Asn	Thr	Arg	Ala	Lys	Ser	Leu	Gly	Glu	Phe	Ile	Lys
1670						1675					1680			
Glu	Leu	Ala	Arg	Asp	Ala	Glu	Ala	Val	Asn	Glu	Lys	Ala	Ile	Lys
1685						1690					1695			

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Leu	Asn	Glu	Thr	Leu	Gly	Thr	Arg	Asp	Glu	Ala	Phe	Glu	Arg	Asn
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Leu	Glu	Gly	Leu	Gln	Lys	Glu	Ile	Asp	Gln	Met	Ile	Lys	Glu	Leu
1715						1720					1725			
Arg	Arg	Lys	Asn	Leu	Glu	Thr	Gln	Lys	Glu	Ile	Ala	Glu	Asp	Glu
1730						1735					1740			
Leu	Val	Ala	Ala	Glu	Ala	Leu	Leu	Lys	Lys	Val	Lys	Lys	Leu	Phe
1745						1750					1755			
Gly	Glu	Ser	Arg	Gly	Glu	Asn	Glu	Glu	Met	Glu	Lys	Asp	Leu	Arg
1760						1765					1770			
Glu	Lys	Leu	Ala	Asp	Tyr	Lys	Asn	Lys	Val	Asp	Asp	Ala	Trp	Asp
1775						1780					1785			
Leu	Leu	Arg	Glu	Ala	Thr	Asp	Lys	Ile	Arg	Glu	Ala	Asn	Arg	Leu
1790						1795					1800			
Phe	Ala	Val	Asn	Gln	Lys	Asn	Met	Thr	Ala	Leu	Glu	Lys	Lys	Lys
1805						1810					1815			
Glu	Ala	Val	Glu	Ser	Gly	Lys	Arg	Gln	Ile	Glu	Asn	Thr	Leu	Lys
1820						1825					1830			
Glu	Gly	Asn	Asp	Ile	Leu	Asp	Glu	Ala	Asn	Arg	Leu	Ala	Asp	Glu
1835						1840					1845			
Ile	Asn	Ser	Ile	Ile	Asp	Tyr	Val	Glu	Asp	Ile	Gln	Thr	Lys	Leu
1850						1855					1860			
Pro	Pro	Met	Ser	Glu	Glu	Leu	Asn	Asp	Lys	Ile	Asp	Asp	Leu	Ser
1865						1870					1875			
Gln	Glu	Ile	Lys	Asp	Arg	Lys	Leu	Ala	Glu	Lys	Val	Ser	Gln	Ala
1880						1885					1890			
Glu	Ser	His	Ala	Ala	Gln	Leu	Asn	Asp	Ser	Ser	Ala	Val	Leu	Asp
1895						1900					1905			
Gly	Ile	Leu	Asp	Glu	Ala	Lys	Asn	Ile	Ser	Phe	Asn	Ala	Thr	Ala
1910						1915					1920			
Ala	Phe	Lys	Ala	Tyr	Ser	Asn	Ile	Lys	Asp	Tyr	Ile	Asp	Glu	Ala
1925						1930					1935			
Glu	Lys	Val	Ala	Lys	Glu	Ala	Lys	Asp	Leu	Ala	His	Glu	Ala	Thr
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Lys	Leu	Ala	Thr	Gly	Pro	Arg	Gly	Leu	Leu	Lys	Glu	Asp	Ala	Lys
1955						1960					1965			
Gly	Cys	Leu	Gln	Lys	Ser	Phe	Arg	Ile	Leu	Asn	Glu	Ala	Lys	Lys
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Leu	Ala	Asn	Asp	Val	Lys	Glu	Asn	Glu	Asp	His	Leu	Asn	Gly	Leu
1985						1990					1995			
Lys	Thr	Arg	Ile	Glu	Asn	Ala	Asp	Ala	Arg	Asn	Gly	Asp	Leu	Leu
2000						2005					2010			
Arg	Thr	Leu	Asn	Asp	Thr	Leu	Gly	Lys	Leu	Ser	Ala	Ile	Pro	Asn
2015						2020					2025			
Asp	Thr	Ala	Ala	Lys	Leu	Gln	Ala	Val	Lys	Asp	Lys	Ala	Arg	Gln
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Ala	Asn	Asp	Thr	Ala	Lys	Asp	Val	Leu	Ala	Gln	Ile	Thr	Glu	Leu
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His	Gln	Asn	Leu	Asp	Gly	Leu	Lys	Lys	Asn	Tyr	Asn	Lys	Leu	Ala
2060						2065					2070			
Asp	Ser	Val	Ala	Lys	Thr	Asn	Ala	Val	Val	Lys	Asp	Pro	Ser	Lys
2075						2080					2085			
Asn	Lys	Ile	Ile	Ala	Asp	Ala	Asp	Ala	Thr	Val	Lys	Asn	Leu	Glu

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Leu	Glu	Asp	Asn	Leu	Lys	Lys	Asn	Ile	Ser	Glu	Ile	Lys	Glu	Leu
2120						2125					2130			
Ile	Asn	Gln	Ala	Arg	Lys	Gln	Ala	Asn	Ser	Ile	Lys	Val	Ser	Val
2135						2140					2145			
Ser	Ser	Gly	Gly	Asp	Cys	Ile	Arg	Thr	Tyr	Lys	Pro	Glu	Ile	Lys
2150						2155					2160			
Lys	Gly	Ser	Tyr	Asn	Asn	Ile	Val	Val	Asn	Val	Lys	Thr	Ala	Val
2165						2170					2175			
Ala	Asp	Asn	Leu	Leu	Phe	Tyr	Leu	Gly	Ser	Ala	Lys	Phe	Ile	Asp
2180						2185					2190			
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2195						2200					2205			
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Arg	Asn	Gly	Thr	Ile	Ser	Val	Arg	Ala	Leu	Asp	Gly	Pro	Lys	Ala
2240						2245					2250			
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Ser	Ala	Leu	Leu	Met	Tyr	Leu	Ala	Thr	Arg	Asp	Leu	Arg	Asp	Phe
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Asp	Gly	Lys	Trp	Lys	Ser	Phe	Thr	Leu	Ser	Arg	Ile	Gln	Lys	Gln
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Ala	Asn	Ile	Ser	Ile	Val	Asp	Ile	Asp	Thr	Asn	Gln	Glu	Glu	Asn
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Ile	Ala	Thr	Ser	Ser	Ser	Gly	Asn	Asn	Phe	Gly	Leu	Asp	Leu	Lys
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Ala	Asp	Asp	Lys	Ile	Tyr	Phe	Gly	Gly	Leu	Pro	Thr	Leu	Arg	Asn
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2525						2530					2535			
Pro	Ile	Asp	Val	Gly	Thr	Glu	Ile	Asn	Leu	Ser	Phe	Ser	Thr	Lys
2540						2545					2550			
Asn	Glu	Ser	Gly	Ile	Ile	Leu	Leu	Gly	Ser	Gly	Gly	Thr	Pro	Ala
2555						2560					2565			
Pro	Pro	Arg	Arg	Lys	Arg	Arg	Gln	Thr	Gly	Gln	Ala	Tyr	Tyr	Val
2570						2575					2580			
Ile	Leu	Leu	Asn	Arg	Gly	Arg	Leu	Glu	Val	His	Leu	Ser	Thr	Gly
2585						2590					2595			
Ala	Arg	Thr	Met	Arg	Lys	Ile	Val	Ile	Arg	Pro	Glu	Pro	Asn	Leu
2600						2605					2610			
Phe	His	Asp	Gly	Arg	Glu	His	Ser	Val	His	Val	Glu	Arg	Thr	Arg
2615						2620					2625			
Gly	Ile	Phe	Thr	Val	Gln	Val	Asp	Glu	Asn	Arg	Arg	Tyr	Met	Gln
2630						2635					2640			
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2675						2680					2685			
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2705						2710					2715			
Ala	Pro	Ala	Glu	Ile	Val	Ile	Gln	Pro	Glu	Pro	Val	Pro	Thr	Pro
2720						2725					2730			
Ala	Phe	Pro	Thr	Pro	Thr	Pro	Val	Leu	Thr	His	Gly	Pro	Cys	Ala
2735						2740					2745			
Ala	Glu	Ser	Glu	Pro	Ala	Leu	Leu	Ile	Gly	Ser	Lys	Gln	Phe	Gly
2750						2755					2760			
Leu	Ser	Arg	Asn	Ser	His	Ile	Ala	Ile	Ala	Phe	Asp	Asp	Thr	Lys
2765						2770					2775			
Val	Lys	Asn	Arg	Leu	Thr	Ile	Glu	Leu	Glu	Val	Arg	Thr	Glu	Ala
2780						2785					2790			
Glu	Ser	Gly	Leu	Leu	Phe	Tyr	Met	Ala	Arg	Ile	Asn	His	Ala	Asp
2795						2800					2805			
Phe	Ala	Thr	Val	Gln	Leu	Arg	Asn	Gly	Leu	Pro	Tyr	Phe	Ser	Tyr
2810						2815					2820			
Asp	Leu	Gly	Ser	Gly	Asp	Thr	His	Thr	Met	Ile	Pro	Thr	Lys	Ile
2825						2830					2835			
Asn	Asp	Gly	Gln	Trp	His	Lys	Ile	Lys	Ile	Met	Arg	Ser	Lys	Gln
2840						2845					2850			
Glu	Gly	Ile	Leu	Tyr	Val	Asp	Gly	Ala	Ser	Asn	Arg	Thr	Ile	Ser
2855						2860					2865			
Pro	Lys	Lys	Ala	Asp	Ile	Leu	Asp	Val	Val	Gly	Met	Leu	Tyr	Val
2870						2875					2880			

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Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro Val
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Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu
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Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val Gly
 2915 2920 2925

Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe Asp Gly Thr
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Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu
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Leu Val Glu Phe Glu Phe Arg Thr Thr Thr Thr Thr Gly Val Leu
 2960 2965 2970

Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met
 2975 2980 2985

Ile Asp Glu Lys Leu Met Phe His Val Asp Asn Gly Ala Gly Arg
 2990 2995 3000

Phe Thr Ala Val Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp
 3005 3010 3015

Gly Gln Trp His Lys Val Thr Ala Asn Lys Ile Lys His Arg Ile
 3020 3025 3030

Glu Leu Thr Val Asp Gly Asn Gln Val Glu Ala Gln Ser Pro Asn
 3035 3040 3045

Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp Pro Val Phe Val Gly
 3050 3055 3060

Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu Thr Thr Ser Ile
 3065 3070 3075

Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr
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Gly Lys Pro Leu Glu Val Asn Phe Ala Lys Ala Leu Glu Leu Arg
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Gly Val Gln Pro Val Ser Cys Pro Ala Asn
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 <211> LENGTH: 3333
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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Gly Ala Thr Ala Arg Asp Pro Gly Ala Ala Ala Gly Leu Ser Leu His
 35 40 45

Pro Thr Tyr Phe Asn Leu Ala Glu Ala Ala Arg Ile Trp Ala Thr Ala
 50 55 60

Thr Cys Gly Glu Arg Gly Pro Gly Glu Gly Arg Pro Gln Pro Glu Leu
 65 70 75 80

Tyr Cys Lys Leu Val Gly Gly Pro Thr Ala Pro Gly Ser Gly His Thr
 85 90 95

Ile Gln Gly Gln Phe Cys Asp Tyr Cys Asn Ser Glu Asp Pro Arg Lys
 100 105 110

Ala His Pro Val Thr Asn Ala Ile Asp Gly Ser Glu Arg Trp Trp Gln
 115 120 125

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Ser Pro Pro Leu Ser Ser Gly Thr Gln Tyr Asn Arg Val Asn Leu Thr
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Leu Asp Leu Gly Gln Leu Phe His Val Ala Tyr Ile Leu Ile Lys Phe
 145 150 155 160

Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg Ser Val Asp
 165 170 175

Phe Gly Ser Thr Tyr Ser Pro Trp Gln Tyr Phe Ala His Ser Lys Val
 180 185 190

Asp Cys Leu Lys Glu Phe Gly Arg Glu Ala Asn Met Ala Val Thr Arg
 195 200 205

Asp Asp Asp Val Leu Cys Val Thr Glu Tyr Ser Arg Ile Val Pro Leu
 210 215 220

Glu Asn Gly Glu Val Val Val Ser Leu Ile Asn Gly Arg Pro Gly Ala
 225 230 235 240

Lys Asn Phe Thr Phe Ser His Thr Leu Arg Glu Phe Thr Lys Ala Thr
 245 250 255

Asn Ile Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu Gly His Leu
 260 265 270

Ile Ser Lys Ala Gln Arg Asp Pro Thr Val Thr Arg Arg Tyr Tyr Tyr
 275 280 285

Ser Ile Lys Asp Ile Ser Ile Gly Gly Gln Cys Val Cys Asn Gly His
 290 295 300

Ala Glu Val Cys Asn Ile Asn Asn Pro Glu Lys Leu Phe Arg Cys Glu
 305 310 315 320

Cys Gln His His Thr Cys Gly Glu Thr Cys Asp Arg Cys Cys Thr Gly
 325 330 335

Tyr Asn Gln Arg Arg Trp Arg Pro Ala Ala Trp Glu Gln Ser His Glu
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Cys Glu Ala Cys Asn Cys His Gly His Ala Ser Asn Cys Tyr Tyr Asp
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Pro Asp Val Glu Arg Gln Gln Ala Ser Leu Asn Thr Gln Gly Ile Tyr
 370 375 380

Ala Gly Gly Gly Val Cys Ile Asn Cys Gln His Asn Thr Ala Gly Val
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Asn Cys Glu Gln Cys Ala Lys Gly Tyr Tyr Arg Pro Tyr Gly Val Pro
 405 410 415

Val Asp Ala Pro Asp Gly Cys Ile Pro Cys Ser Cys Asp Pro Glu His
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Ala Asp Gly Cys Glu Gln Gly Ser Gly Arg Cys His Cys Lys Pro Asn
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Phe His Gly Asp Asn Cys Glu Lys Cys Ala Ile Gly Tyr Tyr Asn Phe
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Pro Phe Cys Leu Arg Ile Pro Ile Phe Pro Val Ser Thr Pro Ser Ser
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Glu Asp Pro Val Ala Gly Asp Ile Lys Gly Cys Asp Cys Asn Leu Glu
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Gly Val Leu Pro Glu Ile Cys Asp Ala His Gly Arg Cys Leu Cys Arg
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Pro Gly Val Glu Gly Pro Arg Cys Asp Thr Cys Arg Ser Gly Phe Tyr
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Ser Phe Pro Ile Cys Gln Ala Cys Trp Cys Ser Ala Leu Gly Ser Tyr
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Gln Met Pro Cys Ser Ser Val Thr Gly Gln Cys Glu Cys Arg Pro Gly
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 Val Thr Gly Gln Arg Cys Asp Arg Cys Leu Ser Gly Ala Tyr Asp Phe
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 Pro His Cys Gln Gly Ser Ser Ser Ala Cys Asp Pro Ala Gly Thr Ile
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 Asn Ser Asn Leu Gly Tyr Cys Gln Cys Lys Leu His Val Glu Gly Pro
 595 600 605
 Thr Cys Ser Arg Cys Lys Leu Leu Tyr Trp Asn Leu Asp Lys Glu Asn
 610 615 620
 Pro Ser Gly Cys Ser Glu Cys Lys Cys His Lys Ala Gly Thr Val Ser
 625 630 635 640
 Gly Thr Gly Glu Cys Arg Gln Gly Asp Gly Asp Cys His Cys Lys Ser
 645 650 655
 His Val Gly Gly Asp Ser Cys Asp Thr Cys Glu Asp Gly Tyr Phe Ala
 660 665 670
 Leu Glu Lys Ser Asn Tyr Phe Gly Cys Gln Gly Cys Gln Cys Asp Ile
 675 680 685
 Gly Gly Ala Leu Ser Ser Met Cys Ser Gly Pro Ser Gly Val Cys Gln
 690 695 700
 Cys Arg Glu His Val Val Gly Lys Val Cys Gln Arg Pro Glu Asn Asn
 705 710 715
 Tyr Tyr Phe Pro Asp Leu His His Met Lys Tyr Glu Ile Glu Asp Gly
 725 730 735
 Ser Thr Pro Asn Gly Arg Asp Leu Arg Phe Gly Phe Asp Pro Leu Ala
 740 745 750
 Phe Pro Glu Phe Ser Trp Arg Gly Tyr Ala Gln Met Thr Ser Val Gln
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 Asn Asp Val Arg Ile Thr Leu Asn Val Gly Lys Ser Ser Gly Ser Leu
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 Phe Arg Val Ile Leu Arg Tyr Val Asn Pro Gly Thr Glu Ala Val Ser
 785 790 795 800
 Gly His Ile Thr Ile Tyr Pro Ser Trp Gly Ala Ala Gln Ser Lys Glu
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 Ile Ile Phe Leu Pro Ser Lys Glu Pro Ala Phe Val Thr Val Pro Gly
 820 825 830
 Asn Gly Phe Ala Asp Pro Phe Ser Ile Thr Pro Gly Ile Trp Val Ala
 835 840 845
 Cys Ile Lys Ala Glu Gly Val Leu Leu Asp Tyr Leu Val Leu Leu Pro
 850 855 860
 Arg Asp Tyr Tyr Glu Ala Ser Val Leu Gln Leu Pro Val Thr Glu Pro
 865 870 875 880
 Cys Ala Tyr Ala Gly Pro Pro Gln Glu Asn Cys Leu Leu Tyr Gln His
 885 890 895
 Leu Pro Val Thr Arg Phe Pro Cys Thr Leu Ala Cys Glu Ala Arg His
 900 905 910
 Phe Leu Leu Asp Gly Glu Pro Arg Pro Val Ala Val Arg Gln Pro Thr
 915 920 925
 Pro Ala His Pro Val Met Val Asp Leu Ser Gly Arg Glu Val Glu Leu
 930 935 940
 His Leu Arg Leu Arg Ile Pro Gln Val Gly His Tyr Val Val Val Val
 945 950 955 960
 Glu Tyr Ser Thr Glu Ala Ala Gln Leu Phe Val Val Asp Val Asn Val

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Asn	Tyr	Ser	Val	Leu	Cys	Arg	Ser	Ala	Val	Ile	Asp	His	Met	Ser	Arg
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Ile	Ala	Met	Tyr	Glu	Leu	Leu	Ala	Asp	Ala	Asp	Ile	Gln	Leu	Lys	
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Gly	His	Met	Ala	Arg	Phe	Leu	Leu	His	Gln	Val	Cys	Ile	Ile	Pro	
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Ile	Ala	Ser	Tyr	Gly	Arg	Phe	Val	Asn	Gln	Ser	Ala	Thr	Cys	Val	
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Ser	Leu	Ala	His	Glu	Thr	Pro	Pro	Thr	Ala	Leu	Ile	Leu	Asp	Val	
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Leu	Ser	Gly	Arg	Pro	Phe	Pro	His	Leu	Pro	Gln	Gln	Ser	Ser	Pro	
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Ser	Val	Asp	Val	Leu	Pro	Gly	Val	Thr	Leu	Lys	Ala	Pro	Gln	Asn	
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Gln	Val	Ser	Val	Asp	Gly	Gly	Trp	Pro	Arg	Ala	Gly	Ser	Phe	His	
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Ala	Ser	Phe	Cys	Pro	His	Val	Leu	Gly	Cys	Arg	Asp	Gln	Val	Ile	
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Ala	Thr	Val	Lys	Val	Pro	Glu	Gly	Lys	Ser	Leu	Val	Leu	Val	Arg	
	1190					1195					1200				
Val	Leu	Val	Val	Pro	Ala	Glu	Asn	Tyr	Asp	Tyr	Gln	Ile	Leu	His	
	1205					1210					1215				
Lys	Lys	Ser	Met	Asp	Lys	Ser	Leu	Glu	Phe	Ile	Thr	Asn	Cys	Gly	
	1220					1225					1230				
Lys	Asn	Ser	Phe	Tyr	Leu	Asp	Pro	Gln	Thr	Ala	Ser	Arg	Phe	Cys	
	1235					1240					1245				
Lys	Asn	Ser	Ala	Arg	Ser	Leu	Val	Ala	Phe	Tyr	His	Lys	Gly	Ala	
	1250					1255					1260				
Leu	Pro	Cys	Glu	Cys	His	Pro	Thr	Gly	Ala	Thr	Gly	Pro	His	Cys	
	1265					1270					1275				
Ser	Pro	Glu	Gly	Gly	Gln	Cys	Pro	Cys	Gln	Pro	Asn	Val	Ile	Gly	
	1280					1285					1290				
Arg	Gln	Cys	Thr	Arg	Cys	Ala	Thr	Gly	His	Tyr	Gly	Phe	Pro	Arg	
	1295					1300					1305				
Cys	Lys	Pro	Cys	Ser	Cys	Gly	Arg	Arg	Leu	Cys	Glu	Glu	Met	Thr	
	1310					1315					1320				
Gly	Gln	Cys	Arg	Cys	Pro	Pro	Arg	Thr	Val	Arg	Pro	Gln	Cys	Glu	
	1325					1330					1335				
Val	Cys	Glu	Thr	His	Ser	Phe	Ser	Phe	His	Pro	Met	Ala	Gly	Cys	
	1340					1345					1350				
Glu	Gly	Cys	Asn	Cys	Ser	Arg	Arg	Gly	Thr	Ile	Glu	Ala	Ala	Met	
	1355					1360					1365				

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Pro	Glu	Cys	Asp	Arg	Asp	Ser	Gly	Gln	Cys	Arg	Cys	Lys	Pro	Arg
1370						1375					1380			
Ile	Thr	Gly	Arg	Gln	Cys	Asp	Arg	Cys	Ala	Ser	Gly	Phe	Tyr	Arg
1385						1390					1395			
Phe	Pro	Glu	Cys	Val	Pro	Cys	Asn	Cys	Asn	Arg	Asp	Gly	Thr	Glu
1400						1405					1410			
Pro	Gly	Val	Cys	Asp	Pro	Gly	Thr	Gly	Ala	Cys	Leu	Cys	Lys	Glu
1415						1420					1425			
Asn	Val	Glu	Gly	Thr	Glu	Cys	Asn	Val	Cys	Arg	Glu	Gly	Ser	Phe
1430						1435					1440			
His	Leu	Asp	Pro	Ala	Asn	Leu	Lys	Gly	Cys	Thr	Ser	Cys	Phe	Cys
1445						1450					1455			
Phe	Gly	Val	Asn	Asn	Gln	Cys	His	Ser	Ser	His	Lys	Arg	Arg	Thr
1460						1465					1470			
Lys	Phe	Val	Asp	Met	Leu	Gly	Trp	His	Leu	Glu	Thr	Ala	Asp	Arg
1475						1480					1485			
Val	Asp	Ile	Pro	Val	Ser	Phe	Asn	Pro	Gly	Ser	Asn	Ser	Met	Val
1490						1495					1500			
Ala	Asp	Leu	Gln	Glu	Leu	Pro	Ala	Thr	Ile	His	Ser	Ala	Ser	Trp
1505						1510					1515			
Val	Ala	Pro	Thr	Ser	Tyr	Leu	Gly	Asp	Lys	Val	Ser	Ser	Tyr	Gly
1520						1525					1530			
Gly	Tyr	Leu	Thr	Tyr	Gln	Ala	Lys	Ser	Phe	Gly	Leu	Pro	Gly	Asp
1535						1540					1545			
Met	Val	Leu	Leu	Glu	Lys	Lys	Pro	Asp	Val	Gln	Leu	Thr	Gly	Gln
1550						1555					1560			
His	Met	Ser	Ile	Ile	Tyr	Glu	Glu	Thr	Asn	Thr	Pro	Arg	Pro	Asp
1565						1570					1575			
Arg	Leu	His	His	Gly	Arg	Val	His	Val	Val	Glu	Gly	Asn	Phe	Arg
1580						1585					1590			
His	Ala	Ser	Ser	Arg	Ala	Pro	Val	Ser	Arg	Glu	Glu	Leu	Met	Thr
1595						1600					1605			
Val	Leu	Ser	Arg	Leu	Ala	Asp	Val	Arg	Ile	Gln	Gly	Leu	Tyr	Phe
1610						1615					1620			
Thr	Glu	Thr	Gln	Arg	Leu	Thr	Leu	Ser	Glu	Val	Gly	Leu	Glu	Glu
1625						1630					1635			
Ala	Ser	Asp	Thr	Gly	Ser	Gly	Arg	Ile	Ala	Leu	Ala	Val	Glu	Ile
1640						1645					1650			
Cys	Ala	Cys	Pro	Pro	Ala	Tyr	Ala	Gly	Asp	Ser	Cys	Gln	Gly	Cys
1655						1660					1665			
Ser	Pro	Gly	Tyr	Tyr	Arg	Asp	His	Lys	Gly	Leu	Tyr	Thr	Gly	Arg
1670						1675					1680			
Cys	Val	Pro	Cys	Asn	Cys	Asn	Gly	His	Ser	Asn	Gln	Cys	Gln	Asp
1685						1690					1695			
Gly	Ser	Gly	Ile	Cys	Val	Asn	Cys	Gln	His	Asn	Thr	Ala	Gly	Glu
1700						1705					1710			
His	Cys	Glu	Arg	Cys	Gln	Glu	Gly	Tyr	Tyr	Gly	Asn	Ala	Val	His
1715						1720					1725			
Gly	Ser	Cys	Arg	Ala	Cys	Pro	Cys	Pro	His	Thr	Asn	Ser	Phe	Ala
1730						1735					1740			
Thr	Gly	Cys	Val	Val	Asn	Gly	Gly	Asp	Val	Arg	Cys	Ser	Cys	Lys
1745						1750					1755			

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Ala	Gly	Tyr	Thr	Gly	Thr	Gln	Cys	Glu	Arg	Cys	Ala	Pro	Gly	Tyr
1760						1765					1770			
Phe	Gly	Asn	Pro	Gln	Lys	Phe	Gly	Gly	Ser	Cys	Gln	Pro	Cys	Ser
1775						1780					1785			
Cys	Asn	Ser	Asn	Gly	Gln	Leu	Gly	Ser	Cys	His	Pro	Leu	Thr	Gly
1790						1795					1800			
Asp	Cys	Ile	Asn	Gln	Glu	Pro	Lys	Asp	Ser	Ser	Pro	Ala	Glu	Glu
1805						1810					1815			
Cys	Asp	Asp	Cys	Asp	Ser	Cys	Val	Met	Thr	Leu	Leu	Asn	Asp	Leu
1820						1825					1830			
Ala	Thr	Met	Gly	Glu	Gln	Leu	Arg	Leu	Val	Lys	Ser	Gln	Leu	Gln
1835						1840					1845			
Gly	Leu	Ser	Ala	Ser	Ala	Gly	Leu	Leu	Glu	Gln	Met	Arg	His	Met
1850						1855					1860			
Glu	Thr	Gln	Ala	Lys	Asp	Leu	Arg	Asn	Gln	Leu	Leu	Asn	Tyr	Arg
1865						1870					1875			
Ser	Ala	Ile	Ser	Asn	His	Gly	Ser	Lys	Ile	Glu	Gly	Leu	Glu	Arg
1880						1885					1890			
Glu	Leu	Thr	Asp	Leu	Asn	Gln	Glu	Phe	Glu	Thr	Leu	Gln	Glu	Lys
1895						1900					1905			
Ala	Gln	Val	Asn	Ser	Arg	Lys	Ala	Gln	Thr	Leu	Asn	Asn	Asn	Val
1910						1915					1920			
Asn	Arg	Ala	Thr	Gln	Ser	Ala	Lys	Glu	Leu	Asp	Val	Lys	Ile	Lys
1925						1930					1935			
Asn	Val	Ile	Arg	Asn	Val	His	Ile	Leu	Leu	Lys	Gln	Ile	Ser	Gly
1940						1945					1950			
Thr	Asp	Gly	Glu	Gly	Asn	Asn	Val	Pro	Ser	Gly	Asp	Phe	Ser	Arg
1955						1960					1965			
Glu	Trp	Ala	Glu	Ala	Gln	Arg	Met	Met	Arg	Glu	Leu	Arg	Asn	Arg
1970						1975					1980			
Asn	Phe	Gly	Lys	His	Leu	Arg	Glu	Ala	Glu	Ala	Asp	Lys	Arg	Glu
1985						1990					1995			
Ser	Gln	Leu	Leu	Leu	Asn	Arg	Ile	Arg	Thr	Trp	Gln	Lys	Thr	His
2000						2005					2010			
Gln	Gly	Glu	Asn	Asn	Gly	Leu	Ala	Asn	Ser	Ile	Arg	Asp	Ser	Leu
2015						2020					2025			
Asn	Glu	Tyr	Glu	Ala	Lys	Leu	Ser	Asp	Leu	Arg	Ala	Arg	Leu	Gln
2030						2035					2040			
Glu	Ala	Ala	Ala	Gln	Ala	Lys	Gln	Ala	Asn	Gly	Leu	Asn	Gln	Glu
2045						2050					2055			
Asn	Glu	Arg	Ala	Leu	Gly	Ala	Ile	Gln	Arg	Gln	Val	Lys	Glu	Ile
2060						2065					2070			
Asn	Ser	Leu	Gln	Ser	Asp	Phe	Thr	Lys	Tyr	Leu	Thr	Thr	Ala	Asp
2075						2080					2085			
Ser	Ser	Leu	Leu	Gln	Thr	Asn	Ile	Ala	Leu	Gln	Leu	Met	Glu	Lys
2090						2095					2100			
Ser	Gln	Lys	Glu	Tyr	Glu	Lys	Leu	Ala	Ala	Ser	Leu	Asn	Glu	Ala
2105						2110					2115			
Arg	Gln	Glu	Leu	Ser	Asp	Lys	Val	Arg	Glu	Leu	Ser	Arg	Ser	Ala
2120						2125					2130			
Gly	Lys	Thr	Ser	Leu	Val	Glu	Glu	Ala	Glu	Lys	His	Ala	Arg	Ser
2135						2140					2145			
Leu	Gln	Glu	Leu	Ala	Lys	Gln	Leu	Glu	Glu	Ile	Lys	Arg	Asn	Ala

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2150	2155	2160
Ser Gly Asp Glu Leu Val Arg Cys Ala Val Asp Ala Ala Thr Ala 2165 2170 2175		
Tyr Glu Asn Ile Leu Asn Ala Ile Lys Ala Ala Glu Asp Ala Ala 2180 2185 2190		
Asn Arg Ala Ala Ser Ala Ser Glu Ser Ala Leu Gln Thr Val Ile 2195 2200 2205		
Lys Glu Asp Leu Pro Arg Lys Ala Lys Thr Leu Ser Ser Asn Ser 2210 2215 2220		
Asp Lys Leu Leu Asn Glu Ala Lys Met Thr Gln Lys Lys Leu Lys 2225 2230 2235		
Gln Glu Val Ser Pro Ala Leu Asn Asn Leu Gln Gln Thr Leu Asn 2240 2245 2250		
Ile Val Thr Val Gln Lys Glu Val Ile Asp Thr Asn Leu Thr Thr 2255 2260 2265		
Leu Arg Asp Gly Leu His Gly Ile Gln Arg Gly Asp Ile Asp Ala 2270 2275 2280		
Met Ile Ser Ser Ala Lys Ser Met Val Arg Lys Ala Asn Asp Ile 2285 2290 2295		
Thr Asp Glu Val Leu Asp Gly Leu Asn Pro Ile Gln Thr Asp Val 2300 2305 2310		
Glu Arg Ile Lys Asp Thr Tyr Gly Arg Thr Gln Asn Glu Asp Phe 2315 2320 2325		
Lys Lys Ala Leu Thr Asp Ala Asp Asn Ser Val Asn Lys Leu Thr 2330 2335 2340		
Asn Lys Leu Pro Asp Leu Trp Arg Lys Ile Glu Ser Ile Asn Gln 2345 2350 2355		
Gln Leu Leu Pro Leu Gly Asn Ile Ser Asp Asn Met Asp Arg Ile 2360 2365 2370		
Arg Glu Leu Ile Gln Gln Ala Arg Asp Ala Ala Ser Lys Val Ala 2375 2380 2385		
Val Pro Met Arg Phe Asn Gly Lys Ser Gly Val Glu Val Arg Leu 2390 2395 2400		
Pro Asn Asp Leu Glu Asp Leu Lys Gly Tyr Thr Ser Leu Ser Leu 2405 2410 2415		
Phe Leu Gln Arg Pro Asn Ser Arg Glu Asn Gly Gly Thr Glu Asn 2420 2425 2430		
Met Phe Val Met Tyr Leu Gly Asn Lys Asp Ala Ser Arg Asp Tyr 2435 2440 2445		
Ile Gly Met Ala Val Val Asp Gly Gln Leu Thr Cys Val Tyr Asn 2450 2455 2460		
Leu Gly Asp Arg Glu Ala Glu Leu Gln Val Asp Gln Ile Leu Thr 2465 2470 2475		
Lys Ser Glu Thr Lys Glu Ala Val Met Asp Arg Val Lys Phe Gln 2480 2485 2490		
Arg Ile Tyr Gln Phe Ala Arg Leu Asn Tyr Thr Lys Gly Ala Thr 2495 2500 2505		
Ser Ser Lys Pro Glu Thr Pro Gly Val Tyr Asp Met Asp Gly Arg 2510 2515 2520		
Asn Ser Asn Thr Leu Leu Asn Leu Asp Pro Glu Asn Val Val Phe 2525 2530 2535		
Tyr Val Gly Gly Tyr Pro Pro Asp Phe Lys Leu Pro Ser Arg Leu 2540 2545 2550		

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Ser	Phe	Pro	Pro	Tyr	Lys	Gly	Cys	Ile	Glu	Leu	Asp	Asp	Leu	Asn
2555						2560					2565			
Glu	Asn	Val	Leu	Ser	Leu	Tyr	Asn	Phe	Lys	Lys	Thr	Phe	Asn	Leu
2570						2575					2580			
Asn	Thr	Thr	Glu	Val	Glu	Pro	Cys	Arg	Arg	Arg	Lys	Glu	Glu	Ser
2585						2590					2595			
Asp	Lys	Asn	Tyr	Phe	Glu	Gly	Thr	Gly	Tyr	Ala	Arg	Val	Pro	Thr
2600						2605					2610			
Gln	Pro	His	Ala	Pro	Ile	Pro	Thr	Phe	Gly	Gln	Thr	Ile	Gln	Thr
2615						2620					2625			
Thr	Val	Asp	Arg	Gly	Leu	Leu	Phe	Phe	Ala	Glu	Asn	Gly	Asp	Arg
2630						2635					2640			
Phe	Ile	Ser	Leu	Asn	Ile	Glu	Asp	Gly	Lys	Leu	Met	Val	Arg	Tyr
2645						2650					2655			
Lys	Leu	Asn	Ser	Glu	Leu	Pro	Lys	Glu	Arg	Gly	Val	Gly	Asp	Ala
2660						2665					2670			
Ile	Asn	Asn	Gly	Arg	Asp	His	Ser	Ile	Gln	Ile	Lys	Ile	Gly	Lys
2675						2680					2685			
Leu	Gln	Lys	Arg	Met	Trp	Ile	Asn	Val	Asp	Val	Gln	Asn	Thr	Ile
2690						2695					2700			
Ile	Asp	Gly	Glu	Val	Phe	Asp	Phe	Ser	Thr	Tyr	Tyr	Leu	Gly	Gly
2705						2710					2715			
Ile	Pro	Ile	Ala	Ile	Arg	Glu	Arg	Phe	Asn	Ile	Ser	Thr	Pro	Ala
2720						2725					2730			
Phe	Arg	Gly	Cys	Met	Lys	Asn	Leu	Lys	Lys	Thr	Ser	Gly	Val	Val
2735						2740					2745			
Arg	Leu	Asn	Asp	Thr	Val	Gly	Val	Thr	Lys	Lys	Cys	Ser	Glu	Asp
2750						2755					2760			
Trp	Lys	Leu	Val	Arg	Ser	Ala	Ser	Phe	Ser	Arg	Gly	Gly	Gln	Leu
2765						2770					2775			
Ser	Phe	Thr	Asp	Leu	Gly	Leu	Pro	Pro	Thr	Asp	His	Leu	Gln	Ala
2780						2785					2790			
Ser	Phe	Gly	Phe	Gln	Thr	Phe	Gln	Pro	Ser	Gly	Ile	Leu	Leu	Asp
2795						2800					2805			
His	Gln	Thr	Trp	Thr	Arg	Asn	Leu	Gln	Val	Thr	Leu	Glu	Asp	Gly
2810						2815					2820			
Tyr	Ile	Glu	Leu	Ser	Thr	Ser	Asp	Ser	Gly	Gly	Pro	Ile	Phe	Lys
2825						2830					2835			
Ser	Pro	Gln	Thr	Tyr	Met	Asp	Gly	Leu	Leu	His	Tyr	Val	Ser	Val
2840						2845					2850			
Ile	Ser	Asp	Asn	Ser	Gly	Leu	Arg	Leu	Leu	Ile	Asp	Asp	Gln	Leu
2855						2860					2865			
Leu	Arg	Asn	Ser	Lys	Arg	Leu	Lys	His	Ile	Ser	Ser	Ser	Arg	Gln
2870						2875					2880			
Ser	Leu	Arg	Leu	Gly	Gly	Ser	Asn	Phe	Glu	Gly	Cys	Ile	Ser	Asn
2885						2890					2895			
Val	Phe	Val	Gln	Arg	Leu	Ser	Leu	Ser	Pro	Glu	Val	Leu	Asp	Leu
2900						2905					2910			
Thr	Ser	Asn	Ser	Leu	Lys	Arg	Asp	Val	Ser	Leu	Gly	Gly	Cys	Ser
2915						2920					2925			
Leu	Asn	Lys	Pro	Pro	Phe	Leu	Met	Leu	Leu	Lys	Gly	Ser	Thr	Arg
2930						2935					2940			

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Phe	Asn	Lys	Thr	Lys	Thr	Phe	Arg	Ile	Asn	Gln	Leu	Leu	Gln	Asp
2945						2950					2955			
Thr	Pro	Val	Ala	Ser	Pro	Arg	Ser	Val	Lys	Val	Trp	Gln	Asp	Ala
2960						2965					2970			
Cys	Ser	Pro	Leu	Pro	Lys	Thr	Gln	Ala	Asn	His	Gly	Ala	Leu	Gln
2975						2980					2985			
Phe	Gly	Asp	Ile	Pro	Thr	Ser	His	Leu	Leu	Phe	Lys	Leu	Pro	Gln
2990						2995					3000			
Glu	Leu	Leu	Lys	Pro	Arg	Ser	Gln	Phe	Ala	Val	Asp	Met	Gln	Thr
3005						3010					3015			
Thr	Ser	Ser	Arg	Gly	Leu	Val	Phe	His	Thr	Gly	Thr	Lys	Asn	Ser
3020						3025					3030			
Phe	Met	Ala	Leu	Tyr	Leu	Ser	Lys	Gly	Arg	Leu	Val	Phe	Ala	Leu
3035						3040					3045			
Gly	Thr	Asp	Gly	Lys	Lys	Leu	Arg	Ile	Lys	Ser	Lys	Glu	Lys	Cys
3050						3055					3060			
Asn	Asp	Gly	Lys	Trp	His	Thr	Val	Val	Phe	Gly	His	Asp	Gly	Glu
3065						3070					3075			
Lys	Gly	Arg	Leu	Val	Val	Asp	Gly	Leu	Arg	Ala	Arg	Glu	Gly	Ser
3080						3085					3090			
Leu	Pro	Gly	Asn	Ser	Thr	Ile	Ser	Ile	Arg	Ala	Pro	Val	Tyr	Leu
3095						3100					3105			
Gly	Ser	Pro	Pro	Ser	Gly	Lys	Pro	Lys	Ser	Leu	Pro	Thr	Asn	Ser
3110						3115					3120			
Phe	Val	Gly	Cys	Leu	Lys	Asn	Phe	Gln	Leu	Asp	Ser	Lys	Pro	Leu
3125						3130					3135			
Tyr	Thr	Pro	Ser	Ser	Ser	Phe	Gly	Val	Ser	Ser	Cys	Leu	Gly	Gly
3140						3145					3150			
Pro	Leu	Glu	Lys	Gly	Ile	Tyr	Phe	Ser	Glu	Glu	Gly	Gly	His	Val
3155						3160					3165			
Val	Leu	Ala	His	Ser	Val	Leu	Leu	Gly	Pro	Glu	Phe	Lys	Leu	Val
3170						3175					3180			
Phe	Ser	Ile	Arg	Pro	Arg	Ser	Leu	Thr	Gly	Ile	Leu	Ile	His	Ile
3185						3190					3195			
Gly	Ser	Gln	Pro	Gly	Lys	His	Leu	Cys	Val	Tyr	Leu	Glu	Ala	Gly
3200						3205					3210			
Lys	Val	Thr	Ala	Ser	Met	Asp	Ser	Gly	Ala	Gly	Gly	Thr	Ser	Thr
3215						3220					3225			
Ser	Val	Thr	Pro	Lys	Gln	Ser	Leu	Cys	Asp	Gly	Gln	Trp	His	Ser
3230						3235					3240			
Val	Ala	Val	Thr	Ile	Lys	Gln	His	Ile	Leu	His	Leu	Glu	Leu	Asp
3245						3250					3255			
Thr	Asp	Ser	Ser	Tyr	Thr	Ala	Gly	Gln	Ile	Pro	Phe	Pro	Pro	Ala
3260						3265					3270			
Ser	Thr	Gln	Glu	Pro	Leu	His	Leu	Gly	Gly	Ala	Pro	Ala	Asn	Leu
3275						3280					3285			
Thr	Thr	Leu	Arg	Ile	Pro	Val	Trp	Lys	Ser	Phe	Phe	Gly	Cys	Leu
3290						3295					3300			
Arg	Asn	Ile	His	Val	Asn	His	Ile	Pro	Val	Pro	Val	Thr	Glu	Ala
3305						3310					3315			
Leu	Glu	Val	Gln	Gly	Pro	Val	Ser	Leu	Asn	Gly	Cys	Pro	Asp	Gln
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<210> SEQ ID NO 29
<211> LENGTH: 1724
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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

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Ala Asp Lys Arg Glu Ser Gln Leu Leu Leu Asn Arg Ile Arg Thr Trp
385 390 395 400

Gln Lys Thr His Gln Gly Glu Asn Asn Gly Leu Ala Asn Ser Ile Arg
405 410 415

Asp Ser Leu Asn Glu Tyr Glu Ala Lys Leu Ser Asp Leu Arg Ala Arg
420 425 430

Leu Gln Glu Ala Ala Ala Gln Ala Lys Gln Ala Asn Gly Leu Asn Gln
435 440 445

Glu Asn Glu Arg Ala Leu Gly Ala Ile Gln Arg Gln Val Lys Glu Ile
450 455 460

Asn Ser Leu Gln Ser Asp Phe Thr Lys Tyr Leu Thr Thr Ala Asp Ser
465 470 475 480

Ser Leu Leu Gln Thr Asn Ile Ala Leu Gln Leu Met Glu Lys Ser Gln
485 490 495

Lys Glu Tyr Glu Lys Leu Ala Ala Ser Leu Asn Glu Ala Arg Gln Glu
500 505 510

Leu Ser Asp Lys Val Arg Glu Leu Ser Arg Ser Ala Gly Lys Thr Ser
515 520 525

Leu Val Glu Glu Ala Glu Lys His Ala Arg Ser Leu Gln Glu Leu Ala
530 535 540

Lys Gln Leu Glu Glu Ile Lys Arg Asn Ala Ser Gly Asp Glu Leu Val
545 550 555 560

Arg Cys Ala Val Asp Ala Ala Thr Ala Tyr Glu Asn Ile Leu Asn Ala
565 570 575

Ile Lys Ala Ala Glu Asp Ala Ala Asn Arg Ala Ala Ser Ala Ser Glu
580 585 590

Ser Ala Leu Gln Thr Val Ile Lys Glu Asp Leu Pro Arg Lys Ala Lys
595 600 605

Thr Leu Ser Ser Asn Ser Asp Lys Leu Leu Asn Glu Ala Lys Met Thr
610 615 620

Gln Lys Lys Leu Lys Gln Glu Val Ser Pro Ala Leu Asn Asn Leu Gln
625 630 635 640

Gln Thr Leu Asn Ile Val Thr Val Gln Lys Glu Val Ile Asp Thr Asn
645 650 655

Leu Thr Thr Leu Arg Asp Gly Leu His Gly Ile Gln Arg Gly Asp Ile
660 665 670

Asp Ala Met Ile Ser Ser Ala Lys Ser Met Val Arg Lys Ala Asn Asp
675 680 685

Ile Thr Asp Glu Val Leu Asp Gly Leu Asn Pro Ile Gln Thr Asp Val
690 695 700

Glu Arg Ile Lys Asp Thr Tyr Gly Arg Thr Gln Asn Glu Asp Phe Lys
705 710 715 720

Lys Ala Leu Thr Asp Ala Asp Asn Ser Val Asn Lys Leu Thr Asn Lys
725 730 735

Leu Pro Asp Leu Trp Arg Lys Ile Glu Ser Ile Asn Gln Gln Leu Leu
740 745 750

Pro Leu Gly Asn Ile Ser Asp Asn Met Asp Arg Ile Arg Glu Leu Ile
755 760 765

Gln Gln Ala Arg Asp Ala Ala Ser Lys Val Ala Val Pro Met Arg Phe
770 775 780

Asn Gly Lys Ser Gly Val Glu Val Arg Leu Pro Asn Asp Leu Glu Asp
785 790 795 800

Leu Lys Gly Tyr Thr Ser Leu Ser Leu Phe Leu Gln Arg Pro Asn Ser

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805					810					815					
Arg	Glu	Asn	Gly	Gly	Thr	Glu	Asn	Met	Phe	Val	Met	Tyr	Leu	Gly	Asn
			820					825					830		
Lys	Asp	Ala	Ser	Arg	Asp	Tyr	Ile	Gly	Met	Ala	Val	Val	Asp	Gly	Gln
		835					840						845		
Leu	Thr	Cys	Val	Tyr	Asn	Leu	Gly	Asp	Arg	Glu	Ala	Glu	Leu	Gln	Val
	850					855						860			
Asp	Gln	Ile	Leu	Thr	Lys	Ser	Glu	Thr	Lys	Glu	Ala	Val	Met	Asp	Arg
865					870					875					880
Val	Lys	Phe	Gln	Arg	Ile	Tyr	Gln	Phe	Ala	Arg	Leu	Asn	Tyr	Thr	Lys
				885					890						895
Gly	Ala	Thr	Ser	Ser	Lys	Pro	Glu	Thr	Pro	Gly	Val	Tyr	Asp	Met	Asp
			900						905					910	
Gly	Arg	Asn	Ser	Asn	Thr	Leu	Leu	Asn	Leu	Asp	Pro	Glu	Asn	Val	Val
		915						920						925	
Phe	Tyr	Val	Gly	Gly	Tyr	Pro	Pro	Asp	Phe	Lys	Leu	Pro	Ser	Arg	Leu
	930					935						940			
Ser	Phe	Pro	Pro	Tyr	Lys	Gly	Cys	Ile	Glu	Leu	Asp	Asp	Leu	Asn	Glu
945					950					955					960
Asn	Val	Leu	Ser	Leu	Tyr	Asn	Phe	Lys	Lys	Thr	Phe	Asn	Leu	Asn	Thr
			965						970						975
Thr	Glu	Val	Glu	Pro	Cys	Arg	Arg	Arg	Lys	Glu	Glu	Ser	Asp	Lys	Asn
			980						985					990	
Tyr	Phe	Glu	Gly	Thr	Gly	Tyr	Ala	Arg	Val	Pro	Thr	Gln	Pro	His	Ala
		995					1000						1005		
Pro	Ile	Pro	Thr	Phe	Gly	Gln	Thr	Ile	Gln	Thr	Thr	Val	Asp	Arg	
	1010					1015						1020			
Gly	Leu	Leu	Phe	Phe	Ala	Glu	Asn	Gly	Asp	Arg	Phe	Ile	Ser	Leu	
	1025					1030						1035			
Asn	Ile	Glu	Asp	Gly	Lys	Leu	Met	Val	Arg	Tyr	Lys	Leu	Asn	Ser	
	1040					1045						1050			
Glu	Leu	Pro	Lys	Glu	Arg	Gly	Val	Gly	Asp	Ala	Ile	Asn	Asn	Gly	
	1055					1060						1065			
Arg	Asp	His	Ser	Ile	Gln	Ile	Lys	Ile	Gly	Lys	Leu	Gln	Lys	Arg	
	1070					1075						1080			
Met	Trp	Ile	Asn	Val	Asp	Val	Gln	Asn	Thr	Ile	Ile	Asp	Gly	Glu	
	1085					1090						1095			
Val	Phe	Asp	Phe	Ser	Thr	Tyr	Tyr	Leu	Gly	Gly	Ile	Pro	Ile	Ala	
	1100					1105						1110			
Ile	Arg	Glu	Arg	Phe	Asn	Ile	Ser	Thr	Pro	Ala	Phe	Arg	Gly	Cys	
	1115					1120						1125			
Met	Lys	Asn	Leu	Lys	Lys	Thr	Ser	Gly	Val	Val	Arg	Leu	Asn	Asp	
	1130					1135						1140			
Thr	Val	Gly	Val	Thr	Lys	Lys	Cys	Ser	Glu	Asp	Trp	Lys	Leu	Val	
	1145					1150						1155			
Arg	Ser	Ala	Ser	Phe	Ser	Arg	Gly	Gly	Gln	Leu	Ser	Phe	Thr	Asp	
	1160					1165						1170			
Leu	Gly	Leu	Pro	Pro	Thr	Asp	His	Leu	Gln	Ala	Ser	Phe	Gly	Phe	
	1175					1180						1185			
Gln	Thr	Phe	Gln	Pro	Ser	Gly	Ile	Leu	Leu	Asp	His	Gln	Thr	Trp	
	1190					1195						1200			
Thr	Arg	Asn	Leu	Gln	Val	Thr	Leu	Glu	Asp	Gly	Tyr	Ile	Glu	Leu	
	1205					1210						1215			

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Ser	Thr	Ser	Asp	Ser	Gly	Gly	Pro	Ile	Phe	Lys	Ser	Pro	Gln	Thr
1220						1225					1230			
Tyr	Met	Asp	Gly	Leu	Leu	His	Tyr	Val	Ser	Val	Ile	Ser	Asp	Asn
1235						1240					1245			
Ser	Gly	Leu	Arg	Leu	Leu	Ile	Asp	Asp	Gln	Leu	Leu	Arg	Asn	Ser
1250						1255					1260			
Lys	Arg	Leu	Lys	His	Ile	Ser	Ser	Ser	Arg	Gln	Ser	Leu	Arg	Leu
1265						1270					1275			
Gly	Gly	Ser	Asn	Phe	Glu	Gly	Cys	Ile	Ser	Asn	Val	Phe	Val	Gln
1280						1285					1290			
Arg	Leu	Ser	Leu	Ser	Pro	Glu	Val	Leu	Asp	Leu	Thr	Ser	Asn	Ser
1295						1300					1305			
Leu	Lys	Arg	Asp	Val	Ser	Leu	Gly	Gly	Cys	Ser	Leu	Asn	Lys	Pro
1310						1315					1320			
Pro	Phe	Leu	Met	Leu	Leu	Lys	Gly	Ser	Thr	Arg	Phe	Asn	Lys	Thr
1325						1330					1335			
Lys	Thr	Phe	Arg	Ile	Asn	Gln	Leu	Leu	Gln	Asp	Thr	Pro	Val	Ala
1340						1345					1350			
Ser	Pro	Arg	Ser	Val	Lys	Val	Trp	Gln	Asp	Ala	Cys	Ser	Pro	Leu
1355						1360					1365			
Pro	Lys	Thr	Gln	Ala	Asn	His	Gly	Ala	Leu	Gln	Phe	Gly	Asp	Ile
1370						1375					1380			
Pro	Thr	Ser	His	Leu	Leu	Phe	Lys	Leu	Pro	Gln	Glu	Leu	Leu	Lys
1385						1390					1395			
Pro	Arg	Ser	Gln	Phe	Ala	Val	Asp	Met	Gln	Thr	Thr	Ser	Ser	Arg
1400						1405					1410			
Gly	Leu	Val	Phe	His	Thr	Gly	Thr	Lys	Asn	Ser	Phe	Met	Ala	Leu
1415						1420					1425			
Tyr	Leu	Ser	Lys	Gly	Arg	Leu	Val	Phe	Ala	Leu	Gly	Thr	Asp	Gly
1430						1435					1440			
Lys	Lys	Leu	Arg	Ile	Lys	Ser	Lys	Glu	Lys	Cys	Asn	Asp	Gly	Lys
1445						1450					1455			
Trp	His	Thr	Val	Val	Phe	Gly	His	Asp	Gly	Glu	Lys	Gly	Arg	Leu
1460						1465					1470			
Val	Val	Asp	Gly	Leu	Arg	Ala	Arg	Glu	Gly	Ser	Leu	Pro	Gly	Asn
1475						1480					1485			
Ser	Thr	Ile	Ser	Ile	Arg	Ala	Pro	Val	Tyr	Leu	Gly	Ser	Pro	Pro
1490						1495					1500			
Ser	Gly	Lys	Pro	Lys	Ser	Leu	Pro	Thr	Asn	Ser	Phe	Val	Gly	Cys
1505						1510					1515			
Leu	Lys	Asn	Phe	Gln	Leu	Asp	Ser	Lys	Pro	Leu	Tyr	Thr	Pro	Ser
1520						1525					1530			
Ser	Ser	Phe	Gly	Val	Ser	Ser	Cys	Leu	Gly	Gly	Pro	Leu	Glu	Lys
1535						1540					1545			
Gly	Ile	Tyr	Phe	Ser	Glu	Glu	Gly	Gly	His	Val	Val	Leu	Ala	His
1550						1555					1560			
Ser	Val	Leu	Leu	Gly	Pro	Glu	Phe	Lys	Leu	Val	Phe	Ser	Ile	Arg
1565						1570					1575			
Pro	Arg	Ser	Leu	Thr	Gly	Ile	Leu	Ile	His	Ile	Gly	Ser	Gln	Pro
1580						1585					1590			
Gly	Lys	His	Leu	Cys	Val	Tyr	Leu	Glu	Ala	Gly	Lys	Val	Thr	Ala
1595						1600					1605			

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Ser Met Asp Ser Gly Ala Gly Gly Thr Ser Thr Ser Val Thr Pro
 1610 1615 1620

Lys Gln Ser Leu Cys Asp Gly Gln Trp His Ser Val Ala Val Thr
 1625 1630 1635

Ile Lys Gln His Ile Leu His Leu Glu Leu Asp Thr Asp Ser Ser
 1640 1645 1650

Tyr Thr Ala Gly Gln Ile Pro Phe Pro Pro Ala Ser Thr Gln Glu
 1655 1660 1665

Pro Leu His Leu Gly Gly Ala Pro Ala Asn Leu Thr Thr Leu Arg
 1670 1675 1680

Ile Pro Val Trp Lys Ser Phe Phe Gly Cys Leu Arg Asn Ile His
 1685 1690 1695

Val Asn His Ile Pro Val Pro Val Thr Glu Ala Leu Glu Val Gln
 1700 1705 1710

Gly Pro Val Ser Leu Asn Gly Cys Pro Asp Gln
 1715 1720

<210> SEQ ID NO 30
 <211> LENGTH: 3277
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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 1 5 10 15

Pro Pro Thr Pro Leu Leu Leu Leu Val Leu Arg Val Leu Pro Ala Cys
 20 25 30

Gly Ala Thr Ala Arg Asp Pro Gly Ala Ala Ala Gly Leu Ser Leu His
 35 40 45

Pro Thr Tyr Phe Asn Leu Ala Glu Ala Ala Arg Ile Trp Ala Thr Ala
 50 55 60

Thr Cys Gly Glu Arg Gly Pro Gly Glu Gly Arg Pro Gln Pro Glu Leu
 65 70 75 80

Tyr Cys Lys Leu Val Gly Gly Pro Thr Ala Pro Gly Ser Gly His Thr
 85 90 95

Ile Gln Gly Gln Phe Cys Asp Tyr Cys Asn Ser Glu Asp Pro Arg Lys
 100 105 110

Ala His Pro Val Thr Asn Ala Ile Asp Gly Ser Glu Arg Trp Trp Gln
 115 120 125

Ser Pro Pro Leu Ser Ser Gly Thr Gln Tyr Asn Arg Val Asn Leu Thr
 130 135 140

Leu Asp Leu Gly Gln Leu Phe His Val Ala Tyr Ile Leu Ile Lys Phe
 145 150 155 160

Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg Ser Val Asp
 165 170 175

Phe Gly Ser Thr Tyr Ser Pro Trp Gln Tyr Phe Ala His Ser Lys Val
 180 185 190

Asp Cys Leu Lys Glu Phe Gly Arg Glu Ala Asn Met Ala Val Thr Arg
 195 200 205

Asp Asp Asp Val Leu Cys Val Thr Glu Tyr Ser Arg Ile Val Pro Leu
 210 215 220

Glu Asn Gly Glu Val Val Val Ser Leu Ile Asn Gly Arg Pro Gly Ala
 225 230 235 240

Lys Asn Phe Thr Phe Ser His Thr Leu Arg Glu Phe Thr Lys Ala Thr
 245 250 255

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Leu Glu Lys Ser Asn Tyr Phe Gly Cys Gln Gly Cys Gln Cys Asp Ile
 675 680 685
 Gly Gly Ala Leu Ser Ser Met Cys Ser Gly Pro Ser Gly Val Cys Gln
 690 695 700
 Cys Arg Glu His Val Val Gly Lys Val Cys Gln Arg Pro Glu Asn Asn
 705 710 715 720
 Tyr Tyr Phe Pro Asp Leu His His Met Lys Tyr Glu Ile Glu Asp Gly
 725 730 735
 Ser Thr Pro Asn Gly Arg Asp Leu Arg Phe Gly Phe Asp Pro Leu Ala
 740 745 750
 Phe Pro Glu Phe Ser Trp Arg Gly Tyr Ala Gln Met Thr Ser Val Gln
 755 760 765
 Asn Asp Val Arg Ile Thr Leu Asn Val Gly Lys Ser Ser Gly Ser Leu
 770 775 780
 Phe Arg Val Ile Leu Arg Tyr Val Asn Pro Gly Thr Glu Ala Val Ser
 785 790 795 800
 Gly His Ile Thr Ile Tyr Pro Ser Trp Gly Ala Ala Gln Ser Lys Glu
 805 810 815
 Ile Ile Phe Leu Pro Ser Lys Glu Pro Ala Phe Val Thr Val Pro Gly
 820 825 830
 Asn Gly Phe Ala Asp Pro Phe Ser Ile Thr Pro Gly Ile Trp Val Ala
 835 840 845
 Cys Ile Lys Ala Glu Gly Val Leu Leu Asp Tyr Leu Val Leu Leu Pro
 850 855 860
 Arg Asp Tyr Tyr Glu Ala Ser Val Leu Gln Leu Pro Val Thr Glu Pro
 865 870 875 880
 Cys Ala Tyr Ala Gly Pro Pro Gln Glu Asn Cys Leu Leu Tyr Gln His
 885 890 895
 Leu Pro Val Thr Arg Phe Pro Cys Thr Leu Ala Cys Glu Ala Arg His
 900 905 910
 Phe Leu Leu Asp Gly Glu Pro Arg Pro Val Ala Val Arg Gln Pro Thr
 915 920 925
 Pro Ala His Pro Val Met Val Asp Leu Ser Gly Arg Glu Val Glu Leu
 930 935 940
 His Leu Arg Leu Arg Ile Pro Gln Val Gly His Tyr Val Val Val Val
 945 950 955 960
 Glu Tyr Ser Thr Glu Ala Ala Gln Leu Phe Val Val Asp Val Asn Val
 965 970 975
 Lys Ser Ser Gly Ser Val Leu Ala Gly Gln Val Asn Ile Tyr Ser Cys
 980 985 990
 Asn Tyr Ser Val Leu Cys Arg Ser Ala Val Ile Asp His Met Ser Arg
 995 1000 1005
 Ile Ala Met Tyr Glu Leu Leu Ala Asp Ala Asp Ile Gln Leu Lys
 1010 1015 1020
 Gly His Met Ala Arg Phe Leu Leu His Gln Val Cys Ile Ile Pro
 1025 1030 1035
 Ile Glu Glu Phe Ser Ala Glu Tyr Val Arg Pro Gln Val His Cys
 1040 1045 1050
 Ile Ala Ser Tyr Gly Arg Phe Val Asn Gln Ser Ala Thr Cys Val
 1055 1060 1065
 Ser Leu Ala His Glu Thr Pro Pro Thr Ala Leu Ile Leu Asp Val
 1070 1075 1080
 Leu Ser Gly Arg Pro Phe Pro His Leu Pro Gln Gln Ser Ser Pro

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1085	1090	1095
Ser Val Asp Val Leu Pro Gly Val Thr Leu Lys Ala Pro Gln Asn 1100 1105 1110		
Gln Val Thr Leu Arg Gly Arg Val Pro His Leu Gly Arg Tyr Val 1115 1120 1125		
Phe Val Ile His Phe Tyr Gln Ala Ala His Pro Thr Phe Pro Ala 1130 1135 1140		
Gln Val Ser Val Asp Gly Gly Trp Pro Arg Ala Gly Ser Phe His 1145 1150 1155		
Ala Ser Phe Cys Pro His Val Leu Gly Cys Arg Asp Gln Val Ile 1160 1165 1170		
Ala Glu Gly Gln Ile Glu Phe Asp Ile Ser Glu Pro Glu Val Ala 1175 1180 1185		
Ala Thr Val Lys Val Pro Glu Gly Lys Ser Leu Val Leu Val Arg 1190 1195 1200		
Val Leu Val Val Pro Ala Glu Asn Tyr Asp Tyr Gln Ile Leu His 1205 1210 1215		
Lys Lys Ser Met Asp Lys Ser Leu Glu Phe Ile Thr Asn Cys Gly 1220 1225 1230		
Lys Asn Ser Phe Tyr Leu Asp Pro Gln Thr Ala Ser Arg Phe Cys 1235 1240 1245		
Lys Asn Ser Ala Arg Ser Leu Val Ala Phe Tyr His Lys Gly Ala 1250 1255 1260		
Leu Pro Cys Glu Cys His Pro Thr Gly Ala Thr Gly Pro His Cys 1265 1270 1275		
Ser Pro Glu Gly Gly Gln Cys Pro Cys Gln Pro Asn Val Ile Gly 1280 1285 1290		
Arg Gln Cys Thr Arg Cys Ala Thr Gly His Tyr Gly Phe Pro Arg 1295 1300 1305		
Cys Lys Pro Cys Ser Cys Gly Arg Arg Leu Cys Glu Glu Met Thr 1310 1315 1320		
Gly Gln Cys Arg Cys Pro Pro Arg Thr Val Arg Pro Gln Cys Glu 1325 1330 1335		
Val Cys Glu Thr His Ser Phe Ser Phe His Pro Met Ala Gly Cys 1340 1345 1350		
Glu Gly Cys Asn Cys Ser Arg Arg Gly Thr Ile Glu Ala Ala Met 1355 1360 1365		
Pro Glu Cys Asp Arg Asp Ser Gly Gln Cys Arg Cys Lys Pro Arg 1370 1375 1380		
Ile Thr Gly Arg Gln Cys Asp Arg Cys Ala Ser Gly Phe Tyr Arg 1385 1390 1395		
Phe Pro Glu Cys Val Pro Cys Asn Cys Asn Arg Asp Gly Thr Glu 1400 1405 1410		
Pro Gly Val Cys Asp Pro Gly Thr Gly Ala Cys Leu Cys Lys Glu 1415 1420 1425		
Asn Val Glu Gly Thr Glu Cys Asn Val Cys Arg Glu Gly Ser Phe 1430 1435 1440		
His Leu Asp Pro Ala Asn Leu Lys Gly Cys Thr Ser Cys Phe Cys 1445 1450 1455		
Phe Gly Val Asn Asn Gln Cys His Ser Ser His Lys Arg Arg Thr 1460 1465 1470		
Lys Phe Val Asp Met Leu Gly Trp His Leu Glu Thr Ala Asp Arg 1475 1480 1485		

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Val	Asp	Ile	Pro	Val	Ser	Phe	Asn	Pro	Gly	Ser	Asn	Ser	Met	Val
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Ala	Asp	Leu	Gln	Glu	Leu	Pro	Ala	Thr	Ile	His	Ser	Ala	Ser	Trp
1505						1510					1515			
Val	Ala	Pro	Thr	Ser	Tyr	Leu	Gly	Asp	Lys	Val	Ser	Ser	Tyr	Gly
1520						1525					1530			
Gly	Tyr	Leu	Thr	Tyr	Gln	Ala	Lys	Ser	Phe	Gly	Leu	Pro	Gly	Asp
1535						1540					1545			
Met	Val	Leu	Leu	Glu	Lys	Lys	Pro	Asp	Val	Gln	Leu	Thr	Gly	Gln
1550						1555					1560			
His	Met	Ser	Ile	Ile	Tyr	Glu	Glu	Thr	Asn	Thr	Pro	Arg	Pro	Asp
1565						1570					1575			
Arg	Leu	His	His	Gly	Arg	Val	His	Val	Val	Glu	Gly	Asn	Phe	Arg
1580						1585					1590			
His	Ala	Ser	Ser	Arg	Ala	Pro	Val	Ser	Arg	Glu	Glu	Leu	Met	Thr
1595						1600					1605			
Val	Leu	Ser	Arg	Leu	Ala	Asp	Val	Arg	Ile	Gln	Gly	Leu	Tyr	Phe
1610						1615					1620			
Thr	Glu	Thr	Gln	Arg	Leu	Thr	Leu	Ser	Glu	Val	Gly	Leu	Glu	Glu
1625						1630					1635			
Ala	Ser	Asp	Thr	Gly	Ser	Gly	Arg	Ile	Ala	Leu	Ala	Val	Glu	Ile
1640						1645					1650			
Cys	Ala	Cys	Pro	Pro	Ala	Tyr	Ala	Gly	Asp	Ser	Cys	Gln	Gly	Cys
1655						1660					1665			
Ser	Pro	Gly	Tyr	Tyr	Arg	Asp	His	Lys	Gly	Leu	Tyr	Thr	Gly	Arg
1670						1675					1680			
Cys	Val	Pro	Cys	Asn	Cys	Asn	Gly	His	Ser	Asn	Gln	Cys	Gln	Asp
1685						1690					1695			
Gly	Ser	Gly	Ile	Cys	Val	Asn	Cys	Gln	His	Asn	Thr	Ala	Gly	Glu
1700						1705					1710			
His	Cys	Glu	Arg	Cys	Gln	Glu	Gly	Tyr	Tyr	Gly	Asn	Ala	Val	His
1715						1720					1725			
Gly	Ser	Cys	Arg	Ala	Cys	Pro	Cys	Pro	His	Thr	Asn	Ser	Phe	Ala
1730						1735					1740			
Thr	Gly	Cys	Val	Val	Asn	Gly	Gly	Asp	Val	Arg	Cys	Ser	Cys	Lys
1745						1750					1755			
Ala	Gly	Tyr	Thr	Gly	Thr	Gln	Cys	Glu	Arg	Cys	Ala	Pro	Gly	Tyr
1760						1765					1770			
Phe	Gly	Asn	Pro	Gln	Lys	Phe	Gly	Gly	Ser	Cys	Gln	Pro	Cys	Ser
1775						1780					1785			
Cys	Asn	Ser	Asn	Gly	Gln	Leu	Gly	Ser	Cys	His	Pro	Leu	Thr	Gly
1790						1795					1800			
Asp	Cys	Ile	Asn	Gln	Glu	Pro	Lys	Asp	Ser	Ser	Pro	Ala	Glu	Glu
1805						1810					1815			
Cys	Asp	Asp	Cys	Asp	Ser	Cys	Val	Met	Thr	Leu	Leu	Asn	Asp	Leu
1820						1825					1830			
Ala	Thr	Met	Gly	Glu	Gln	Leu	Arg	Leu	Val	Lys	Ser	Gln	Leu	Gln
1835						1840					1845			
Gly	Leu	Ser	Ala	Ser	Ala	Gly	Leu	Leu	Glu	Gln	Met	Arg	His	Met
1850						1855					1860			
Glu	Thr	Gln	Ala	Lys	Asp	Leu	Arg	Asn	Gln	Leu	Leu	Asn	Tyr	Arg
1865						1870					1875			

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Ser	Ala	Ile	Ser	Asn	His	Gly	Ser	Lys	Ile	Glu	Gly	Leu	Glu	Arg
1880						1885					1890			
Glu	Leu	Thr	Asp	Leu	Asn	Gln	Glu	Phe	Glu	Thr	Leu	Gln	Glu	Lys
1895						1900					1905			
Ala	Gln	Val	Asn	Ser	Arg	Lys	Ala	Gln	Thr	Leu	Asn	Asn	Asn	Val
1910						1915					1920			
Asn	Arg	Ala	Thr	Gln	Ser	Ala	Lys	Glu	Leu	Asp	Val	Lys	Ile	Lys
1925						1930					1935			
Asn	Val	Ile	Arg	Asn	Val	His	Met	Leu	Asn	Arg	Ile	Arg	Thr	Trp
1940						1945					1950			
Gln	Lys	Thr	His	Gln	Gly	Glu	Asn	Asn	Gly	Leu	Ala	Asn	Ser	Ile
1955						1960					1965			
Arg	Asp	Ser	Leu	Asn	Glu	Tyr	Glu	Ala	Lys	Leu	Ser	Asp	Leu	Arg
1970						1975					1980			
Ala	Arg	Leu	Gln	Glu	Ala	Ala	Ala	Gln	Ala	Lys	Gln	Ala	Asn	Gly
1985						1990					1995			
Leu	Asn	Gln	Glu	Asn	Glu	Arg	Ala	Leu	Gly	Ala	Ile	Gln	Arg	Gln
2000						2005					2010			
Val	Lys	Glu	Ile	Asn	Ser	Leu	Gln	Ser	Asp	Phe	Thr	Lys	Tyr	Leu
2015						2020					2025			
Thr	Thr	Ala	Asp	Ser	Ser	Leu	Leu	Gln	Thr	Asn	Ile	Ala	Leu	Gln
2030						2035					2040			
Leu	Met	Glu	Lys	Ser	Gln	Lys	Glu	Tyr	Glu	Lys	Leu	Ala	Ala	Ser
2045						2050					2055			
Leu	Asn	Glu	Ala	Arg	Gln	Glu	Leu	Ser	Asp	Lys	Val	Arg	Glu	Leu
2060						2065					2070			
Ser	Arg	Ser	Ala	Gly	Lys	Thr	Ser	Leu	Val	Glu	Glu	Ala	Glu	Lys
2075						2080					2085			
His	Ala	Arg	Ser	Leu	Gln	Glu	Leu	Ala	Lys	Gln	Leu	Glu	Glu	Ile
2090						2095					2100			
Lys	Arg	Asn	Ala	Ser	Gly	Asp	Glu	Leu	Val	Arg	Cys	Ala	Val	Asp
2105						2110					2115			
Ala	Ala	Thr	Ala	Tyr	Glu	Asn	Ile	Leu	Asn	Ala	Ile	Lys	Ala	Ala
2120						2125					2130			
Glu	Asp	Ala	Ala	Asn	Arg	Ala	Ala	Ser	Ala	Ser	Glu	Ser	Ala	Leu
2135						2140					2145			
Gln	Thr	Val	Ile	Lys	Glu	Asp	Leu	Pro	Arg	Lys	Ala	Lys	Thr	Leu
2150						2155					2160			
Ser	Ser	Asn	Ser	Asp	Lys	Leu	Leu	Asn	Glu	Ala	Lys	Met	Thr	Gln
2165						2170					2175			
Lys	Lys	Leu	Lys	Gln	Glu	Val	Ser	Pro	Ala	Leu	Asn	Asn	Leu	Gln
2180						2185					2190			
Gln	Thr	Leu	Asn	Ile	Val	Thr	Val	Gln	Lys	Glu	Val	Ile	Asp	Thr
2195						2200					2205			
Asn	Leu	Thr	Thr	Leu	Arg	Asp	Gly	Leu	His	Gly	Ile	Gln	Arg	Gly
2210						2215					2220			
Asp	Ile	Asp	Ala	Met	Ile	Ser	Ser	Ala	Lys	Ser	Met	Val	Arg	Lys
2225						2230					2235			
Ala	Asn	Asp	Ile	Thr	Asp	Glu	Val	Leu	Asp	Gly	Leu	Asn	Pro	Ile
2240						2245					2250			
Gln	Thr	Asp	Val	Glu	Arg	Ile	Lys	Asp	Thr	Tyr	Gly	Arg	Thr	Gln
2255						2260					2265			
Asn	Glu	Asp	Phe	Lys	Lys	Ala	Leu	Thr	Asp	Ala	Asp	Asn	Ser	Val

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2270	2275	2280
Asn Lys Leu Thr Asn Lys Leu	Pro Asp Leu Trp Arg	Lys Ile Glu
2285	2290	2295
Ser Ile Asn Gln Gln Leu Leu	Pro Leu Gly Asn Ile	Ser Asp Asn
2300	2305	2310
Met Asp Arg Ile Arg Glu Leu	Ile Gln Gln Ala Arg	Asp Ala Ala
2315	2320	2325
Ser Lys Val Ala Val Pro Met	Arg Phe Asn Gly Lys	Ser Gly Val
2330	2335	2340
Glu Val Arg Leu Pro Asn Asp	Leu Glu Asp Leu Lys	Gly Tyr Thr
2345	2350	2355
Ser Leu Ser Leu Phe Leu Gln	Arg Pro Asn Ser Arg	Glu Asn Gly
2360	2365	2370
Gly Thr Glu Asn Met Phe Val	Met Tyr Leu Gly Asn	Lys Asp Ala
2375	2380	2385
Ser Arg Asp Tyr Ile Gly Met	Ala Val Val Asp Gly	Gln Leu Thr
2390	2395	2400
Cys Val Tyr Asn Leu Gly Asp	Arg Glu Ala Glu Leu	Gln Val Asp
2405	2410	2415
Gln Ile Leu Thr Lys Ser Glu	Thr Lys Glu Ala Val	Met Asp Arg
2420	2425	2430
Val Lys Phe Gln Arg Ile Tyr	Gln Phe Ala Arg Leu	Asn Tyr Thr
2435	2440	2445
Lys Gly Ala Thr Ser Ser Lys	Pro Glu Thr Pro Gly	Val Tyr Asp
2450	2455	2460
Met Asp Gly Arg Asn Ser Asn	Thr Leu Leu Asn Leu	Asp Pro Glu
2465	2470	2475
Asn Val Val Phe Tyr Val Gly	Gly Tyr Pro Pro Asp	Phe Lys Leu
2480	2485	2490
Pro Ser Arg Leu Ser Phe Pro	Pro Tyr Lys Gly Cys	Ile Glu Leu
2495	2500	2505
Asp Asp Leu Asn Glu Asn Val	Leu Ser Leu Tyr Asn	Phe Lys Lys
2510	2515	2520
Thr Phe Asn Leu Asn Thr Thr	Glu Val Glu Pro Cys	Arg Arg Arg
2525	2530	2535
Lys Glu Glu Ser Asp Lys Asn	Tyr Phe Glu Gly Thr	Gly Tyr Ala
2540	2545	2550
Arg Val Pro Thr Gln Pro His	Ala Pro Ile Pro Thr	Phe Gly Gln
2555	2560	2565
Thr Ile Gln Thr Thr Val Asp	Arg Gly Leu Leu Phe	Phe Ala Glu
2570	2575	2580
Asn Gly Asp Arg Phe Ile Ser	Leu Asn Ile Glu Asp	Gly Lys Leu
2585	2590	2595
Met Val Arg Tyr Lys Leu Asn	Ser Glu Leu Pro Lys	Glu Arg Gly
2600	2605	2610
Val Gly Asp Ala Ile Asn Asn	Gly Arg Asp His Ser	Ile Gln Ile
2615	2620	2625
Lys Ile Gly Lys Leu Gln Lys	Arg Met Trp Ile Asn	Val Asp Val
2630	2635	2640
Gln Asn Thr Ile Ile Asp Gly	Glu Val Phe Asp Phe	Ser Thr Tyr
2645	2650	2655
Tyr Leu Gly Gly Ile Pro Ile	Ala Ile Arg Glu Arg	Phe Asn Ile
2660	2665	2670

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Ser	Thr	Pro	Ala	Phe	Arg	Gly	Cys	Met	Lys	Asn	Leu	Lys	Lys	Thr
2675						2680					2685			
Ser	Gly	Val	Val	Arg	Leu	Asn	Asp	Thr	Val	Gly	Val	Thr	Lys	Lys
2690						2695					2700			
Cys	Ser	Glu	Asp	Trp	Lys	Leu	Val	Arg	Ser	Ala	Ser	Phe	Ser	Arg
2705						2710					2715			
Gly	Gly	Gln	Leu	Ser	Phe	Thr	Asp	Leu	Gly	Leu	Pro	Pro	Thr	Asp
2720						2725					2730			
His	Leu	Gln	Ala	Ser	Phe	Gly	Phe	Gln	Thr	Phe	Gln	Pro	Ser	Gly
2735						2740					2745			
Ile	Leu	Leu	Asp	His	Gln	Thr	Trp	Thr	Arg	Asn	Leu	Gln	Val	Thr
2750						2755					2760			
Leu	Glu	Asp	Gly	Tyr	Ile	Glu	Leu	Ser	Thr	Ser	Asp	Ser	Gly	Gly
2765						2770					2775			
Pro	Ile	Phe	Lys	Ser	Pro	Gln	Thr	Tyr	Met	Asp	Gly	Leu	Leu	His
2780						2785					2790			
Tyr	Val	Ser	Val	Ile	Ser	Asp	Asn	Ser	Gly	Leu	Arg	Leu	Leu	Ile
2795						2800					2805			
Asp	Asp	Gln	Leu	Leu	Arg	Asn	Ser	Lys	Arg	Leu	Lys	His	Ile	Ser
2810						2815					2820			
Ser	Ser	Arg	Gln	Ser	Leu	Arg	Leu	Gly	Gly	Ser	Asn	Phe	Glu	Gly
2825						2830					2835			
Cys	Ile	Ser	Asn	Val	Phe	Val	Gln	Arg	Leu	Ser	Leu	Ser	Pro	Glu
2840						2845					2850			
Val	Leu	Asp	Leu	Thr	Ser	Asn	Ser	Leu	Lys	Arg	Asp	Val	Ser	Leu
2855						2860					2865			
Gly	Gly	Cys	Ser	Leu	Asn	Lys	Pro	Pro	Phe	Leu	Met	Leu	Leu	Lys
2870						2875					2880			
Gly	Ser	Thr	Arg	Phe	Asn	Lys	Thr	Lys	Thr	Phe	Arg	Ile	Asn	Gln
2885						2890					2895			
Leu	Leu	Gln	Asp	Thr	Pro	Val	Ala	Ser	Pro	Arg	Ser	Val	Lys	Val
2900						2905					2910			
Trp	Gln	Asp	Ala	Cys	Ser	Pro	Leu	Pro	Lys	Thr	Gln	Ala	Asn	His
2915						2920					2925			
Gly	Ala	Leu	Gln	Phe	Gly	Asp	Ile	Pro	Thr	Ser	His	Leu	Leu	Phe
2930						2935					2940			
Lys	Leu	Pro	Gln	Glu	Leu	Leu	Lys	Pro	Arg	Ser	Gln	Phe	Ala	Val
2945						2950					2955			
Asp	Met	Gln	Thr	Thr	Ser	Ser	Arg	Gly	Leu	Val	Phe	His	Thr	Gly
2960						2965					2970			
Thr	Lys	Asn	Ser	Phe	Met	Ala	Leu	Tyr	Leu	Ser	Lys	Gly	Arg	Leu
2975						2980					2985			
Val	Phe	Ala	Leu	Gly	Thr	Asp	Gly	Lys	Lys	Leu	Arg	Ile	Lys	Ser
2990						2995					3000			
Lys	Glu	Lys	Cys	Asn	Asp	Gly	Lys	Trp	His	Thr	Val	Val	Phe	Gly
3005						3010					3015			
His	Asp	Gly	Glu	Lys	Gly	Arg	Leu	Val	Val	Asp	Gly	Leu	Arg	Ala
3020						3025					3030			
Arg	Glu	Gly	Ser	Leu	Pro	Gly	Asn	Ser	Thr	Ile	Ser	Ile	Arg	Ala
3035						3040					3045			
Pro	Val	Tyr	Leu	Gly	Ser	Pro	Pro	Ser	Gly	Lys	Pro	Lys	Ser	Leu
3050						3055					3060			

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Pro Thr Asn Ser Phe Val Gly Cys Leu Lys Asn Phe Gln Leu Asp
 3065 3070 3075

Ser Lys Pro Leu Tyr Thr Pro Ser Ser Ser Phe Gly Val Ser Ser
 3080 3085 3090

Cys Leu Gly Gly Pro Leu Glu Lys Gly Ile Tyr Phe Ser Glu Glu
 3095 3100 3105

Gly Gly His Val Val Leu Ala His Ser Val Leu Leu Gly Pro Glu
 3110 3115 3120

Phe Lys Leu Val Phe Ser Ile Arg Pro Arg Ser Leu Thr Gly Ile
 3125 3130 3135

Leu Ile His Ile Gly Ser Gln Pro Gly Lys His Leu Cys Val Tyr
 3140 3145 3150

Leu Glu Ala Gly Lys Val Thr Ala Ser Met Asp Ser Gly Ala Gly
 3155 3160 3165

Gly Thr Ser Thr Ser Val Thr Pro Lys Gln Ser Leu Cys Asp Gly
 3170 3175 3180

Gln Trp His Ser Val Ala Val Thr Ile Lys Gln His Ile Leu His
 3185 3190 3195

Leu Glu Leu Asp Thr Asp Ser Ser Tyr Thr Ala Gly Gln Ile Pro
 3200 3205 3210

Phe Pro Pro Ala Ser Thr Gln Glu Pro Leu His Leu Gly Gly Ala
 3215 3220 3225

Pro Ala Asn Leu Thr Thr Leu Arg Ile Pro Val Trp Lys Ser Phe
 3230 3235 3240

Phe Gly Cys Leu Arg Asn Ile His Val Asn His Ile Pro Val Pro
 3245 3250 3255

Val Thr Glu Ala Leu Glu Val Gln Gly Pro Val Ser Leu Asn Gly
 3260 3265 3270

Cys Pro Asp Gln
 3275

<210> SEQ ID NO 31
 <211> LENGTH: 1668
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Met Pro Pro Ala Val Arg Arg Ser Ala Cys Ser Met Gly Trp Leu Trp
 1 5 10 15

Ile Phe Gly Ala Ala Leu Gly Gln Cys Leu Gly Tyr Ser Ser Gln Gln
 20 25 30

Gln Arg Val Pro Phe Leu Gln Pro Pro Gly Gln Ser Gln Leu Gln Ala
 35 40 45

Ser Tyr Val Glu Phe Arg Pro Ser Gln Gly Cys Ser Pro Gly Tyr Tyr
 50 55 60

Arg Asp His Lys Gly Leu Tyr Thr Gly Arg Cys Val Pro Cys Asn Cys
 65 70 75 80

Asn Gly His Ser Asn Gln Cys Gln Asp Gly Ser Gly Ile Cys Val Asn
 85 90 95

Cys Gln His Asn Thr Ala Gly Glu His Cys Glu Arg Cys Gln Glu Gly
 100 105 110

Tyr Tyr Gly Asn Ala Val His Gly Ser Cys Arg Ala Cys Pro Cys Pro
 115 120 125

His Thr Asn Ser Phe Ala Thr Gly Cys Val Val Asn Gly Gly Asp Val
 130 135 140

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Arg Cys Ser Cys Lys Ala Gly Tyr Thr Gly Thr Gln Cys Glu Arg Cys
 145 150 155 160

Ala Pro Gly Tyr Phe Gly Asn Pro Gln Lys Phe Gly Gly Ser Cys Gln
 165 170 175

Pro Cys Ser Cys Asn Ser Asn Gly Gln Leu Gly Ser Cys His Pro Leu
 180 185 190

Thr Gly Asp Cys Ile Asn Gln Glu Pro Lys Asp Ser Ser Pro Ala Glu
 195 200 205

Glu Cys Asp Asp Cys Asp Ser Cys Val Met Thr Leu Leu Asn Asp Leu
 210 215 220

Ala Thr Met Gly Glu Gln Leu Arg Leu Val Lys Ser Gln Leu Gln Gly
 225 230 235 240

Leu Ser Ala Ser Ala Gly Leu Leu Glu Gln Met Arg His Met Glu Thr
 245 250 255

Gln Ala Lys Asp Leu Arg Asn Gln Leu Leu Asn Tyr Arg Ser Ala Ile
 260 265 270

Ser Asn His Gly Ser Lys Ile Glu Gly Leu Glu Arg Glu Leu Thr Asp
 275 280 285

Leu Asn Gln Glu Phe Glu Thr Leu Gln Glu Lys Ala Gln Val Asn Ser
 290 295 300

Arg Lys Ala Gln Thr Leu Asn Asn Asn Val Asn Arg Ala Thr Gln Ser
 305 310 315 320

Ala Lys Glu Leu Asp Val Lys Ile Lys Asn Val Ile Arg Asn Val His
 325 330 335

Met Leu Asn Arg Ile Arg Thr Trp Gln Lys Thr His Gln Gly Glu Asn
 340 345 350

Asn Gly Leu Ala Asn Ser Ile Arg Asp Ser Leu Asn Glu Tyr Glu Ala
 355 360 365

Lys Leu Ser Asp Leu Arg Ala Arg Leu Gln Glu Ala Ala Ala Gln Ala
 370 375 380

Lys Gln Ala Asn Gly Leu Asn Gln Glu Asn Glu Arg Ala Leu Gly Ala
 385 390 395 400

Ile Gln Arg Gln Val Lys Glu Ile Asn Ser Leu Gln Ser Asp Phe Thr
 405 410 415

Lys Tyr Leu Thr Thr Ala Asp Ser Ser Leu Leu Gln Thr Asn Ile Ala
 420 425 430

Leu Gln Leu Met Glu Lys Ser Gln Lys Glu Tyr Glu Lys Leu Ala Ala
 435 440 445

Ser Leu Asn Glu Ala Arg Gln Glu Leu Ser Asp Lys Val Arg Glu Leu
 450 455 460

Ser Arg Ser Ala Gly Lys Thr Ser Leu Val Glu Glu Ala Glu Lys His
 465 470 475 480

Ala Arg Ser Leu Gln Glu Leu Ala Lys Gln Leu Glu Glu Ile Lys Arg
 485 490 495

Asn Ala Ser Gly Asp Glu Leu Val Arg Cys Ala Val Asp Ala Ala Thr
 500 505 510

Ala Tyr Glu Asn Ile Leu Asn Ala Ile Lys Ala Ala Glu Asp Ala Ala
 515 520 525

Asn Arg Ala Ala Ser Ala Ser Glu Ser Ala Leu Gln Thr Val Ile Lys
 530 535 540

Glu Asp Leu Pro Arg Lys Ala Lys Thr Leu Ser Ser Asn Ser Asp Lys
 545 550 555 560

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Leu Leu Asn Glu Ala Lys Met Thr Gln Lys Lys Leu Lys Gln Glu Val
 565 570 575

Ser Pro Ala Leu Asn Asn Leu Gln Gln Thr Leu Asn Ile Val Thr Val
 580 585 590

Gln Lys Glu Val Ile Asp Thr Asn Leu Thr Thr Leu Arg Asp Gly Leu
 595 600 605

His Gly Ile Gln Arg Gly Asp Ile Asp Ala Met Ile Ser Ser Ala Lys
 610 615 620

Ser Met Val Arg Lys Ala Asn Asp Ile Thr Asp Glu Val Leu Asp Gly
 625 630 635 640

Leu Asn Pro Ile Gln Thr Asp Val Glu Arg Ile Lys Asp Thr Tyr Gly
 645 650 655

Arg Thr Gln Asn Glu Asp Phe Lys Lys Ala Leu Thr Asp Ala Asp Asn
 660 665 670

Ser Val Asn Lys Leu Thr Asn Lys Leu Pro Asp Leu Trp Arg Lys Ile
 675 680 685

Glu Ser Ile Asn Gln Gln Leu Leu Pro Leu Gly Asn Ile Ser Asp Asn
 690 695 700

Met Asp Arg Ile Arg Glu Leu Ile Gln Gln Ala Arg Asp Ala Ala Ser
 705 710 715 720

Lys Val Ala Val Pro Met Arg Phe Asn Gly Lys Ser Gly Val Glu Val
 725 730 735

Arg Leu Pro Asn Asp Leu Glu Asp Leu Lys Gly Tyr Thr Ser Leu Ser
 740 745 750

Leu Phe Leu Gln Arg Pro Asn Ser Arg Glu Asn Gly Gly Thr Glu Asn
 755 760 765

Met Phe Val Met Tyr Leu Gly Asn Lys Asp Ala Ser Arg Asp Tyr Ile
 770 775 780

Gly Met Ala Val Val Asp Gly Gln Leu Thr Cys Val Tyr Asn Leu Gly
 785 790 795 800

Asp Arg Glu Ala Glu Leu Gln Val Asp Gln Ile Leu Thr Lys Ser Glu
 805 810 815

Thr Lys Glu Ala Val Met Asp Arg Val Lys Phe Gln Arg Ile Tyr Gln
 820 825 830

Phe Ala Arg Leu Asn Tyr Thr Lys Gly Ala Thr Ser Ser Lys Pro Glu
 835 840 845

Thr Pro Gly Val Tyr Asp Met Asp Gly Arg Asn Ser Asn Thr Leu Leu
 850 855 860

Asn Leu Asp Pro Glu Asn Val Val Phe Tyr Val Gly Gly Tyr Pro Pro
 865 870 875 880

Asp Phe Lys Leu Pro Ser Arg Leu Ser Phe Pro Pro Tyr Lys Gly Cys
 885 890 895

Ile Glu Leu Asp Asp Leu Asn Glu Asn Val Leu Ser Leu Tyr Asn Phe
 900 905 910

Lys Lys Thr Phe Asn Leu Asn Thr Thr Glu Val Glu Pro Cys Arg Arg
 915 920 925

Arg Lys Glu Glu Ser Asp Lys Asn Tyr Phe Glu Gly Thr Gly Tyr Ala
 930 935 940

Arg Val Pro Thr Gln Pro His Ala Pro Ile Pro Thr Phe Gly Gln Thr
 945 950 955 960

Ile Gln Thr Thr Val Asp Arg Gly Leu Leu Phe Phe Ala Glu Asn Gly
 965 970 975

Asp Arg Phe Ile Ser Leu Asn Ile Glu Asp Gly Lys Leu Met Val Arg

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980			985			990									
Tyr	Lys	Leu	Asn	Ser	Glu	Leu	Pro	Lys	Glu	Arg	Gly	Val	Gly	Asp	Ala
		995					1000					1005			
Ile	Asn	Asn	Gly	Arg	Asp	His	Ser	Ile	Gln	Ile	Lys	Ile	Gly	Lys	
	1010					1015					1020				
Leu	Gln	Lys	Arg	Met	Trp	Ile	Asn	Val	Asp	Val	Gln	Asn	Thr	Ile	
	1025					1030					1035				
Ile	Asp	Gly	Glu	Val	Phe	Asp	Phe	Ser	Thr	Tyr	Tyr	Leu	Gly	Gly	
	1040					1045					1050				
Ile	Pro	Ile	Ala	Ile	Arg	Glu	Arg	Phe	Asn	Ile	Ser	Thr	Pro	Ala	
	1055					1060					1065				
Phe	Arg	Gly	Cys	Met	Lys	Asn	Leu	Lys	Lys	Thr	Ser	Gly	Val	Val	
	1070					1075					1080				
Arg	Leu	Asn	Asp	Thr	Val	Gly	Val	Thr	Lys	Lys	Cys	Ser	Glu	Asp	
	1085					1090					1095				
Trp	Lys	Leu	Val	Arg	Ser	Ala	Ser	Phe	Ser	Arg	Gly	Gly	Gln	Leu	
	1100					1105					1110				
Ser	Phe	Thr	Asp	Leu	Gly	Leu	Pro	Pro	Thr	Asp	His	Leu	Gln	Ala	
	1115					1120					1125				
Ser	Phe	Gly	Phe	Gln	Thr	Phe	Gln	Pro	Ser	Gly	Ile	Leu	Leu	Asp	
	1130					1135					1140				
His	Gln	Thr	Trp	Thr	Arg	Asn	Leu	Gln	Val	Thr	Leu	Glu	Asp	Gly	
	1145					1150					1155				
Tyr	Ile	Glu	Leu	Ser	Thr	Ser	Asp	Ser	Gly	Gly	Pro	Ile	Phe	Lys	
	1160					1165					1170				
Ser	Pro	Gln	Thr	Tyr	Met	Asp	Gly	Leu	Leu	His	Tyr	Val	Ser	Val	
	1175					1180					1185				
Ile	Ser	Asp	Asn	Ser	Gly	Leu	Arg	Leu	Leu	Ile	Asp	Asp	Gln	Leu	
	1190					1195					1200				
Leu	Arg	Asn	Ser	Lys	Arg	Leu	Lys	His	Ile	Ser	Ser	Ser	Arg	Gln	
	1205					1210					1215				
Ser	Leu	Arg	Leu	Gly	Gly	Ser	Asn	Phe	Glu	Gly	Cys	Ile	Ser	Asn	
	1220					1225					1230				
Val	Phe	Val	Gln	Arg	Leu	Ser	Leu	Ser	Pro	Glu	Val	Leu	Asp	Leu	
	1235					1240					1245				
Thr	Ser	Asn	Ser	Leu	Lys	Arg	Asp	Val	Ser	Leu	Gly	Gly	Cys	Ser	
	1250					1255					1260				
Leu	Asn	Lys	Pro	Pro	Phe	Leu	Met	Leu	Leu	Lys	Gly	Ser	Thr	Arg	
	1265					1270					1275				
Phe	Asn	Lys	Thr	Lys	Thr	Phe	Arg	Ile	Asn	Gln	Leu	Leu	Gln	Asp	
	1280					1285					1290				
Thr	Pro	Val	Ala	Ser	Pro	Arg	Ser	Val	Lys	Val	Trp	Gln	Asp	Ala	
	1295					1300					1305				
Cys	Ser	Pro	Leu	Pro	Lys	Thr	Gln	Ala	Asn	His	Gly	Ala	Leu	Gln	
	1310					1315					1320				
Phe	Gly	Asp	Ile	Pro	Thr	Ser	His	Leu	Leu	Phe	Lys	Leu	Pro	Gln	
	1325					1330					1335				
Glu	Leu	Leu	Lys	Pro	Arg	Ser	Gln	Phe	Ala	Val	Asp	Met	Gln	Thr	
	1340					1345					1350				
Thr	Ser	Ser	Arg	Gly	Leu	Val	Phe	His	Thr	Gly	Thr	Lys	Asn	Ser	
	1355					1360					1365				
Phe	Met	Ala	Leu	Tyr	Leu	Ser	Lys	Gly	Arg	Leu	Val	Phe	Ala	Leu	
	1370					1375					1380				

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Gly Thr Asp Gly Lys Lys Leu Arg Ile Lys Ser Lys Glu Lys Cys
 1385 1390 1395

Asn Asp Gly Lys Trp His Thr Val Val Phe Gly His Asp Gly Glu
 1400 1405 1410

Lys Gly Arg Leu Val Val Asp Gly Leu Arg Ala Arg Glu Gly Ser
 1415 1420 1425

Leu Pro Gly Asn Ser Thr Ile Ser Ile Arg Ala Pro Val Tyr Leu
 1430 1435 1440

Gly Ser Pro Pro Ser Gly Lys Pro Lys Ser Leu Pro Thr Asn Ser
 1445 1450 1455

Phe Val Gly Cys Leu Lys Asn Phe Gln Leu Asp Ser Lys Pro Leu
 1460 1465 1470

Tyr Thr Pro Ser Ser Ser Phe Gly Val Ser Ser Cys Leu Gly Gly
 1475 1480 1485

Pro Leu Glu Lys Gly Ile Tyr Phe Ser Glu Glu Gly Gly His Val
 1490 1495 1500

Val Leu Ala His Ser Val Leu Leu Gly Pro Glu Phe Lys Leu Val
 1505 1510 1515

Phe Ser Ile Arg Pro Arg Ser Leu Thr Gly Ile Leu Ile His Ile
 1520 1525 1530

Gly Ser Gln Pro Gly Lys His Leu Cys Val Tyr Leu Glu Ala Gly
 1535 1540 1545

Lys Val Thr Ala Ser Met Asp Ser Gly Ala Gly Gly Thr Ser Thr
 1550 1555 1560

Ser Val Thr Pro Lys Gln Ser Leu Cys Asp Gly Gln Trp His Ser
 1565 1570 1575

Val Ala Val Thr Ile Lys Gln His Ile Leu His Leu Glu Leu Asp
 1580 1585 1590

Thr Asp Ser Ser Tyr Thr Ala Gly Gln Ile Pro Phe Pro Pro Ala
 1595 1600 1605

Ser Thr Gln Glu Pro Leu His Leu Gly Gly Ala Pro Ala Asn Leu
 1610 1615 1620

Thr Thr Leu Arg Ile Pro Val Trp Lys Ser Phe Phe Gly Cys Leu
 1625 1630 1635

Arg Asn Ile His Val Asn His Ile Pro Val Pro Val Thr Glu Ala
 1640 1645 1650

Leu Glu Val Gln Gly Pro Val Ser Leu Asn Gly Cys Pro Asp Gln
 1655 1660 1665

<210> SEQ ID NO 32
 <211> LENGTH: 488
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Met Ala Ala Ala Ala Arg Pro Arg Gly Arg Ala Leu Gly Pro Val Leu
 1 5 10 15

Pro Pro Thr Pro Leu Leu Leu Leu Val Leu Arg Val Leu Pro Ala Cys
 20 25 30

Gly Ala Thr Ala Arg Asp Pro Gly Ala Ala Ala Gly Leu Ser Leu His
 35 40 45

Pro Thr Tyr Phe Asn Leu Ala Glu Ala Ala Arg Ile Trp Ala Thr Ala
 50 55 60

Thr Cys Gly Glu Arg Gly Pro Gly Glu Gly Arg Pro Gln Pro Glu Leu

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65	70	75	80
Tyr Cys Lys Leu Val Gly Gly Pro Thr Ala Pro Gly Ser Gly His Thr	85	90	95
Ile Gln Gly Gln Phe Cys Asp Tyr Cys Asn Ser Glu Asp Pro Arg Lys	100	105	110
Ala His Pro Val Thr Asn Ala Ile Asp Gly Ser Glu Arg Trp Trp Gln	115	120	125
Ser Pro Pro Leu Ser Ser Gly Thr Gln Tyr Asn Arg Val Asn Leu Thr	130	135	140
Leu Asp Leu Gly Gln Leu Phe His Val Ala Tyr Ile Leu Ile Lys Phe	145	150	155
Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg Ser Val Asp	165	170	175
Phe Gly Ser Thr Tyr Ser Pro Trp Gln Tyr Phe Ala His Ser Lys Val	180	185	190
Asp Cys Leu Lys Glu Phe Gly Arg Glu Ala Asn Met Ala Val Thr Arg	195	200	205
Asp Asp Asp Val Leu Cys Val Thr Glu Tyr Ser Arg Ile Val Pro Leu	210	215	220
Glu Asn Gly Glu Val Val Val Ser Leu Ile Asn Gly Arg Pro Gly Ala	225	230	235
Lys Asn Phe Thr Phe Ser His Thr Leu Arg Glu Phe Thr Lys Ala Thr	245	250	255
Asn Ile Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu Gly His Leu	260	265	270
Ile Ser Lys Ala Gln Arg Asp Pro Thr Val Thr Arg Arg Tyr Tyr Tyr	275	280	285
Ser Ile Lys Asp Ile Ser Ile Gly Gly Gln Cys Val Cys Asn Gly His	290	295	300
Ala Glu Val Cys Asn Ile Asn Asn Pro Glu Lys Leu Phe Arg Cys Glu	305	310	315
Cys Gln His His Thr Cys Gly Glu Thr Cys Asp Arg Cys Cys Thr Gly	325	330	335
Tyr Asn Gln Arg Arg Trp Arg Pro Ala Ala Trp Glu Gln Ser His Glu	340	345	350
Cys Glu Ala Cys Asn Cys His Gly His Ala Ser Asn Cys Tyr Tyr Asp	355	360	365
Pro Asp Val Glu Arg Gln Gln Ala Ser Leu Asn Thr Gln Gly Ile Tyr	370	375	380
Ala Gly Gly Gly Val Cys Ile Asn Cys Gln His Asn Thr Ala Gly Val	385	390	395
Asn Cys Glu Gln Cys Ala Lys Gly Tyr Tyr Arg Pro Tyr Gly Val Pro	405	410	415
Val Asp Ala Pro Asp Gly Cys Ile Arg Lys Phe His Phe Lys Leu Val	420	425	430
Tyr Leu Ser Leu Cys Val Leu Pro Gln Arg Ser His Gln Ala Asn Phe	435	440	445
Gly Ser Val Asn Asn Phe Leu His Ala Leu Ser Leu Gln Ser Ile Ser	450	455	460
Cys Ala Arg Tyr Val Thr Ser Val Thr Tyr Thr Val Ser Leu Asn Phe	465	470	475
Gly Phe Ile Ala Cys Lys Trp Lys	485		

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<210> SEQ ID NO 33
<211> LENGTH: 1823
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

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

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Gly	Phe	Gln	Phe	Gln	Lys	Lys	Asp	Phe	Asn	Leu	Leu	Glu	Gln	Thr
1205						1210						1215		
Glu	Thr	Leu	Gly	Val	Gly	Tyr	Gly	Cys	Pro	Glu	Asp	Ser	Leu	Ile
1220						1225						1230		
Ser	Arg	Arg	Ala	Tyr	Phe	Asn	Gly	Gln	Ser	Phe	Ile	Ala	Ser	Ile
1235						1240						1245		
Gln	Lys	Ile	Ser	Phe	Phe	Asp	Gly	Phe	Glu	Gly	Gly	Phe	Asn	Phe
1250						1255						1260		
Arg	Thr	Leu	Gln	Pro	Asn	Gly	Leu	Leu	Phe	Tyr	Tyr	Ala	Ser	Gly
1265						1270						1275		
Ser	Asp	Val	Phe	Ser	Ile	Ser	Leu	Asp	Asn	Gly	Thr	Val	Ile	Met
1280						1285						1290		
Asp	Val	Lys	Gly	Ile	Lys	Val	Gln	Ser	Val	Asp	Lys	Gln	Tyr	Asn
1295						1300						1305		
Asp	Gly	Leu	Ser	His	Phe	Val	Ile	Ser	Ser	Val	Ser	Pro	Thr	Arg
1310						1315						1320		
Tyr	Glu	Leu	Ile	Val	Asp	Lys	Ser	Arg	Val	Gly	Ser	Lys	Asn	Pro
1325						1330						1335		
Thr	Lys	Gly	Lys	Ile	Glu	Gln	Thr	Gln	Ala	Ser	Glu	Lys	Lys	Phe
1340						1345						1350		
Tyr	Phe	Gly	Gly	Ser	Pro	Ile	Ser	Ala	Gln	Tyr	Ala	Asn	Phe	Thr
1355						1360						1365		
Gly	Cys	Ile	Ser	Asn	Ala	Tyr	Phe	Thr	Arg	Val	Asp	Arg	Asp	Val
1370						1375						1380		
Glu	Val	Glu	Asp	Phe	Gln	Arg	Tyr	Thr	Glu	Lys	Val	His	Thr	Ser
1385						1390						1395		
Leu	Tyr	Glu	Cys	Pro	Ile	Glu	Ser	Ser	Pro	Leu	Phe	Leu	Leu	His
1400						1405						1410		
Lys	Lys	Gly	Lys	Asn	Leu	Ser	Lys	Pro	Lys	Ala	Ser	Gln	Asn	Lys
1415						1420						1425		
Lys	Gly	Gly	Lys	Ser	Lys	Asp	Ala	Pro	Ser	Trp	Asp	Pro	Val	Ala
1430						1435						1440		
Leu	Lys	Leu	Pro	Glu	Arg	Asn	Thr	Pro	Arg	Asn	Ser	His	Cys	His
1445						1450						1455		
Leu	Ser	Asn	Ser	Pro	Arg	Ala	Ile	Glu	His	Ala	Tyr	Gln	Tyr	Gly
1460						1465						1470		
Gly	Thr	Ala	Asn	Ser	Arg	Gln	Glu	Phe	Glu	His	Leu	Lys	Gly	Asp
1475						1480						1485		
Phe	Gly	Ala	Lys	Ser	Gln	Phe	Ser	Ile	Arg	Leu	Arg	Thr	Arg	Ser
1490						1495						1500		
Ser	His	Gly	Met	Ile	Phe	Tyr	Val	Ser	Asp	Gln	Glu	Glu	Asn	Asp
1505						1510						1515		
Phe	Met	Thr	Leu	Phe	Leu	Ala	His	Gly	Arg	Leu	Val	Tyr	Met	Phe
1520						1525						1530		
Asn	Val	Gly	His	Lys	Lys	Leu	Lys	Ile	Arg	Ser	Gln	Glu	Lys	Tyr
1535						1540						1545		
Asn	Asp	Gly	Leu	Trp	His	Asp	Val	Ile	Phe	Ile	Arg	Glu	Arg	Ser
1550						1555						1560		
Ser	Gly	Arg	Leu	Val	Ile	Asp	Gly	Leu	Arg	Val	Leu	Glu	Glu	Ser
1565						1570						1575		
Leu	Pro	Pro	Thr	Glu	Ala	Thr	Trp	Lys	Ile	Lys	Gly	Pro	Ile	Tyr
1580						1585						1590		
Leu	Gly	Gly	Val	Ala	Pro	Gly	Lys	Ala	Val	Lys	Asn	Val	Gln	Ile

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1595	1600	1605
Asn Ser Ile Tyr Ser Phe Ser Gly Cys Leu Ser Asn Leu Gln Leu 1610 1615 1620		
Asn Gly Ala Ser Ile Thr Ser Ala Ser Gln Thr Phe Ser Val Thr 1625 1630 1635		
Pro Cys Phe Glu Gly Pro Met Glu Thr Gly Thr Tyr Phe Ser Thr 1640 1645 1650		
Glu Gly Gly Tyr Val Val Leu Asp Glu Ser Phe Asn Ile Gly Leu 1655 1660 1665		
Lys Phe Glu Ile Ala Phe Glu Val Arg Pro Arg Ser Ser Ser Gly 1670 1675 1680		
Thr Leu Val His Gly His Ser Val Asn Gly Glu Tyr Leu Asn Val 1685 1690 1695		
His Met Lys Asn Gly Gln Val Ile Val Lys Val Asn Asn Gly Ile 1700 1705 1710		
Arg Asp Phe Ser Thr Ser Val Thr Pro Lys Gln Ser Leu Cys Asp 1715 1720 1725		
Gly Arg Trp His Arg Ile Thr Val Ile Arg Asp Ser Asn Val Val 1730 1735 1740		
Gln Leu Asp Val Asp Ser Glu Val Asn His Val Val Gly Pro Leu 1745 1750 1755		
Asn Pro Lys Pro Ile Asp His Arg Glu Pro Val Phe Val Gly Gly 1760 1765 1770		
Val Pro Glu Ser Leu Leu Thr Pro Arg Leu Ala Pro Ser Lys Pro 1775 1780 1785		
Phe Thr Gly Cys Ile Arg His Phe Val Ile Asp Gly His Pro Val 1790 1795 1800		
Ser Phe Ser Lys Ala Ala Leu Val Ser Gly Ala Val Ser Ile Asn 1805 1810 1815		
Ser Cys Pro Ala Ala 1820		

<210> SEQ ID NO 34
 <211> LENGTH: 1816
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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

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

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545		550		555		560
Ala Lys Ser Glu Leu Gln Val Lys Leu Ser Asn Leu Ser Asn Leu Ser		565		570		575
His Asp Leu Val Gln Glu Ala Ile Asp His Ala Gln Asp Leu Gln Gln		580		585		590
Glu Ala Asn Glu Leu Ser Arg Lys Leu His Ser Ser Asp Met Asn Gly		595		600		605
Leu Val Gln Lys Ala Leu Asp Ala Ser Asn Val Tyr Glu Asn Ile Val		610		615		620
Asn Tyr Val Ser Glu Ala Asn Glu Thr Ala Glu Phe Ala Leu Asn Thr		625		630		635
Thr Asp Arg Ile Tyr Asp Ala Val Ser Gly Ile Asp Thr Gln Ile Ile		645		650		655
Tyr His Lys Asp Glu Ser Glu Asn Leu Leu Asn Gln Ala Arg Glu Leu		660		665		670
Gln Ala Lys Ala Glu Ser Ser Ser Asp Glu Ala Val Ala Asp Thr Ser		675		680		685
Arg Arg Val Gly Gly Ala Leu Ala Arg Lys Ser Ala Leu Lys Thr Arg		690		695		700
Leu Ser Asp Ala Val Lys Gln Leu Gln Ala Ala Glu Arg Gly Asp Ala		705		710		715
Gln Gln Arg Leu Gly Gln Ser Arg Leu Ile Thr Glu Glu Ala Asn Arg		725		730		735
Thr Thr Met Glu Val Gln Gln Ala Thr Ala Pro Met Ala Asn Asn Leu		740		745		750
Thr Asn Trp Ser Gln Asn Leu Gln His Phe Asp Ser Ser Ala Tyr Asn		755		760		765
Thr Ala Val Asn Ser Ala Arg Asp Ala Val Arg Asn Leu Thr Glu Val		770		775		780
Val Pro Gln Leu Leu Asp Gln Leu Arg Thr Val Glu Gln Lys Arg Pro		785		790		795
Ala Ser Asn Val Ser Ala Ser Ile Gln Arg Ile Arg Glu Leu Ile Ala		805		810		815
Gln Thr Arg Ser Val Ala Ser Lys Ile Gln Val Ser Met Met Phe Asp		820		825		830
Gly Gln Ser Ala Val Glu Val His Ser Arg Thr Ser Met Asp Asp Leu		835		840		845
Lys Ala Phe Thr Ser Leu Ser Leu Tyr Met Lys Pro Pro Val Lys Arg		850		855		860
Pro Glu Leu Thr Glu Thr Ala Asp Gln Phe Ile Leu Tyr Leu Gly Ser		865		870		875
Lys Asn Ala Lys Lys Glu Tyr Met Gly Leu Ala Ile Lys Asn Asp Asn		885		890		895
Leu Val Tyr Val Tyr Asn Leu Gly Thr Lys Asp Val Glu Ile Pro Leu		900		905		910
Asp Ser Lys Pro Val Ser Ser Trp Pro Ala Tyr Phe Ser Ile Val Lys		915		920		925
Ile Glu Arg Val Gly Lys His Gly Lys Val Phe Leu Thr Val Pro Ser		930		935		940
Leu Ser Ser Thr Ala Glu Glu Lys Phe Ile Lys Lys Gly Glu Phe Ser		945		950		955
Gly Asp Asp Ser Leu Leu Asp Leu Asp Pro Glu Asp Thr Val Phe Tyr		965		970		975

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Val Gly Gly Val Pro Ser Asn Phe Lys Leu Pro Thr Ser Leu Asn Leu
 980 985 990

Pro Gly Phe Val Gly Cys Leu Glu Leu Ala Thr Leu Asn Asn Asp Val
 995 1000 1005

Ile Ser Leu Tyr Asn Phe Lys His Ile Tyr Asn Met Asp Pro Ser
 1010 1015 1020

Thr Ser Val Pro Cys Ala Arg Asp Lys Leu Ala Phe Thr Gln Ser
 1025 1030 1035

Arg Ala Ala Ser Tyr Phe Phe Asp Gly Ser Gly Tyr Ala Val Val
 1040 1045 1050

Arg Asp Ile Thr Arg Arg Gly Lys Phe Gly Gln Val Thr Arg Phe
 1055 1060 1065

Asp Ile Glu Val Arg Thr Pro Ala Asp Asn Gly Leu Ile Leu Leu
 1070 1075 1080

Met Val Asn Gly Ser Met Phe Phe Arg Leu Glu Met Arg Asn Gly
 1085 1090 1095

Tyr Leu His Val Phe Tyr Asp Phe Gly Phe Ser Gly Gly Pro Val
 1100 1105 1110

His Leu Glu Asp Thr Leu Lys Lys Ala Gln Ile Asn Asp Ala Lys
 1115 1120 1125

Tyr His Glu Ile Ser Ile Ile Tyr His Asn Asp Lys Lys Met Ile
 1130 1135 1140

Leu Val Val Asp Arg Arg His Val Lys Ser Met Asp Asn Glu Lys
 1145 1150 1155

Met Lys Ile Pro Phe Thr Asp Ile Tyr Ile Gly Gly Ala Pro Pro
 1160 1165 1170

Glu Ile Leu Gln Ser Arg Ala Leu Arg Ala His Leu Pro Leu Asp
 1175 1180 1185

Ile Asn Phe Arg Gly Cys Met Lys Gly Phe Gln Phe Gln Lys Lys
 1190 1195 1200

Asp Phe Asn Leu Leu Glu Gln Thr Glu Thr Leu Gly Val Gly Tyr
 1205 1210 1215

Gly Cys Pro Glu Asp Ser Leu Ile Ser Arg Arg Ala Tyr Phe Asn
 1220 1225 1230

Gly Gln Ser Phe Ile Ala Ser Ile Gln Lys Ile Ser Phe Phe Asp
 1235 1240 1245

Gly Phe Glu Gly Gly Phe Asn Phe Arg Thr Leu Gln Pro Asn Gly
 1250 1255 1260

Leu Leu Phe Tyr Tyr Ala Ser Gly Ser Asp Val Phe Ser Ile Ser
 1265 1270 1275

Leu Asp Asn Gly Thr Val Ile Met Asp Val Lys Gly Ile Lys Val
 1280 1285 1290

Gln Ser Val Asp Lys Gln Tyr Asn Asp Gly Leu Ser His Phe Val
 1295 1300 1305

Ile Ser Ser Val Ser Pro Thr Arg Tyr Glu Leu Ile Val Asp Lys
 1310 1315 1320

Ser Arg Val Gly Ser Lys Asn Pro Thr Lys Gly Lys Ile Glu Gln
 1325 1330 1335

Thr Gln Ala Ser Glu Lys Lys Phe Tyr Phe Gly Gly Ser Pro Ile
 1340 1345 1350

Ser Ala Gln Tyr Ala Asn Phe Thr Gly Cys Ile Ser Asn Ala Tyr
 1355 1360 1365

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Phe Thr	Arg Val Asp Arg Asp	Val Glu Val Glu Asp	Phe Gln Arg
1370	1375	1380	
Tyr Thr	Glu Lys Val His Thr	Ser Leu Tyr Glu Cys	Pro Ile Glu
1385	1390	1395	
Ser Ser	Pro Leu Phe Leu Leu	His Lys Lys Gly Lys	Asn Leu Ser
1400	1405	1410	
Lys Pro	Lys Ala Ser Gln Asn	Lys Lys Gly Gly Lys	Ser Lys Asp
1415	1420	1425	
Ala Pro	Ser Trp Asp Pro Val	Ala Leu Lys Leu Pro	Glu Arg Asn
1430	1435	1440	
Thr Pro	Arg Asn Ser His Cys	His Leu Ser Asn Ser	Pro Arg Ala
1445	1450	1455	
Ile Glu	His Ala Tyr Gln Tyr	Gly Gly Thr Ala Asn	Ser Arg Gln
1460	1465	1470	
Glu Phe	Glu His Leu Lys Gly	Asp Phe Gly Ala Lys	Ser Gln Phe
1475	1480	1485	
Ser Ile	Arg Leu Arg Thr Arg	Ser Ser His Gly Met	Ile Phe Tyr
1490	1495	1500	
Val Ser	Asp Gln Glu Glu Asn	Asp Phe Met Thr Leu	Phe Leu Ala
1505	1510	1515	
His Gly	Arg Leu Val Tyr Met	Phe Asn Val Gly His	Lys Lys Leu
1520	1525	1530	
Lys Ile	Arg Ser Gln Glu Lys	Tyr Asn Asp Gly Leu	Trp His Asp
1535	1540	1545	
Val Ile	Phe Ile Arg Glu Arg	Ser Ser Gly Arg Leu	Val Ile Asp
1550	1555	1560	
Gly Leu	Arg Val Leu Glu Glu	Ser Leu Pro Pro Thr	Glu Ala Thr
1565	1570	1575	
Trp Lys	Ile Lys Gly Pro Ile	Tyr Leu Gly Gly Val	Ala Pro Gly
1580	1585	1590	
Lys Ala	Val Lys Asn Val Gln	Ile Asn Ser Ile Tyr	Ser Phe Ser
1595	1600	1605	
Gly Cys	Leu Ser Asn Leu Gln	Leu Asn Gly Ala Ser	Ile Thr Ser
1610	1615	1620	
Ala Ser	Gln Thr Phe Ser Val	Thr Pro Cys Phe Glu	Gly Pro Met
1625	1630	1635	
Glu Thr	Gly Thr Tyr Phe Ser	Thr Glu Gly Gly Tyr	Val Val Leu
1640	1645	1650	
Asp Glu	Ser Phe Asn Ile Gly	Leu Lys Phe Glu Ile	Ala Phe Glu
1655	1660	1665	
Val Arg	Pro Arg Ser Ser Ser	Gly Thr Leu Val His	Gly His Ser
1670	1675	1680	
Val Asn	Gly Glu Tyr Leu Asn	Val His Met Lys Asn	Gly Gln Val
1685	1690	1695	
Ile Val	Lys Val Asn Asn Gly	Ile Arg Asp Phe Ser	Thr Ser Val
1700	1705	1710	
Thr Pro	Lys Gln Ser Leu Cys	Asp Gly Arg Trp His	Arg Ile Thr
1715	1720	1725	
Val Ile	Arg Asp Ser Asn Val	Val Gln Leu Asp Val	Asp Ser Glu
1730	1735	1740	
Val Asn	His Val Val Gly Pro	Leu Asn Pro Lys Pro	Ile Asp His
1745	1750	1755	
Arg Glu	Pro Val Phe Val Gly	Gly Val Pro Glu Ser	Leu Leu Thr

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1760	1765	1770
Pro Arg Leu Ala Pro Ser Lys	Pro Phe Thr Gly Cys	Ile Arg His
1775	1780	1785
Phe Val Ile Asp Gly His Pro	Val Ser Phe Ser Lys	Ala Ala Leu
1790	1795	1800
Val Ser Gly Ala Val Ser Ile	Asn Ser Cys Pro Ala	Ala
1805	1810	1815

<210> SEQ ID NO 35
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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

<210> SEQ ID NO 36
 <211> LENGTH: 3695
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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

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

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Gly Tyr Phe His Phe Pro Leu Cys Gln Leu Cys Gly Cys Ser Pro Ala
 580 585 590

Gly Thr Leu Pro Glu Gly Cys Asp Glu Ala Gly Arg Cys Leu Cys Gln
 595 600 605

Pro Glu Phe Ala Gly Pro His Cys Asp Arg Cys Arg Pro Gly Tyr His
 610 615 620

Gly Phe Pro Asn Cys Gln Ala Cys Thr Cys Asp Pro Arg Gly Ala Leu
 625 630 635 640

Asp Gln Leu Cys Gly Ala Gly Gly Leu Cys Arg Cys Arg Pro Gly Tyr
 645 650 655

Thr Gly Thr Ala Cys Gln Glu Cys Ser Pro Gly Phe His Gly Phe Pro
 660 665 670

Ser Cys Val Pro Cys His Cys Ser Ala Glu Gly Ser Leu His Ala Ala
 675 680 685

Cys Asp Pro Arg Ser Gly Gln Cys Ser Cys Arg Pro Arg Val Thr Gly
 690 695 700

Leu Arg Cys Asp Thr Cys Val Pro Gly Ala Tyr Asn Phe Pro Tyr Cys
 705 710 715 720

Glu Ala Gly Ser Cys His Pro Ala Gly Leu Ala Pro Val Asp Pro Ala
 725 730 735

Leu Pro Glu Ala Gln Val Pro Cys Met Cys Arg Ala His Val Glu Gly
 740 745 750

Pro Ser Cys Asp Arg Cys Lys Pro Gly Phe Trp Gly Leu Ser Pro Ser
 755 760 765

Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Leu Arg Gly Thr Leu
 770 775 780

Gly Gly Val Ala Glu Cys Gln Pro Gly Thr Gly Gln Cys Phe Cys Lys
 785 790 795 800

Pro His Val Cys Gly Gln Ala Cys Ala Ser Cys Lys Asp Gly Phe Phe
 805 810 815

Gly Leu Asp Gln Ala Asp Tyr Phe Gly Cys Arg Ser Cys Arg Cys Asp
 820 825 830

Ile Gly Gly Ala Leu Gly Gln Ser Cys Glu Pro Arg Thr Gly Val Cys
 835 840 845

Arg Cys Arg Pro Asn Thr Gln Gly Pro Thr Cys Ser Glu Pro Ala Arg
 850 855 860

Asp His Tyr Leu Pro Asp Leu His His Leu Arg Leu Glu Leu Glu
 865 870 875 880

Ala Ala Thr Pro Glu Gly His Ala Val Arg Phe Gly Phe Asn Pro Leu
 885 890 895

Glu Phe Glu Asn Phe Ser Trp Arg Gly Tyr Ala Gln Met Ala Pro Val
 900 905 910

Gln Pro Arg Ile Val Ala Arg Leu Asn Leu Thr Ser Pro Asp Leu Phe
 915 920 925

Trp Leu Val Phe Arg Tyr Val Asn Arg Gly Ala Met Ser Val Ser Gly
 930 935 940

Arg Val Ser Val Arg Glu Glu Gly Arg Ser Ala Thr Cys Ala Asn Cys
 945 950 955 960

Thr Ala Gln Ser Gln Pro Val Ala Phe Pro Pro Ser Thr Glu Pro Ala
 965 970 975

Phe Ile Thr Val Pro Gln Arg Gly Phe Gly Glu Pro Phe Val Leu Asn
 980 985 990

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Pro Gly Thr Trp Ala Leu Arg Val Glu Ala Glu Gly Val Leu Leu Asp	995	1000	1005
Tyr Val Val Leu Leu Pro Ser Ala Tyr Tyr Glu Ala Ala Leu Leu	1010	1015	1020
Gln Leu Arg Val Thr Glu Ala Cys Thr Tyr Arg Pro Ser Ala Gln	1025	1030	1035
Gln Ser Gly Asp Asn Cys Leu Leu Tyr Thr His Leu Pro Leu Asp	1040	1045	1050
Gly Phe Pro Ser Ala Ala Gly Leu Glu Ala Leu Cys Arg Gln Asp	1055	1060	1065
Asn Ser Leu Pro Arg Pro Cys Pro Thr Glu Gln Leu Ser Pro Ser	1070	1075	1080
His Pro Pro Leu Ile Thr Cys Thr Gly Ser Asp Val Asp Val Gln	1085	1090	1095
Leu Gln Val Ala Val Pro Gln Pro Gly Arg Tyr Ala Leu Val Val	1100	1105	1110
Glu Tyr Ala Asn Glu Asp Ala Arg Gln Glu Val Gly Val Ala Val	1115	1120	1125
His Thr Pro Gln Arg Ala Pro Gln Gln Gly Leu Leu Ser Leu His	1130	1135	1140
Pro Cys Leu Tyr Ser Thr Leu Cys Arg Gly Thr Ala Arg Asp Thr	1145	1150	1155
Gln Asp His Leu Ala Val Phe His Leu Asp Ser Glu Ala Ser Val	1160	1165	1170
Arg Leu Thr Ala Glu Gln Ala Arg Phe Phe Leu His Gly Val Thr	1175	1180	1185
Leu Val Pro Ile Glu Glu Phe Ser Pro Glu Phe Val Glu Pro Arg	1190	1195	1200
Val Ser Cys Ile Ser Ser His Gly Ala Phe Gly Pro Asn Ser Ala	1205	1210	1215
Ala Cys Leu Pro Ser Arg Phe Pro Lys Pro Pro Gln Pro Ile Ile	1220	1225	1230
Leu Arg Asp Cys Gln Val Ile Pro Leu Pro Pro Gly Leu Pro Leu	1235	1240	1245
Thr His Ala Gln Asp Leu Thr Pro Ala Met Ser Pro Ala Gly Pro	1250	1255	1260
Arg Pro Arg Pro Pro Thr Ala Val Asp Pro Asp Ala Glu Pro Thr	1265	1270	1275
Leu Leu Arg Glu Pro Gln Ala Thr Val Val Phe Thr Thr His Val	1280	1285	1290
Pro Thr Leu Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro	1295	1300	1305
Ala His Pro Thr Phe Pro Val Glu Val Leu Ile Asn Ala Gly Arg	1310	1315	1320
Val Trp Gln Gly His Ala Asn Ala Ser Phe Cys Pro His Gly Tyr	1325	1330	1335
Gly Cys Arg Thr Leu Val Val Cys Glu Gly Gln Ala Leu Leu Asp	1340	1345	1350
Val Thr His Ser Glu Leu Thr Val Thr Val Arg Val Pro Lys Gly	1355	1360	1365
Arg Trp Leu Trp Leu Asp Tyr Val Leu Val Val Pro Glu Asn Val	1370	1375	1380
Tyr Ser Phe Gly Tyr Leu Arg Glu Glu Pro Leu Asp Lys Ser Tyr			

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1385	1390	1395
Asp Phe Ile Ser His Cys Ala	Ala Gln Gly Tyr His Ile Ser Pro	
1400	1405	1410
Ser Ser Ser Ser Leu Phe Cys	Arg Asn Ala Ala Ala Ser Leu Ser	
1415	1420	1425
Leu Phe Tyr Asn Asn Gly Ala	Arg Pro Cys Gly Cys His Glu Val	
1430	1435	1440
Gly Ala Thr Gly Pro Thr Cys	Glu Pro Phe Gly Gly Gln Cys Pro	
1445	1450	1455
Cys His Ala His Val Ile Gly	Arg Asp Cys Ser Arg Cys Ala Thr	
1460	1465	1470
Gly Tyr Trp Gly Phe Pro Asn	Cys Arg Pro Cys Asp Cys Gly Ala	
1475	1480	1485
Arg Leu Cys Asp Glu Leu Thr	Gly Gln Cys Ile Cys Pro Pro Arg	
1490	1495	1500
Thr Ile Pro Pro Asp Cys Leu	Leu Cys Gln Pro Gln Thr Phe Gly	
1505	1510	1515
Cys His Pro Leu Val Gly Cys	Glu Glu Cys Asn Cys Ser Gly Pro	
1520	1525	1530
Gly Ile Gln Glu Leu Thr Asp	Pro Thr Cys Asp Thr Asp Ser Gly	
1535	1540	1545
Gln Cys Lys Cys Arg Pro Asn	Val Thr Gly Arg Arg Cys Asp Thr	
1550	1555	1560
Cys Ser Pro Gly Phe His Gly	Tyr Pro Arg Cys Arg Pro Cys Asp	
1565	1570	1575
Cys His Glu Ala Gly Thr Ala	Pro Gly Val Cys Asp Pro Leu Thr	
1580	1585	1590
Gly Gln Cys Tyr Cys Lys Glu	Asn Val Gln Gly Pro Lys Cys Asp	
1595	1600	1605
Gln Cys Ser Leu Gly Thr Phe	Ser Leu Asp Ala Ala Asn Pro Lys	
1610	1615	1620
Gly Cys Thr Arg Cys Phe Cys	Phe Gly Ala Thr Glu Arg Cys Arg	
1625	1630	1635
Ser Ser Ser Tyr Thr Arg Gln	Glu Phe Val Asp Met Glu Gly Trp	
1640	1645	1650
Val Leu Leu Ser Thr Asp Arg	Gln Val Val Pro His Glu Arg Gln	
1655	1660	1665
Pro Gly Thr Glu Met Leu Arg	Ala Asp Leu Arg His Val Pro Glu	
1670	1675	1680
Ala Val Pro Glu Ala Phe Pro	Glu Leu Tyr Trp Gln Ala Pro Pro	
1685	1690	1695
Ser Tyr Leu Gly Asp Arg Val	Ser Ser Tyr Gly Gly Thr Leu Arg	
1700	1705	1710
Tyr Glu Leu His Ser Glu Thr	Gln Arg Gly Asp Val Phe Val Pro	
1715	1720	1725
Met Glu Ser Arg Pro Asp Val	Val Leu Gln Gly Asn Gln Met Ser	
1730	1735	1740
Ile Thr Phe Leu Glu Pro Ala	Tyr Pro Thr Pro Gly His Val His	
1745	1750	1755
Arg Gly Gln Leu Gln Leu Val	Glu Gly Asn Phe Arg His Thr Glu	
1760	1765	1770
Thr Arg Asn Thr Val Ser Arg	Glu Glu Leu Met Met Val Leu Ala	
1775	1780	1785

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Ser	Leu	Glu	Gln	Leu	Gln	Ile	Arg	Ala	Leu	Phe	Ser	Gln	Ile	Ser
1790						1795					1800			
Ser	Ala	Val	Phe	Leu	Arg	Arg	Val	Ala	Leu	Glu	Val	Ala	Ser	Pro
1805						1810					1815			
Ala	Gly	Gln	Gly	Ala	Leu	Ala	Ser	Asn	Val	Glu	Leu	Cys	Leu	Cys
1820						1825					1830			
Pro	Ala	Ser	Tyr	Arg	Gly	Asp	Ser	Cys	Gln	Glu	Cys	Ala	Pro	Gly
1835						1840					1845			
Phe	Tyr	Arg	Asp	Val	Lys	Gly	Leu	Phe	Leu	Gly	Arg	Cys	Val	Pro
1850						1855					1860			
Cys	Gln	Cys	His	Gly	His	Ser	Asp	Arg	Cys	Leu	Pro	Gly	Ser	Gly
1865						1870					1875			
Val	Cys	Val	Asp	Cys	Gln	His	Asn	Thr	Glu	Gly	Ala	His	Cys	Glu
1880						1885					1890			
Arg	Cys	Gln	Ala	Gly	Phe	Val	Ser	Ser	Arg	Asp	Asp	Pro	Ser	Ala
1895						1900					1905			
Pro	Cys	Val	Ser	Cys	Pro	Cys	Pro	Leu	Ser	Val	Pro	Ser	Asn	Asn
1910						1915					1920			
Phe	Ala	Glu	Gly	Cys	Val	Leu	Arg	Gly	Gly	Arg	Thr	Gln	Cys	Leu
1925						1930					1935			
Cys	Lys	Pro	Gly	Tyr	Ala	Gly	Ala	Ser	Cys	Glu	Arg	Cys	Ala	Pro
1940						1945					1950			
Gly	Phe	Phe	Gly	Asn	Pro	Leu	Val	Leu	Gly	Ser	Ser	Cys	Gln	Pro
1955						1960					1965			
Cys	Asp	Cys	Ser	Gly	Asn	Gly	Asp	Pro	Asn	Leu	Leu	Phe	Ser	Asp
1970						1975					1980			
Cys	Asp	Pro	Leu	Thr	Gly	Ala	Cys	Arg	Gly	Cys	Leu	Arg	His	Thr
1985						1990					1995			
Thr	Gly	Pro	Arg	Cys	Glu	Ile	Cys	Ala	Pro	Gly	Phe	Tyr	Gly	Asn
2000						2005					2010			
Ala	Leu	Leu	Pro	Gly	Asn	Cys	Thr	Arg	Cys	Asp	Cys	Thr	Pro	Cys
2015						2020					2025			
Gly	Thr	Glu	Ala	Cys	Asp	Pro	His	Ser	Gly	His	Cys	Leu	Cys	Lys
2030						2035					2040			
Ala	Gly	Val	Thr	Gly	Arg	Arg	Cys	Asp	Arg	Cys	Gln	Glu	Gly	His
2045						2050					2055			
Phe	Gly	Phe	Asp	Gly	Cys	Gly	Gly	Cys	Arg	Pro	Cys	Ala	Cys	Gly
2060						2065					2070			
Pro	Ala	Ala	Glu	Gly	Ser	Glu	Cys	His	Pro	Gln	Ser	Gly	Gln	Cys
2075						2080					2085			
His	Cys	Arg	Pro	Gly	Thr	Met	Gly	Pro	Gln	Cys	Arg	Glu	Cys	Ala
2090						2095					2100			
Pro	Gly	Tyr	Trp	Gly	Leu	Pro	Glu	Gln	Gly	Cys	Arg	Arg	Cys	Gln
2105						2110					2115			
Cys	Pro	Gly	Gly	Arg	Cys	Asp	Pro	His	Thr	Gly	Arg	Cys	Asn	Cys
2120						2125					2130			
Pro	Pro	Gly	Leu	Ser	Gly	Glu	Arg	Cys	Asp	Thr	Cys	Ser	Gln	Gln
2135						2140					2145			
His	Gln	Val	Pro	Val	Pro	Gly	Gly	Pro	Val	Gly	His	Ser	Ile	His
2150						2155					2160			
Cys	Glu	Val	Cys	Asp	His	Cys	Val	Val	Leu	Leu	Leu	Asp	Asp	Leu
2165						2170					2175			

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Glu	Arg	Ala	Gly	Ala	Leu	Leu	Pro	Ala	Ile	His	Glu	Gln	Leu	Arg
2180						2185					2190			
Gly	Ile	Asn	Ala	Ser	Ser	Met	Ala	Trp	Ala	Arg	Leu	His	Arg	Leu
2195						2200					2205			
Asn	Ala	Ser	Ile	Ala	Asp	Leu	Gln	Ser	Gln	Leu	Arg	Ser	Pro	Leu
2210						2215					2220			
Gly	Pro	Arg	His	Glu	Thr	Ala	Gln	Gln	Leu	Glu	Val	Leu	Glu	Gln
2225						2230					2235			
Gln	Ser	Thr	Ser	Leu	Gly	Gln	Asp	Ala	Arg	Arg	Leu	Gly	Gly	Gln
2240						2245					2250			
Ala	Val	Gly	Thr	Arg	Asp	Gln	Ala	Ser	Gln	Leu	Leu	Ala	Gly	Thr
2255						2260					2265			
Glu	Ala	Thr	Leu	Gly	His	Ala	Lys	Thr	Leu	Leu	Ala	Ala	Ile	Arg
2270						2275					2280			
Ala	Val	Asp	Arg	Thr	Leu	Ser	Glu	Leu	Met	Ser	Gln	Thr	Gly	His
2285						2290					2295			
Leu	Gly	Leu	Ala	Asn	Ala	Ser	Ala	Pro	Ser	Gly	Glu	Gln	Leu	Leu
2300						2305					2310			
Arg	Thr	Leu	Ala	Glu	Val	Glu	Arg	Leu	Leu	Trp	Glu	Met	Arg	Ala
2315						2320					2325			
Arg	Asp	Leu	Gly	Ala	Pro	Gln	Ala	Ala	Ala	Glu	Ala	Glu	Leu	Ala
2330						2335					2340			
Ala	Ala	Gln	Arg	Leu	Leu	Ala	Arg	Val	Gln	Glu	Gln	Leu	Ser	Ser
2345						2350					2355			
Leu	Trp	Glu	Glu	Asn	Gln	Ala	Leu	Ala	Thr	Gln	Thr	Arg	Asp	Arg
2360						2365					2370			
Leu	Ala	Gln	His	Glu	Ala	Gly	Leu	Met	Asp	Leu	Arg	Glu	Ala	Leu
2375						2380					2385			
Asn	Arg	Ala	Val	Asp	Ala	Thr	Arg	Glu	Ala	Gln	Glu	Leu	Asn	Ser
2390						2395					2400			
Arg	Asn	Gln	Glu	Arg	Leu	Glu	Glu	Ala	Leu	Gln	Arg	Lys	Gln	Glu
2405						2410					2415			
Leu	Ser	Arg	Asp	Asn	Ala	Thr	Leu	Gln	Ala	Thr	Leu	His	Ala	Ala
2420						2425					2430			
Arg	Asp	Thr	Leu	Ala	Ser	Val	Phe	Arg	Leu	Leu	His	Ser	Leu	Asp
2435						2440					2445			
Gln	Ala	Lys	Glu	Glu	Leu	Glu	Arg	Leu	Ala	Ala	Ser	Leu	Asp	Gly
2450						2455					2460			
Ala	Arg	Thr	Pro	Leu	Leu	Gln	Arg	Met	Gln	Thr	Phe	Ser	Pro	Ala
2465						2470					2475			
Gly	Ser	Lys	Leu	Arg	Leu	Val	Glu	Ala	Ala	Glu	Ala	His	Ala	Gln
2480						2485					2490			
Gln	Leu	Gly	Gln	Leu	Ala	Leu	Asn	Leu	Ser	Ser	Ile	Ile	Leu	Asp
2495						2500					2505			
Val	Asn	Gln	Asp	Arg	Leu	Thr	Gln	Arg	Ala	Ile	Glu	Ala	Ser	Asn
2510						2515					2520			
Ala	Tyr	Ser	Arg	Ile	Leu	Gln	Ala	Val	Gln	Ala	Ala	Glu	Asp	Ala
2525						2530					2535			
Ala	Gly	Gln	Ala	Leu	Gln	Gln	Ala	Asp	His	Thr	Trp	Ala	Thr	Val
2540						2545					2550			
Val	Arg	Gln	Gly	Leu	Val	Asp	Arg	Ala	Gln	Gln	Leu	Leu	Ala	Asn
2555						2560					2565			
Ser	Thr	Ala	Leu	Glu	Glu	Ala	Met	Leu	Gln	Glu	Gln	Gln	Arg	Leu

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2570	2575	2580
Gly Leu Val Trp Ala Ala 2585	Leu Gln Gly Ala Arg 2590	Thr Gln Leu Arg 2595
Asp Val Arg Ala Lys Lys 2600	Asp Gln Leu Glu Ala 2605	His Ile Gln Ala 2610
Ala Gln Ala Met Leu Ala 2615	Met Asp Thr Asp 2620	Glu Thr Ser Lys Lys 2625
Ile Ala His Ala Lys Ala 2630	Val Ala Ala Glu Ala 2635	Gln Asp Thr Ala 2640
Thr Arg Val Gln Ser Gln 2645	Leu Gln Ala Met Gln 2650	Glu Asn Val Glu 2655
Arg Trp Gln Gly Gln Tyr 2660	Glu Gly Leu Arg Gly 2665	Gln Asp Leu Gly 2670
Gln Ala Val Leu Asp Ala 2675	Gly His Ser Val Ser 2680	Thr Leu Glu Lys 2685
Thr Leu Pro Gln Leu Leu 2690	Ala Lys Leu Ser Ile 2695	Leu Glu Asn Arg 2700
Gly Val His Asn Ala Ser 2705	Leu Ala Leu Ser Ala 2710	Ser Ile Gly Arg 2715
Val Arg Glu Leu Ile Ala 2720	Gln Ala Arg Gly Ala 2725	Ala Ser Lys Val 2730
Lys Val Pro Met Lys Phe 2735	Asn Gly Arg Ser Gly 2740	Val Gln Leu Arg 2745
Thr Pro Arg Asp Leu Ala 2750	Asp Leu Ala Ala Tyr 2755	Thr Ala Leu Lys 2760
Phe Tyr Leu Gln Gly Pro 2765	Glu Pro Glu Pro Gly 2770	Gln Gly Thr Glu 2775
Asp Arg Phe Val Met Tyr 2780	Met Gly Ser Arg Gln 2785	Ala Thr Gly Asp 2790
Tyr Met Gly Val Ser Leu 2795	Arg Asp Lys Lys Val 2800	His Trp Val Tyr 2805
Gln Leu Gly Glu Ala Gly 2810	Pro Ala Val Leu Ser 2815	Ile Asp Glu Asp 2820
Ile Gly Glu Gln Phe Ala 2825	Ala Val Ser Leu Asp 2830	Arg Thr Leu Gln 2835
Phe Gly His Met Ser Val 2840	Thr Val Glu Arg Gln 2845	Met Ile Gln Glu 2850
Thr Lys Gly Asp Thr Val 2855	Ala Pro Gly Ala Glu 2860	Gly Leu Leu Asn 2865
Leu Arg Pro Asp Asp Phe 2870	Val Phe Tyr Val Gly 2875	Gly Tyr Pro Ser 2880
Thr Phe Thr Pro Pro Pro 2885	Leu Leu Arg Phe Pro 2890	Gly Tyr Arg Gly 2895
Cys Ile Glu Met Asp Thr 2900	Leu Asn Glu Glu Val 2905	Val Ser Leu Tyr 2910
Asn Phe Glu Arg Thr Phe 2915	Gln Leu Asp Thr Ala 2920	Val Asp Arg Pro 2925
Cys Ala Arg Ser Lys Ser 2930	Thr Gly Asp Pro Trp 2935	Leu Thr Asp Gly 2940
Ser Tyr Leu Asp Gly Thr 2945	Gly Phe Ala Arg Ile 2950	Ser Phe Asp Ser 2955
Gln Ile Ser Thr Thr Lys 2960	Arg Phe Glu Gln Glu 2965	Leu Arg Leu Val 2970

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Ser	Tyr	Ser	Gly	Val	Leu	Phe	Phe	Leu	Lys	Gln	Gln	Ser	Gln	Phe
2975						2980					2985			
Leu	Cys	Leu	Ala	Val	Gln	Glu	Gly	Ser	Leu	Val	Leu	Leu	Tyr	Asp
2990						2995					3000			
Phe	Gly	Ala	Gly	Leu	Lys	Lys	Ala	Val	Pro	Leu	Gln	Pro	Pro	Pro
3005						3010					3015			
Pro	Leu	Thr	Ser	Ala	Ser	Lys	Ala	Ile	Gln	Val	Phe	Leu	Leu	Gly
3020						3025					3030			
Gly	Ser	Arg	Lys	Arg	Val	Leu	Val	Arg	Val	Glu	Arg	Ala	Thr	Val
3035						3040					3045			
Tyr	Ser	Val	Glu	Gln	Asp	Asn	Asp	Leu	Glu	Leu	Ala	Asp	Ala	Tyr
3050						3055					3060			
Tyr	Leu	Gly	Gly	Val	Pro	Pro	Asp	Gln	Leu	Pro	Pro	Ser	Leu	Arg
3065						3070					3075			
Arg	Leu	Phe	Pro	Thr	Gly	Gly	Ser	Val	Arg	Gly	Cys	Val	Lys	Gly
3080						3085					3090			
Ile	Lys	Ala	Leu	Gly	Lys	Tyr	Val	Asp	Leu	Lys	Arg	Leu	Asn	Thr
3095						3100					3105			
Thr	Gly	Val	Ser	Ala	Gly	Cys	Thr	Ala	Asp	Leu	Leu	Val	Gly	Arg
3110						3115					3120			
Ala	Met	Thr	Phe	His	Gly	His	Gly	Phe	Leu	Arg	Leu	Ala	Leu	Ser
3125						3130					3135			
Asn	Val	Ala	Pro	Leu	Thr	Gly	Asn	Val	Tyr	Ser	Gly	Phe	Gly	Phe
3140						3145					3150			
His	Ser	Ala	Gln	Asp	Ser	Ala	Leu	Leu	Tyr	Tyr	Arg	Ala	Ser	Pro
3155						3160					3165			
Asp	Gly	Leu	Cys	Gln	Val	Ser	Leu	Gln	Gln	Gly	Arg	Val	Ser	Leu
3170						3175					3180			
Gln	Leu	Leu	Arg	Thr	Glu	Val	Lys	Thr	Gln	Ala	Gly	Phe	Ala	Asp
3185						3190					3195			
Gly	Ala	Pro	His	Tyr	Val	Ala	Phe	Tyr	Ser	Asn	Ala	Thr	Gly	Val
3200						3205					3210			
Trp	Leu	Tyr	Val	Asp	Asp	Gln	Leu	Gln	Gln	Met	Lys	Pro	His	Arg
3215						3220					3225			
Gly	Pro	Pro	Pro	Glu	Leu	Gln	Pro	Gln	Pro	Glu	Gly	Pro	Pro	Arg
3230						3235					3240			
Leu	Leu	Leu	Gly	Gly	Leu	Pro	Glu	Ser	Gly	Thr	Ile	Tyr	Asn	Phe
3245						3250					3255			
Ser	Gly	Cys	Ile	Ser	Asn	Val	Phe	Val	Gln	Arg	Leu	Leu	Gly	Pro
3260						3265					3270			
Gln	Arg	Val	Phe	Asp	Leu	Gln	Gln	Asn	Leu	Gly	Ser	Val	Asn	Val
3275						3280					3285			
Ser	Thr	Gly	Cys	Ala	Pro	Ala	Leu	Gln	Ala	Gln	Thr	Pro	Gly	Leu
3290						3295					3300			
Gly	Pro	Arg	Gly	Leu	Gln	Ala	Thr	Ala	Arg	Lys	Ala	Ser	Arg	Arg
3305						3310					3315			
Ser	Arg	Gln	Pro	Ala	Arg	His	Pro	Ala	Cys	Met	Leu	Pro	Pro	His
3320						3325					3330			
Leu	Arg	Thr	Thr	Arg	Asp	Ser	Tyr	Gln	Phe	Gly	Gly	Ser	Leu	Ser
3335						3340					3345			
Ser	His	Leu	Glu	Phe	Val	Gly	Ile	Leu	Ala	Arg	His	Arg	Asn	Trp
3350						3355					3360			

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Pro Ser Leu Ser Met His Val Leu Pro Arg Ser Ser Arg Gly Leu
 3365 3370 3375

Leu Leu Phe Thr Ala Arg Leu Arg Pro Gly Ser Pro Ser Leu Ala
 3380 3385 3390

Leu Phe Leu Ser Asn Gly His Phe Val Ala Gln Met Glu Gly Leu
 3395 3400 3405

Gly Thr Arg Leu Arg Ala Gln Ser Arg Gln Arg Ser Arg Pro Gly
 3410 3415 3420

Arg Trp His Lys Val Ser Val Arg Trp Glu Lys Asn Arg Ile Leu
 3425 3430 3435

Leu Val Thr Asp Gly Ala Arg Ala Trp Ser Gln Glu Gly Pro His
 3440 3445 3450

Arg Gln His Gln Gly Ala Glu His Pro Gln Pro His Thr Leu Phe
 3455 3460 3465

Val Gly Gly Leu Pro Ala Ser Ser His Ser Ser Lys Leu Pro Val
 3470 3475 3480

Thr Val Gly Phe Ser Gly Cys Val Lys Arg Leu Arg Leu His Gly
 3485 3490 3495

Arg Pro Leu Gly Ala Pro Thr Arg Met Ala Gly Val Thr Pro Cys
 3500 3505 3510

Ile Leu Gly Pro Leu Glu Ala Gly Leu Phe Phe Pro Gly Ser Gly
 3515 3520 3525

Gly Val Ile Thr Leu Asp Leu Pro Gly Ala Thr Leu Pro Asp Val
 3530 3535 3540

Gly Leu Glu Leu Glu Val Arg Pro Leu Ala Val Thr Gly Leu Ile
 3545 3550 3555

Phe His Leu Gly Gln Ala Arg Thr Pro Pro Tyr Leu Gln Leu Gln
 3560 3565 3570

Val Thr Glu Lys Gln Val Leu Leu Arg Ala Asp Asp Gly Ala Gly
 3575 3580 3585

Glu Phe Ser Thr Ser Val Thr Arg Pro Ser Val Leu Cys Asp Gly
 3590 3595 3600

Gln Trp His Arg Leu Ala Val Met Lys Ser Gly Asn Val Leu Arg
 3605 3610 3615

Leu Glu Val Asp Ala Gln Ser Asn His Thr Val Gly Pro Leu Leu
 3620 3625 3630

Ala Ala Ala Ala Gly Ala Pro Ala Pro Leu Tyr Leu Gly Gly Leu
 3635 3640 3645

Pro Glu Pro Met Ala Val Gln Pro Trp Pro Pro Ala Tyr Cys Gly
 3650 3655 3660

Cys Met Arg Arg Leu Ala Val Asn Arg Ser Pro Val Ala Met Thr
 3665 3670 3675

Arg Ser Val Glu Val His Gly Ala Val Gly Ala Ser Gly Cys Pro
 3680 3685 3690

Ala Ala
 3695

<210> SEQ ID NO 37
 <211> LENGTH: 1786
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg
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Ala Arg Val Arg Ala Gln Glu Pro Glu Phe Ser Tyr Gly Cys Ala Glu
 20 25 30

Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln
 35 40 45

Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr
 50 55 60

Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn
 65 70 75 80

Ser Gln Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile
 85 90 95

Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp
 100 105 110

Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu
 115 120 125

Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg
 130 135 140

Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp
 145 150 155 160

Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ala Ser Phe Pro Gly
 165 170 175

Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser
 180 185 190

Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg
 195 200 205

Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile
 210 215 220

Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu
 225 230 235 240

His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu
 245 250 255

Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe
 260 265 270

Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu
 275 280 285

Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr
 290 295 300

Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro
 305 310 315 320

Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn
 325 330 335

Cys Asn Glu His Ser Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu
 340 345 350

Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn
 355 360 365

Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His
 370 375 380

Pro Glu Arg Asp Ile Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys
 385 390 395 400

Asp Pro Ala Gly Ser Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp
 405 410 415

Phe Ser Thr Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu Asn Val
 420 425 430

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Glu	Gly	Glu	His	Cys	Asp	Val	Cys	Lys	Glu	Gly	Phe	Tyr	Asp	Leu	Ser
		435					440					445			
Ser	Glu	Asp	Pro	Phe	Gly	Cys	Lys	Ser	Cys	Ala	Cys	Asn	Pro	Leu	Gly
	450					455					460				
Thr	Ile	Pro	Gly	Gly	Asn	Pro	Cys	Asp	Ser	Glu	Thr	Gly	His	Cys	Tyr
465					470					475				480	
Cys	Lys	Arg	Leu	Val	Thr	Gly	Gln	His	Cys	Asp	Gln	Cys	Leu	Pro	Glu
			485						490					495	
His	Trp	Gly	Leu	Ser	Asn	Asp	Leu	Asp	Gly	Cys	Arg	Pro	Cys	Asp	Cys
		500						505					510		
Asp	Leu	Gly	Gly	Ala	Leu	Asn	Asn	Ser	Cys	Phe	Ala	Glu	Ser	Gly	Gln
	515						520					525			
Cys	Ser	Cys	Arg	Pro	His	Met	Ile	Gly	Arg	Gln	Cys	Asn	Glu	Val	Glu
	530					535						540			
Pro	Gly	Tyr	Tyr	Phe	Ala	Thr	Leu	Asp	His	Tyr	Leu	Tyr	Glu	Ala	Glu
545					550					555					560
Glu	Ala	Asn	Leu	Gly	Pro	Gly	Val	Ser	Ile	Val	Glu	Arg	Gln	Tyr	Ile
			565							570					575
Gln	Asp	Arg	Ile	Pro	Ser	Trp	Thr	Gly	Ala	Gly	Phe	Val	Arg	Val	Pro
			580						585				590		
Glu	Gly	Ala	Tyr	Leu	Glu	Phe	Phe	Ile	Asp	Asn	Ile	Pro	Tyr	Ser	Met
		595					600					605			
Glu	Tyr	Asp	Ile	Leu	Ile	Arg	Tyr	Glu	Pro	Gln	Leu	Pro	Asp	His	Trp
	610					615						620			
Glu	Lys	Ala	Val	Ile	Thr	Val	Gln	Arg	Pro	Gly	Arg	Ile	Pro	Thr	Ser
625						630				635					640
Ser	Arg	Cys	Gly	Asn	Thr	Ile	Pro	Asp	Asp	Asp	Asn	Gln	Val	Val	Ser
				645					650						655
Leu	Ser	Pro	Gly	Ser	Arg	Tyr	Val	Val	Leu	Pro	Arg	Pro	Val	Cys	Phe
			660						665					670	
Glu	Lys	Gly	Thr	Asn	Tyr	Thr	Val	Arg	Leu	Glu	Leu	Pro	Gln	Tyr	Thr
		675					680						685		
Ser	Ser	Asp	Ser	Asp	Val	Glu	Ser	Pro	Tyr	Thr	Leu	Ile	Asp	Ser	Leu
	690					695					700				
Val	Leu	Met	Pro	Tyr	Cys	Lys	Ser	Leu	Asp	Ile	Phe	Thr	Val	Gly	Gly
705						710				715					720
Ser	Gly	Asp	Gly	Val	Val	Thr	Asn	Ser	Ala	Trp	Glu	Thr	Phe	Gln	Arg
				725					730					735	
Tyr	Arg	Cys	Leu	Glu	Asn	Ser	Arg	Ser	Val	Val	Lys	Thr	Pro	Met	Thr
			740					745						750	
Asp	Val	Cys	Arg	Asn	Ile	Ile	Phe	Ser	Ile	Ser	Ala	Leu	Leu	His	Gln
		755					760					765			
Thr	Gly	Leu	Ala	Cys	Glu	Cys	Asp	Pro	Gln	Gly	Ser	Leu	Ser	Ser	Val
	770						775					780			
Cys	Asp	Pro	Asn	Gly	Gly	Gln	Cys	Gln	Cys	Arg	Pro	Asn	Val	Val	Gly
785						790				795					800
Arg	Thr	Cys	Asn	Arg	Cys	Ala	Pro	Gly	Thr	Phe	Gly	Phe	Gly	Pro	Ser
			805						810					815	
Gly	Cys	Lys	Pro	Cys	Glu	Cys	His	Leu	Gln	Gly	Ser	Val	Asn	Ala	Phe
			820						825					830	
Cys	Asn	Pro	Val	Thr	Gly	Gln	Cys	His	Cys	Phe	Gln	Gly	Val	Tyr	Ala
	835							840				845			
Arg	Gln	Cys	Asp	Arg	Cys	Leu	Pro	Gly	His	Trp	Gly	Phe	Pro	Ser	Cys

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850			855			860									
Gln	Pro	Cys	Gln	Cys	Asn	Gly	His	Ala	Asp	Asp	Cys	Asp	Pro	Val	Thr
865					870					875					880
Gly	Glu	Cys	Leu	Asn	Cys	Gln	Asp	Tyr	Thr	Met	Gly	His	Asn	Cys	Glu
			885						890					895	
Arg	Cys	Leu	Ala	Gly	Tyr	Tyr	Gly	Asp	Pro	Ile	Ile	Gly	Ser	Gly	Asp
			900					905					910		
His	Cys	Arg	Pro	Cys	Pro	Cys	Pro	Asp	Gly	Pro	Asp	Ser	Gly	Arg	Gln
		915						920				925			
Phe	Ala	Arg	Ser	Cys	Tyr	Gln	Asp	Pro	Val	Thr	Leu	Gln	Leu	Ala	Cys
		930				935					940				
Val	Cys	Asp	Pro	Gly	Tyr	Ile	Gly	Ser	Arg	Cys	Asp	Asp	Cys	Ala	Ser
945					950					955					960
Gly	Tyr	Phe	Gly	Asn	Pro	Ser	Glu	Val	Gly	Gly	Ser	Cys	Gln	Pro	Cys
			965						970					975	
Gln	Cys	His	Asn	Asn	Ile	Asp	Thr	Thr	Asp	Pro	Glu	Ala	Cys	Asp	Lys
			980					985						990	
Glu	Thr	Gly	Arg	Cys	Leu	Lys	Cys	Leu	Tyr	His	Thr	Glu	Gly	Glu	His
		995					1000					1005			
Cys	Gln	Phe	Cys	Arg	Phe	Gly	Tyr	Tyr	Gly	Asp	Ala	Leu	Gln	Gln	
	1010					1015					1020				
Asp	Cys	Arg	Lys	Cys	Val	Cys	Asn	Tyr	Leu	Gly	Thr	Val	Gln	Glu	
	1025					1030					1035				
His	Cys	Asn	Gly	Ser	Asp	Cys	Gln	Cys	Asp	Lys	Ala	Thr	Gly	Gln	
	1040					1045					1050				
Cys	Leu	Cys	Leu	Pro	Asn	Val	Ile	Gly	Gln	Asn	Cys	Asp	Arg	Cys	
	1055					1060					1065				
Ala	Pro	Asn	Thr	Trp	Gln	Leu	Ala	Ser	Gly	Thr	Gly	Cys	Asp	Pro	
	1070					1075					1080				
Cys	Asn	Cys	Asn	Ala	Ala	His	Ser	Phe	Gly	Pro	Ser	Cys	Asn	Glu	
	1085					1090					1095				
Phe	Thr	Gly	Gln	Cys	Gln	Cys	Met	Pro	Gly	Phe	Gly	Gly	Arg	Thr	
	1100					1105					1110				
Cys	Ser	Glu	Cys	Gln	Glu	Leu	Phe	Trp	Gly	Asp	Pro	Asp	Val	Glu	
	1115					1120					1125				
Cys	Arg	Ala	Cys	Asp	Cys	Asp	Pro	Arg	Gly	Ile	Glu	Thr	Pro	Gln	
	1130					1135					1140				
Cys	Asp	Gln	Ser	Thr	Gly	Gln	Cys	Val	Cys	Val	Glu	Gly	Val	Glu	
	1145					1150					1155				
Gly	Pro	Arg	Cys	Asp	Lys	Cys	Thr	Arg	Gly	Tyr	Ser	Gly	Val	Phe	
	1160					1165					1170				
Pro	Asp	Cys	Thr	Pro	Cys	His	Gln	Cys	Phe	Ala	Leu	Trp	Asp	Val	
	1175					1180					1185				
Ile	Ile	Ala	Glu	Leu	Thr	Asn	Arg	Thr	His	Arg	Phe	Leu	Glu	Lys	
	1190					1195					1200				
Ala	Lys	Ala	Leu	Lys	Ile	Ser	Gly	Val	Ile	Gly	Pro	Tyr	Arg	Glu	
	1205					1210					1215				
Thr	Val	Asp	Ser	Val	Glu	Arg	Lys	Val	Ser	Glu	Ile	Lys	Asp	Ile	
	1220					1225					1230				
Leu	Ala	Gln	Ser	Pro	Ala	Ala	Glu	Pro	Leu	Lys	Asn	Ile	Gly	Asn	
	1235					1240					1245				
Leu	Phe	Glu	Glu	Ala	Glu	Lys	Leu	Ile	Lys	Asp	Val	Thr	Glu	Met	
	1250					1255					1260				

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Met	Ala	Gln	Val	Glu	Val	Lys	Leu	Ser	Asp	Thr	Thr	Ser	Gln	Ser
1265						1270					1275			
Asn	Ser	Thr	Ala	Lys	Glu	Leu	Asp	Ser	Leu	Gln	Thr	Glu	Ala	Glu
1280						1285					1290			
Ser	Leu	Asp	Asn	Thr	Val	Lys	Glu	Leu	Ala	Glu	Gln	Leu	Glu	Phe
1295						1300					1305			
Ile	Lys	Asn	Ser	Asp	Ile	Arg	Gly	Ala	Leu	Asp	Ser	Ile	Thr	Lys
1310						1315					1320			
Tyr	Phe	Gln	Met	Ser	Leu	Glu	Ala	Glu	Glu	Arg	Val	Asn	Ala	Ser
1325						1330					1335			
Thr	Thr	Glu	Pro	Asn	Ser	Thr	Val	Glu	Gln	Ser	Ala	Leu	Met	Arg
1340						1345					1350			
Asp	Arg	Val	Glu	Asp	Val	Met	Met	Glu	Arg	Glu	Ser	Gln	Phe	Lys
1355						1360					1365			
Glu	Lys	Gln	Glu	Glu	Gln	Ala	Arg	Leu	Leu	Asp	Glu	Leu	Ala	Gly
1370						1375					1380			
Lys	Leu	Gln	Ser	Leu	Asp	Leu	Ser	Ala	Ala	Ala	Glu	Met	Thr	Cys
1385						1390					1395			
Gly	Thr	Pro	Pro	Gly	Ala	Ser	Cys	Ser	Glu	Thr	Glu	Cys	Gly	Gly
1400						1405					1410			
Pro	Asn	Cys	Arg	Thr	Asp	Glu	Gly	Glu	Arg	Lys	Cys	Gly	Gly	Pro
1415						1420					1425			
Gly	Cys	Gly	Gly	Leu	Val	Thr	Val	Ala	His	Asn	Ala	Trp	Gln	Lys
1430						1435					1440			
Ala	Met	Asp	Leu	Asp	Gln	Asp	Val	Leu	Ser	Ala	Leu	Ala	Glu	Val
1445						1450					1455			
Glu	Gln	Leu	Ser	Lys	Met	Val	Ser	Glu	Ala	Lys	Leu	Arg	Ala	Asp
1460						1465					1470			
Glu	Ala	Lys	Gln	Ser	Ala	Glu	Asp	Ile	Leu	Leu	Lys	Thr	Asn	Ala
1475						1480					1485			
Thr	Lys	Glu	Lys	Met	Asp	Lys	Ser	Asn	Glu	Glu	Leu	Arg	Asn	Leu
1490						1495					1500			
Ile	Lys	Gln	Ile	Arg	Asn	Phe	Leu	Thr	Gln	Asp	Ser	Ala	Asp	Leu
1505						1510					1515			
Asp	Ser	Ile	Glu	Ala	Val	Ala	Asn	Glu	Val	Leu	Lys	Met	Glu	Met
1520						1525					1530			
Pro	Ser	Thr	Pro	Gln	Gln	Leu	Gln	Asn	Leu	Thr	Glu	Asp	Ile	Arg
1535						1540					1545			
Glu	Arg	Val	Glu	Ser	Leu	Ser	Gln	Val	Glu	Val	Ile	Leu	Gln	His
1550						1555					1560			
Ser	Ala	Ala	Asp	Ile	Ala	Arg	Ala	Glu	Met	Leu	Leu	Glu	Glu	Ala
1565						1570					1575			
Lys	Arg	Ala	Ser	Lys	Ser	Ala	Thr	Asp	Val	Lys	Val	Thr	Ala	Asp
1580						1585					1590			
Met	Val	Lys	Glu	Ala	Leu	Glu	Glu	Ala	Glu	Lys	Ala	Gln	Val	Ala
1595						1600					1605			
Ala	Glu	Lys	Ala	Ile	Lys	Gln	Ala	Asp	Glu	Asp	Ile	Gln	Gly	Thr
1610						1615					1620			
Gln	Asn	Leu	Leu	Thr	Ser	Ile	Glu	Ser	Glu	Thr	Ala	Ala	Ser	Glu
1625						1630					1635			
Glu	Thr	Leu	Phe	Asn	Ala	Ser	Gln	Arg	Ile	Ser	Glu	Leu	Glu	Arg
1640						1645					1650			

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Asn Val  Glu Glu Leu Lys Arg  Lys Ala Ala Gln Asn  Ser Gly Glu
1655                                1660                                1665

Ala Glu  Tyr Ile Glu Lys Val  Val Tyr Thr Val Lys  Gln Ser Ala
1670                                1675                                1680

Glu Asp  Val Lys Lys Thr Leu  Asp Gly Glu Leu Asp  Glu Lys Tyr
1685                                1690                                1695

Lys Lys  Val Glu Asn Leu Ile  Ala Lys Lys Thr Glu  Glu Ser Ala
1700                                1705                                1710

Asp Ala  Arg Arg Lys Ala Glu  Met Leu Gln Asn Glu  Ala Lys Thr
1715                                1720                                1725

Leu Leu  Ala Gln Ala Asn Ser  Lys Leu Gln Leu Leu  Lys Asp Leu
1730                                1735                                1740

Glu Arg  Lys Tyr Glu Asp Asn  Gln Arg Tyr Leu Glu  Asp Lys Ala
1745                                1750                                1755

Gln Glu  Leu Ala Arg Leu Glu  Gly Glu Val Arg Ser  Leu Leu Lys
1760                                1765                                1770

Asp Ile  Ser Gln Lys Val Ala  Val Tyr Ser Thr Cys  Leu
1775                                1780                                1785
    
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<210> SEQ ID NO 38
<211> LENGTH: 1798
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38
    
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Met Glu Leu Thr Ser Arg Glu Arg Gly Arg Gly Gln Pro Leu Pro Trp
1      5      10      15

Glu Leu Arg Leu Gly Leu Leu Leu Ser Val Leu Ala Ala Thr Leu Ala
20     25     30

Gln Ala Pro Ala Pro Asp Val Pro Gly Cys Ser Arg Gly Ser Cys Tyr
35     40     45

Pro Ala Thr Gly Asp Leu Leu Val Gly Arg Ala Asp Arg Leu Thr Ala
50     55     60

Ser Ser Thr Cys Gly Leu Asn Gly Pro Gln Pro Tyr Cys Ile Val Ser
65     70     75     80

His Leu Gln Asp Glu Lys Lys Cys Phe Leu Cys Asp Ser Arg Arg Pro
85     90     95

Phe Ser Ala Arg Asp Asn Pro His Ser His Arg Ile Gln Asn Val Val
100    105    110

Thr Ser Phe Ala Pro Gln Arg Arg Ala Ala Trp Trp Gln Ser Glu Asn
115    120    125

Gly Ile Pro Ala Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His
130    135    140

Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met
145    150    155    160

Leu Val Glu Arg Ser Ala Asp Phe Gly Arg Thr Trp His Val Tyr Arg
165    170    175

Tyr Phe Ser Tyr Asp Cys Gly Ala Asp Phe Pro Gly Val Pro Leu Ala
180    185    190

Pro Pro Arg His Trp Asp Asp Val Val Cys Glu Ser Arg Tyr Ser Glu
195    200    205

Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Tyr Arg Val Leu Asp Pro
210    215    220

Ala Ile Pro Ile Pro Asp Pro Tyr Ser Ser Arg Ile Gln Asn Leu Leu
225    230    235    240
    
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Lys Ile Thr Asn Leu Arg Val Asn Leu Thr Arg Leu His Thr Leu Gly
 245 250 255

Asp Asn Leu Leu Asp Pro Arg Arg Glu Ile Arg Glu Lys Tyr Tyr Tyr
 260 265 270

Ala Leu Tyr Glu Leu Val Val Arg Gly Asn Cys Phe Cys Tyr Gly His
 275 280 285

Ala Ser Glu Cys Ala Pro Ala Pro Gly Ala Pro Ala His Ala Glu Gly
 290 295 300

Met Val His Gly Ala Cys Ile Cys Lys His Asn Thr Arg Gly Leu Asn
 305 310 315

Cys Glu Gln Cys Gln Asp Phe Tyr Arg Asp Leu Pro Trp Arg Pro Ala
 325 330 335

Glu Asp Gly His Ser His Ala Cys Arg Lys Cys Glu Cys His Gly His
 340 345 350

Thr His Ser Cys His Phe Asp Met Ala Val Tyr Leu Ala Ser Gly Asn
 355 360 365

Val Ser Gly Gly Val Cys Asp Gly Cys Gln His Asn Thr Ala Gly Arg
 370 375 380

His Cys Glu Leu Cys Arg Pro Phe Phe Tyr Arg Asp Pro Thr Lys Asp
 385 390 395 400

Leu Arg Asp Pro Ala Val Cys Arg Ser Cys Asp Cys Asp Pro Met Gly
 405 410 415

Ser Gln Asp Gly Gly Arg Cys Asp Ser His Asp Asp Pro Ala Leu Gly
 420 425 430

Leu Val Ser Gly Gln Cys Arg Cys Lys Glu His Val Val Gly Thr Arg
 435 440 445

Cys Gln Gln Cys Arg Asp Gly Phe Phe Gly Leu Ser Ile Ser Asp Arg
 450 455 460

Leu Gly Cys Arg Arg Cys Gln Cys Asn Ala Arg Gly Thr Val Pro Gly
 465 470 475 480

Ser Thr Pro Cys Asp Pro Asn Ser Gly Ser Cys Tyr Cys Lys Arg Leu
 485 490 495

Val Thr Gly Arg Gly Cys Asp Arg Cys Leu Pro Gly His Trp Gly Leu
 500 505 510

Ser His Asp Leu Leu Gly Cys Arg Pro Cys Asp Cys Asp Val Gly Gly
 515 520 525

Ala Leu Asp Pro Gln Cys Asp Glu Gly Thr Gly Gln Cys His Cys Arg
 530 535 540

Gln His Met Val Gly Arg Arg Cys Glu Gln Val Gln Pro Gly Tyr Phe
 545 550 555 560

Arg Pro Phe Leu Asp His Leu Ile Trp Glu Ala Glu Asp Thr Arg Gly
 565 570 575

Gln Val Leu Asp Val Val Glu Arg Leu Val Thr Pro Gly Glu Thr Pro
 580 585 590

Ser Trp Thr Gly Ser Gly Phe Val Arg Leu Gln Glu Gly Gln Thr Leu
 595 600 605

Glu Phe Leu Val Ala Ser Val Pro Lys Ala Met Asp Tyr Asp Leu Leu
 610 615 620

Leu Arg Leu Glu Pro Gln Val Pro Glu Gln Trp Ala Glu Leu Glu Leu
 625 630 635 640

Ile Val Gln Arg Pro Gly Pro Val Pro Ala His Ser Leu Cys Gly His
 645 650 655

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Leu Val Pro Lys Asp Asp Arg Ile Gln Gly Thr Leu Gln Pro His Ala
 660 665 670
 Arg Tyr Leu Ile Phe Pro Asn Pro Val Cys Leu Glu Pro Gly Ile Ser
 675 680 685
 Tyr Lys Leu His Leu Lys Leu Val Arg Thr Gly Gly Ser Ala Gln Pro
 690 695 700
 Glu Thr Pro Tyr Ser Gly Pro Gly Leu Leu Ile Asp Ser Leu Val Leu
 705 710 715 720
 Leu Pro Arg Val Leu Val Leu Glu Met Phe Ser Gly Gly Asp Ala Ala
 725 730 735
 Ala Leu Glu Arg Gln Ala Thr Phe Glu Arg Tyr Gln Cys His Glu Glu
 740 745 750
 Gly Leu Val Pro Ser Lys Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu
 755 760 765
 Leu Ile Ser Leu Ser Thr Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln
 770 775 780
 Cys Asn Pro Gln Gly Ser Leu Ser Ser Glu Cys Asn Pro His Gly Gly
 785 790 795 800
 Gln Cys Leu Cys Lys Pro Gly Val Val Gly Arg Arg Cys Asp Leu Cys
 805 810 815
 Ala Pro Gly Tyr Tyr Gly Phe Gly Pro Thr Gly Cys Gln Ala Cys Gln
 820 825 830
 Cys Ser His Glu Gly Ala Leu Ser Ser Leu Cys Glu Lys Thr Ser Gly
 835 840 845
 Gln Cys Leu Cys Arg Thr Gly Ala Phe Gly Leu Arg Cys Asp Arg Cys
 850 855 860
 Gln Arg Gly Gln Trp Gly Phe Pro Ser Cys Arg Pro Cys Val Cys Asn
 865 870 875 880
 Gly His Ala Asp Glu Cys Asn Thr His Thr Gly Ala Cys Leu Gly Cys
 885 890 895
 Arg Asp His Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe
 900 905 910
 His Gly Asp Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro
 915 920 925
 Cys Pro Glu Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His
 930 935 940
 Gln Asp Glu Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr
 945 950 955 960
 Thr Gly Leu Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro
 965 970 975
 Ser Arg Pro Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile
 980 985 990
 Asp Pro Met Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu
 995 1000 1005
 Arg Cys Leu His His Thr Glu Gly Pro His Cys Ala His Cys Lys
 1010 1015 1020
 Pro Gly Phe His Gly Gln Ala Ala Arg Gln Ser Cys His Arg Cys
 1025 1030 1035
 Thr Cys Asn Leu Leu Gly Thr Asn Pro Gln Gln Cys Pro Ser Pro
 1040 1045 1050
 Asp Gln Cys His Cys Asp Pro Ser Ser Gly Gln Cys Pro Cys Leu
 1055 1060 1065
 Pro Asn Val Gln Gly Pro Ser Cys Asp Arg Cys Ala Pro Asn Phe

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1070	1075	1080
Trp Asn Leu Thr Ser Gly His 1085	Gly Cys Gln Pro 1090	Cys Ala Cys His 1095
Pro Ser Arg Ala Arg Gly Pro 1100	Thr Cys Asn Glu Phe 1105	Thr Gly Gln 1110
Cys His Cys Arg Ala Gly Phe 1115	Gly Gly Arg Thr Cys 1120	Ser Glu Cys 1125
Gln Glu Leu His Trp Gly Asp 1130	Pro Gly Leu Gln Cys 1135	His Ala Cys 1140
Asp Cys Asp Ser Arg Gly Ile 1145	Asp Thr Pro Gln Cys 1150	His Arg Phe 1155
Thr Gly His Cys Ser Cys Arg 1160	Pro Gly Val Ser Gly 1165	Val Arg Cys 1170
Asp Gln Cys Ala Arg Gly Phe 1175	Ser Gly Ile Phe Pro 1180	Ala Cys His 1185
Pro Cys His Ala Cys Phe Gly 1190	Asp Trp Asp Arg Val 1195	Val Gln Asp 1200
Leu Ala Ala Arg Thr Gln Arg 1205	Leu Glu Gln Arg Ala 1210	Gln Glu Leu 1215
Gln Gln Thr Gly Val Leu Gly 1220	Ala Phe Glu Ser Ser 1225	Phe Trp His 1230
Met Gln Glu Lys Leu Gly Ile 1235	Val Gln Gly Ile Val 1240	Gly Ala Arg 1245
Asn Thr Ser Ala Ala Ser Thr 1250	Ala Gln Leu Val Glu 1255	Ala Thr Glu 1260
Glu Leu Arg Arg Glu Ile Gly 1265	Glu Ala Thr Glu His 1270	Leu Thr Gln 1275
Leu Glu Ala Asp Leu Thr Asp 1280	Val Gln Asp Glu Asn 1285	Phe Asn Ala 1290
Asn His Ala Leu Ser Gly Leu 1295	Glu Arg Asp Arg Leu 1300	Ala Leu Asn 1305
Leu Thr Leu Arg Gln Leu Asp 1310	Gln His Leu Asp Leu 1315	Leu Lys His 1320
Ser Asn Phe Leu Gly Ala Tyr 1325	Asp Ser Ile Arg His 1330	Ala His Ser 1335
Gln Ser Ala Glu Ala Glu Arg 1340	Arg Ala Asn Thr Ser 1345	Ala Leu Ala 1350
Val Pro Ser Pro Val Ser Asn 1355	Ser Ala Ser Ala Arg 1360	His Arg Thr 1365
Glu Ala Leu Met Asp Ala Gln 1370	Lys Glu Asp Phe Asn 1375	Ser Lys His 1380
Met Ala Asn Gln Arg Ala Leu 1385	Gly Lys Leu Ser Ala 1390	His Thr His 1395
Thr Leu Ser Leu Thr Asp Ile 1400	Asn Glu Leu Val Cys 1405	Gly Ala Pro 1410
Gly Asp Ala Pro Cys Ala Thr 1415	Ser Pro Cys Gly Gly 1420	Ala Gly Cys 1425
Arg Asp Glu Asp Gly Gln Pro 1430	Arg Cys Gly Gly Leu 1435	Ser Cys Asn 1440
Gly Ala Ala Ala Thr Ala Asp 1445	Leu Ala Leu Gly Arg 1450	Ala Arg His 1455
Thr Gln Ala Glu Leu Gln Arg 1460	Ala Leu Ala Glu Gly 1465	Gly Ser Ile 1470

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Leu Ser Arg Val Ala Glu Thr Arg Arg Gln Ala Ser Glu Ala Gln
 1475 1480 1485

Gln Arg Ala Gln Ala Ala Leu Asp Lys Ala Asn Ala Ser Arg Gly
 1490 1495 1500

Gln Val Glu Gln Ala Asn Gln Glu Leu Gln Glu Leu Ile Gln Ser
 1505 1510 1515

Val Lys Asp Phe Leu Asn Gln Glu Gly Ala Asp Pro Asp Ser Ile
 1520 1525 1530

Glu Met Val Ala Thr Arg Val Leu Glu Leu Ser Ile Pro Ala Ser
 1535 1540 1545

Ala Glu Gln Ile Gln His Leu Ala Gly Ala Ile Ala Glu Arg Val
 1550 1555 1560

Arg Ser Leu Ala Asp Val Asp Ala Ile Leu Ala Arg Thr Val Gly
 1565 1570 1575

Asp Val Arg Arg Ala Glu Gln Leu Leu Gln Asp Ala Arg Arg Ala
 1580 1585 1590

Arg Ser Trp Ala Glu Asp Glu Lys Gln Lys Ala Glu Thr Val Gln
 1595 1600 1605

Ala Ala Leu Glu Glu Ala Gln Arg Ala Gln Gly Ile Ala Gln Gly
 1610 1615 1620

Ala Ile Arg Gly Ala Val Ala Asp Thr Arg Asp Thr Glu Gln Thr
 1625 1630 1635

Leu Tyr Gln Val Gln Glu Arg Met Ala Gly Ala Glu Arg Ala Leu
 1640 1645 1650

Ser Ser Ala Gly Glu Arg Ala Arg Gln Leu Asp Ala Leu Leu Glu
 1655 1660 1665

Ala Leu Lys Leu Lys Arg Ala Gly Asn Ser Leu Ala Ala Ser Thr
 1670 1675 1680

Ala Glu Glu Thr Ala Gly Ser Ala Gln Gly Arg Ala Gln Glu Ala
 1685 1690 1695

Glu Gln Leu Leu Arg Gly Pro Leu Gly Asp Gln Tyr Gln Thr Val
 1700 1705 1710

Lys Ala Leu Ala Glu Arg Lys Ala Gln Gly Val Leu Ala Ala Gln
 1715 1720 1725

Ala Arg Ala Glu Gln Leu Arg Asp Glu Ala Arg Asp Leu Leu Gln
 1730 1735 1740

Ala Ala Gln Asp Lys Leu Gln Arg Leu Gln Glu Leu Glu Gly Thr
 1745 1750 1755

Tyr Glu Glu Asn Glu Arg Ala Leu Glu Ser Lys Ala Ala Gln Leu
 1760 1765 1770

Asp Gly Leu Glu Ala Arg Met Arg Ser Val Leu Gln Ala Ile Asn
 1775 1780 1785

Leu Gln Val Gln Ile Tyr Asn Thr Cys Gln
 1790 1795

<210> SEQ ID NO 39
 <211> LENGTH: 1172
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Arg Pro Phe Phe Leu Leu Cys Phe Ala Leu Pro Gly Leu Leu His
 1 5 10 15

Ala Gln Gln Ala Cys Ser Arg Gly Ala Cys Tyr Pro Pro Val Gly Asp

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

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Gly Arg Cys Leu Cys Leu Pro Asn Val Val Gly Pro Lys Cys Asp Gln
 450 455 460

Cys Ala Pro Tyr His Trp Lys Leu Ala Ser Gly Gln Gly Cys Glu Pro
 465 470 475 480

Cys Ala Cys Asp Pro His Asn Ser Leu Ser Pro Gln Cys Asn Gln Phe
 485 490 495

Thr Gly Gln Cys Pro Cys Arg Glu Gly Phe Gly Gly Leu Met Cys Ser
 500 505 510

Ala Ala Ala Ile Arg Gln Cys Pro Asp Arg Thr Tyr Gly Asp Val Ala
 515 520 525

Thr Gly Cys Arg Ala Cys Asp Cys Asp Phe Arg Gly Thr Glu Gly Pro
 530 535 540

Gly Cys Asp Lys Ala Ser Gly Arg Cys Leu Cys Arg Pro Gly Leu Thr
 545 550 555 560

Gly Pro Arg Cys Asp Gln Cys Gln Arg Gly Tyr Cys Asn Arg Tyr Pro
 565 570 575

Val Cys Val Ala Cys His Pro Cys Phe Gln Thr Tyr Asp Ala Asp Leu
 580 585 590

Arg Glu Gln Ala Leu Arg Phe Gly Arg Leu Arg Asn Ala Thr Ala Ser
 595 600 605

Leu Trp Ser Gly Pro Gly Leu Glu Asp Arg Gly Leu Ala Ser Arg Ile
 610 615 620

Leu Asp Ala Lys Ser Lys Ile Glu Gln Ile Arg Ala Val Leu Ser Ser
 625 630 635 640

Pro Ala Val Thr Glu Gln Glu Val Ala Gln Val Ala Ser Ala Ile Leu
 645 650 655

Ser Leu Arg Arg Thr Leu Gln Gly Leu Gln Leu Asp Leu Pro Leu Glu
 660 665 670

Glu Glu Thr Leu Ser Leu Pro Arg Asp Leu Glu Ser Leu Asp Arg Ser
 675 680 685

Phe Asn Gly Leu Leu Thr Met Tyr Gln Arg Lys Arg Glu Gln Phe Glu
 690 695 700

Lys Ile Ser Ser Ala Asp Pro Ser Gly Ala Phe Arg Met Leu Ser Thr
 705 710 715 720

Ala Tyr Glu Gln Ser Ala Gln Ala Ala Gln Gln Val Ser Asp Ser Ser
 725 730 735

Arg Leu Leu Asp Gln Leu Arg Asp Ser Arg Arg Glu Ala Glu Arg Leu
 740 745 750

Val Arg Gln Ala Gly Gly Gly Gly Thr Gly Ser Pro Lys Leu Val
 755 760 765

Ala Leu Arg Leu Glu Met Ser Ser Leu Pro Asp Leu Thr Pro Thr Phe
 770 775 780

Asn Lys Leu Cys Gly Asn Ser Arg Gln Met Ala Cys Thr Pro Ile Ser
 785 790 795 800

Cys Pro Gly Glu Leu Cys Pro Gln Asp Asn Gly Thr Ala Cys Gly Ser
 805 810 815

Arg Cys Arg Gly Val Leu Pro Arg Ala Gly Gly Ala Phe Leu Met Ala
 820 825 830

Gly Gln Val Ala Glu Gln Leu Arg Gly Phe Asn Ala Gln Leu Gln Arg
 835 840 845

Thr Arg Gln Met Ile Arg Ala Ala Glu Glu Ser Ala Ser Gln Ile Gln
 850 855 860

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Ser Ser Ala Gln Arg Leu Glu Thr Gln Val Ser Ala Ser Arg Ser Gln
 865 870 875 880

Met Glu Glu Asp Val Arg Arg Thr Arg Leu Leu Ile Gln Gln Val Arg
 885 890 895

Asp Phe Leu Thr Asp Pro Asp Thr Asp Ala Ala Thr Ile Gln Glu Val
 900 905 910

Ser Glu Ala Val Leu Ala Leu Trp Leu Pro Thr Asp Ser Ala Thr Val
 915 920 925

Leu Gln Lys Met Asn Glu Ile Gln Ala Ile Ala Ala Arg Leu Pro Asn
 930 935 940

Val Asp Leu Val Leu Ser Gln Thr Lys Gln Asp Ile Ala Arg Ala Arg
 945 950 955 960

Arg Leu Gln Ala Glu Ala Glu Glu Ala Arg Ser Arg Ala His Ala Val
 965 970 975

Glu Gly Gln Val Glu Asp Val Val Gly Asn Leu Arg Gln Gly Thr Val
 980 985 990

Ala Leu Gln Glu Ala Gln Asp Thr Met Gln Gly Thr Ser Arg Ser Leu
 995 1000 1005

Arg Leu Ile Gln Asp Arg Val Ala Glu Val Gln Gln Val Leu Arg
 1010 1015 1020

Pro Ala Glu Lys Leu Val Thr Ser Met Thr Lys Gln Leu Gly Asp
 1025 1030 1035

Phe Trp Thr Arg Met Glu Glu Leu Arg His Gln Ala Arg Gln Gln
 1040 1045 1050

Gly Ala Glu Ala Val Gln Ala Gln Gln Leu Ala Glu Gly Ala Ser
 1055 1060 1065

Glu Gln Ala Leu Ser Ala Gln Glu Gly Phe Glu Arg Ile Lys Gln
 1070 1075 1080

Lys Tyr Ala Glu Leu Lys Asp Arg Leu Gly Gln Ser Ser Met Leu
 1085 1090 1095

Gly Glu Gln Gly Ala Arg Ile Gln Ser Val Lys Thr Glu Ala Glu
 1100 1105 1110

Glu Leu Phe Gly Glu Thr Met Glu Met Met Asp Arg Met Lys Asp
 1115 1120 1125

Met Glu Leu Glu Leu Leu Arg Gly Ser Gln Ala Ile Met Leu Arg
 1130 1135 1140

Ser Ala Asp Leu Thr Gly Leu Glu Lys Arg Val Glu Gln Ile Arg
 1145 1150 1155

Asp His Ile Asn Gly Arg Val Leu Tyr Tyr Ala Thr Cys Lys
 1160 1165 1170

<210> SEQ ID NO 40
 <211> LENGTH: 1761
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Met Gln Phe Gln Leu Thr Leu Phe Leu His Leu Gly Trp Leu Ser Tyr
 1 5 10 15

Ser Lys Ala Gln Asp Asp Cys Asn Arg Gly Ala Cys His Pro Thr Thr
 20 25 30

Gly Asp Leu Leu Val Gly Arg Asn Thr Gln Leu Met Ala Ser Ser Thr
 35 40 45

Cys Gly Leu Ser Arg Ala Gln Lys Tyr Cys Ile Leu Ser Tyr Leu Glu
 50 55 60

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Gly Glu Gln Lys Cys Phe Ile Cys Asp Ser Arg Phe Pro Tyr Asp Pro
 65 70 75 80
 Tyr Asp Gln Pro Asn Ser His Thr Ile Glu Asn Val Ile Val Ser Phe
 85 90 95
 Glu Pro Asp Arg Glu Lys Lys Trp Trp Gln Ser Glu Asn Gly Leu Asp
 100 105 110
 His Val Ser Ile Arg Leu Asp Leu Glu Ala Leu Phe Arg Phe Ser His
 115 120 125
 Leu Ile Leu Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu Val Glu
 130 135 140
 Arg Ser Thr Asp Tyr Gly His Asn Trp Lys Val Phe Lys Tyr Phe Ala
 145 150 155 160
 Lys Asp Cys Ala Thr Ser Phe Pro Asn Ile Thr Ser Gly Gln Ala Gln
 165 170 175
 Gly Val Gly Asp Ile Val Cys Asp Ser Lys Tyr Ser Asp Ile Glu Pro
 180 185 190
 Ser Thr Gly Gly Glu Val Val Leu Lys Val Leu Asp Pro Ser Phe Glu
 195 200 205
 Ile Glu Asn Pro Tyr Ser Pro Tyr Ile Gln Asp Leu Val Thr Leu Thr
 210 215 220
 Asn Leu Arg Ile Asn Phe Thr Lys Leu His Thr Leu Gly Asp Ala Leu
 225 230 235 240
 Leu Gly Arg Arg Gln Asn Asp Ser Leu Asp Lys Tyr Tyr Tyr Ala Leu
 245 250 255
 Tyr Glu Met Ile Val Arg Gly Ser Cys Phe Cys Asn Gly His Ala Ser
 260 265 270
 Glu Cys Arg Pro Met Gln Lys Met Arg Gly Asp Val Phe Ser Pro Pro
 275 280 285
 Gly Met Val His Gly Gln Cys Val Cys Gln His Asn Thr Asp Gly Pro
 290 295 300
 Asn Cys Glu Arg Cys Lys Asp Phe Phe Gln Asp Ala Pro Trp Arg Pro
 305 310 315 320
 Ala Ala Asp Leu Gln Asp Asn Ala Cys Arg Ser Cys Ser Cys Asn Ser
 325 330 335
 His Ser Ser Arg Cys His Phe Asp Met Thr Thr Tyr Leu Ala Ser Gly
 340 345 350
 Gly Leu Ser Gly Gly Val Cys Glu Asp Cys Gln His Asn Thr Glu Gly
 355 360 365
 Gln His Cys Asp Arg Cys Arg Pro Leu Phe Tyr Arg Asp Pro Leu Lys
 370 375 380
 Thr Ile Ser Asp Pro Tyr Ala Cys Ile Pro Cys Glu Cys Asp Pro Asp
 385 390 395 400
 Gly Thr Ile Ser Gly Gly Ile Cys Val Ser His Ser Asp Pro Ala Leu
 405 410 415
 Gly Ser Val Ala Gly Gln Cys Leu Cys Lys Glu Asn Val Glu Gly Ala
 420 425 430
 Lys Cys Asp Gln Cys Lys Pro Asn His Tyr Gly Leu Ser Ala Thr Asp
 435 440 445
 Pro Leu Gly Cys Gln Pro Cys Asp Cys Asn Pro Leu Gly Ser Leu Pro
 450 455 460
 Phe Leu Thr Cys Asp Val Asp Thr Gly Gln Cys Leu Cys Leu Ser Tyr
 465 470 475 480

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Val	Thr	Gly	Ala	His	Cys	Glu	Glu	Cys	Thr	Val	Gly	Tyr	Trp	Gly	Leu
				485					490					495	
Gly	Asn	His	Leu	His	Gly	Cys	Ser	Pro	Cys	Asp	Cys	Asp	Ile	Gly	Gly
			500					505					510		
Ala	Tyr	Ser	Asn	Val	Cys	Ser	Pro	Lys	Asn	Gly	Gln	Cys	Glu	Cys	Arg
		515					520					525			
Pro	His	Val	Thr	Gly	Arg	Ser	Cys	Ser	Glu	Pro	Ala	Pro	Gly	Tyr	Phe
	530					535					540				
Phe	Ala	Pro	Leu	Asn	Phe	Tyr	Leu	Tyr	Glu	Ala	Glu	Glu	Ala	Thr	Thr
545				550						555					560
Leu	Gln	Gly	Leu	Ala	Pro	Leu	Gly	Ser	Glu	Thr	Phe	Gly	Gln	Ser	Pro
			565						570					575	
Ala	Val	His	Val	Val	Leu	Gly	Glu	Pro	Val	Pro	Gly	Asn	Pro	Val	Thr
			580					585					590		
Trp	Thr	Gly	Pro	Gly	Phe	Ala	Arg	Val	Leu	Pro	Gly	Ala	Gly	Leu	Arg
		595					600					605			
Phe	Ala	Val	Asn	Asn	Ile	Pro	Phe	Pro	Val	Asp	Phe	Thr	Ile	Ala	Ile
610					615						620				
His	Tyr	Glu	Thr	Gln	Ser	Ala	Ala	Asp	Trp	Thr	Val	Gln	Ile	Val	Val
625				630						635					640
Asn	Pro	Pro	Gly	Gly	Ser	Glu	His	Cys	Ile	Pro	Lys	Thr	Leu	Gln	Ser
			645						650					655	
Lys	Pro	Gln	Ser	Phe	Ala	Leu	Pro	Ala	Ala	Thr	Arg	Ile	Met	Leu	Leu
		660						665					670		
Pro	Thr	Pro	Ile	Cys	Leu	Glu	Pro	Asp	Val	Gln	Tyr	Ser	Ile	Asp	Val
		675					680					685			
Tyr	Phe	Ser	Gln	Pro	Leu	Gln	Gly	Glu	Ser	His	Ala	His	Ser	His	Val
	690					695					700				
Leu	Val	Asp	Ser	Leu	Gly	Leu	Ile	Pro	Gln	Ile	Asn	Ser	Leu	Glu	Asn
705					710					715					720
Phe	Cys	Ser	Lys	Gln	Asp	Leu	Asp	Glu	Tyr	Gln	Leu	His	Asn	Cys	Val
			725						730					735	
Glu	Ile	Ala	Ser	Ala	Met	Gly	Pro	Gln	Val	Leu	Pro	Gly	Ala	Cys	Glu
			740					745					750		
Arg	Leu	Ile	Ile	Ser	Met	Ser	Ala	Lys	Leu	His	Asp	Gly	Ala	Val	Ala
		755					760					765			
Cys	Lys	Cys	His	Pro	Gln	Gly	Ser	Val	Gly	Ser	Ser	Cys	Ser	Arg	Leu
	770					775						780			
Gly	Gly	Gln	Cys	Gln	Cys	Lys	Pro	Leu	Val	Val	Gly	Arg	Cys	Cys	Asp
785				790						795					800
Arg	Cys	Ser	Thr	Gly	Ser	Tyr	Asp	Leu	Gly	His	His	Gly	Cys	His	Pro
			805						810					815	
Cys	His	Cys	His	Pro	Gln	Gly	Ser	Lys	Asp	Thr	Val	Cys	Asp	Gln	Val
			820					825					830		
Thr	Gly	Gln	Cys	Pro	Cys	His	Gly	Glu	Val	Ser	Gly	Arg	Arg	Cys	Asp
		835					840					845			
Arg	Cys	Leu	Ala	Gly	Tyr	Phe	Gly	Phe	Pro	Ser	Cys	His	Pro	Cys	Pro
	850					855						860			
Cys	Asn	Arg	Phe	Ala	Glu	Leu	Cys	Asp	Pro	Glu	Thr	Gly	Ser	Cys	Phe
865					870					875					880
Asn	Cys	Gly	Gly	Phe	Thr	Thr	Gly	Arg	Asn	Cys	Glu	Arg	Cys	Ile	Asp
			885						890					895	
Gly	Tyr	Tyr	Gly	Asn	Pro	Ser	Ser	Gly	Gln	Pro	Cys	Arg	Pro	Cys	Leu

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900					905					910					
Cys	Pro	Asp	Asp	Pro	Ser	Ser	Asn	Gln	Tyr	Phe	Ala	His	Ser	Cys	Tyr
		915					920					925			
Gln	Asn	Leu	Trp	Ser	Ser	Asp	Val	Ile	Cys	Asn	Cys	Leu	Gln	Gly	Tyr
		930				935					940				
Thr	Gly	Thr	Gln	Cys	Gly	Glu	Cys	Ser	Thr	Gly	Phe	Tyr	Gly	Asn	Pro
945					950					955					960
Arg	Ile	Ser	Gly	Ala	Pro	Cys	Gln	Pro	Cys	Ala	Cys	Asn	Asn	Asn	Ile
				965						970					975
Asp	Val	Thr	Asp	Pro	Glu	Ser	Cys	Ser	Arg	Val	Thr	Gly	Glu	Cys	Leu
			980					985					990		
Arg	Cys	Leu	His	Asn	Thr	Gln	Gly	Ala	Asn	Cys	Gln	Leu	Cys	Lys	Pro
		995					1000					1005			
Gly	His	Tyr	Gly	Ser	Ala	Leu	Asn	Gln	Thr	Cys	Arg	Arg	Cys	Ser	
	1010					1015					1020				
Cys	His	Ala	Ser	Gly	Val	Ser	Pro	Met	Glu	Cys	Pro	Pro	Gly	Gly	
	1025					1030					1035				
Gly	Ala	Cys	Leu	Cys	Asp	Pro	Val	Thr	Gly	Ala	Cys	Pro	Cys	Leu	
	1040					1045					1050				
Pro	Asn	Val	Thr	Gly	Leu	Ala	Cys	Asp	Arg	Cys	Ala	Asp	Gly	Tyr	
	1055					1060					1065				
Trp	Asn	Leu	Val	Pro	Gly	Arg	Gly	Cys	Gln	Ser	Cys	Asp	Cys	Asp	
	1070					1075					1080				
Pro	Arg	Thr	Ser	Gln	Ser	His	Cys	Asp	Gln	Leu	Thr	Gly	Gln		
	1085					1090					1095				
Cys	Pro	Cys	Lys	Leu	Gly	Tyr	Gly	Gly	Lys	Arg	Cys	Ser	Glu	Cys	
	1100					1105					1110				
Gln	Glu	Asn	Tyr	Tyr	Gly	Asp	Pro	Pro	Gly	Arg	Cys	Ile	Pro	Cys	
	1115					1120					1125				
Asp	Cys	Asn	Arg	Ala	Gly	Thr	Gln	Lys	Pro	Ile	Cys	Asp	Pro	Asp	
	1130					1135					1140				
Thr	Gly	Met	Cys	Arg	Cys	Arg	Glu	Gly	Val	Ser	Gly	Gln	Arg	Cys	
	1145					1150					1155				
Asp	Arg	Cys	Ala	Arg	Gly	His	Ser	Gln	Glu	Phe	Pro	Thr	Cys	Leu	
	1160					1165					1170				
Gln	Cys	His	Leu	Cys	Phe	Asp	Gln	Trp	Asp	His	Thr	Ile	Ser	Ser	
	1175					1180					1185				
Leu	Ser	Lys	Ala	Val	Gln	Gly	Leu	Met	Arg	Leu	Ala	Ala	Asn	Met	
	1190					1195					1200				
Glu	Asp	Lys	Arg	Glu	Thr	Leu	Pro	Val	Cys	Glu	Ala	Asp	Phe	Lys	
	1205					1210					1215				
Asp	Leu	Arg	Gly	Asn	Val	Ser	Glu	Ile	Glu	Arg	Ile	Leu	Lys	His	
	1220					1225					1230				
Pro	Val	Phe	Pro	Ser	Gly	Lys	Phe	Leu	Lys	Val	Lys	Asp	Tyr	His	
	1235					1240					1245				
Asp	Ser	Val	Arg	Arg	Gln	Ile	Met	Gln	Leu	Asn	Glu	Gln	Leu	Lys	
	1250					1255					1260				
Ala	Val	Tyr	Glu	Phe	Gln	Asp	Leu	Lys	Asp	Thr	Ile	Glu	Arg	Ala	
	1265					1270					1275				
Lys	Asn	Glu	Ala	Asp	Leu	Leu	Leu	Glu	Asp	Leu	Gln	Glu	Glu	Ile	
	1280					1285					1290				
Asp	Leu	Gln	Ser	Ser	Val	Leu	Asn	Ala	Ser	Ile	Ala	Asp	Ser	Ser	
	1295					1300					1305				

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Glu	Asn	Ile	Lys	Lys	Tyr	Tyr	His	Ile	Ser	Ser	Ser	Ala	Glu	Lys
1310						1315					1320			
Lys	Ile	Asn	Glu	Thr	Ser	Ser	Thr	Ile	Asn	Thr	Ser	Ala	Asn	Thr
1325						1330					1335			
Arg	Asn	Asp	Leu	Leu	Thr	Ile	Leu	Asp	Thr	Leu	Thr	Ser	Lys	Gly
1340						1345					1350			
Asn	Leu	Ser	Leu	Glu	Arg	Leu	Lys	Gln	Ile	Lys	Ile	Pro	Asp	Ile
1355						1360					1365			
Gln	Ile	Leu	Asn	Glu	Lys	Val	Cys	Gly	Asp	Pro	Gly	Asn	Val	Pro
1370						1375					1380			
Cys	Val	Pro	Leu	Pro	Cys	Gly	Gly	Ala	Leu	Cys	Thr	Gly	Arg	Lys
1385						1390					1395			
Gly	His	Arg	Lys	Cys	Arg	Gly	Pro	Gly	Cys	His	Gly	Ser	Leu	Thr
1400						1405					1410			
Leu	Ser	Thr	Asn	Ala	Leu	Gln	Lys	Ala	Gln	Glu	Ala	Lys	Ser	Ile
1415						1420					1425			
Ile	Arg	Asn	Leu	Asp	Lys	Gln	Val	Arg	Gly	Leu	Lys	Asn	Gln	Ile
1430						1435					1440			
Glu	Ser	Ile	Ser	Glu	Gln	Ala	Glu	Val	Ser	Lys	Asn	Asn	Ala	Leu
1445						1450					1455			
Gln	Leu	Arg	Glu	Lys	Leu	Gly	Asn	Ile	Arg	Asn	Gln	Ser	Asp	Ser
1460						1465					1470			
Glu	Glu	Glu	Asn	Ile	Asn	Leu	Phe	Ile	Lys	Lys	Val	Lys	Asn	Phe
1475						1480					1485			
Leu	Leu	Glu	Glu	Asn	Val	Pro	Pro	Glu	Asp	Ile	Glu	Lys	Val	Ala
1490						1495					1500			
Asn	Gly	Val	Leu	Asp	Ile	His	Leu	Pro	Ile	Pro	Ser	Gln	Asn	Leu
1505						1510					1515			
Thr	Asp	Glu	Leu	Val	Lys	Ile	Gln	Lys	His	Met	Gln	Leu	Cys	Glu
1520						1525					1530			
Asp	Tyr	Arg	Thr	Asp	Glu	Asn	Arg	Leu	Asn	Glu	Glu	Ala	Asp	Gly
1535						1540					1545			
Ala	Gln	Lys	Leu	Leu	Val	Lys	Ala	Lys	Ala	Ala	Glu	Lys	Ala	Ala
1550						1555					1560			
Asn	Ile	Leu	Leu	Asn	Leu	Asp	Lys	Thr	Leu	Asn	Gln	Leu	Gln	Gln
1565						1570					1575			
Ala	Gln	Ile	Thr	Gln	Gly	Arg	Ala	Asn	Ser	Thr	Ile	Thr	Gln	Leu
1580						1585					1590			
Thr	Ala	Asn	Ile	Thr	Lys	Ile	Lys	Lys	Asn	Val	Leu	Gln	Ala	Glu
1595						1600					1605			
Asn	Gln	Thr	Arg	Glu	Met	Lys	Ser	Glu	Leu	Glu	Leu	Ala	Lys	Gln
1610						1615					1620			
Arg	Ser	Gly	Leu	Glu	Asp	Gly	Leu	Ser	Leu	Leu	Gln	Thr	Lys	Leu
1625						1630					1635			
Gln	Arg	His	Gln	Asp	His	Ala	Val	Asn	Ala	Lys	Val	Gln	Ala	Glu
1640						1645					1650			
Ser	Ala	Gln	His	Gln	Ala	Gly	Ser	Leu	Glu	Lys	Glu	Phe	Val	Glu
1655						1660					1665			
Leu	Lys	Lys	Gln	Tyr	Ala	Ile	Leu	Gln	Arg	Lys	Thr	Ser	Thr	Thr
1670						1675					1680			
Gly	Leu	Thr	Lys	Glu	Thr	Leu	Gly	Lys	Val	Lys	Gln	Leu	Lys	Asp
1685						1690					1695			

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Ala Ala Glu Lys Leu Ala Gly Asp Thr Glu Ala Lys Ile Arg Arg
 1700 1705 1710

Ile Thr Asp Leu Glu Arg Lys Ile Gln Asp Leu Asn Leu Ser Arg
 1715 1720 1725

Gln Ala Lys Ala Asp Gln Leu Arg Ile Leu Glu Asp Gln Val Val
 1730 1735 1740

Ala Ile Lys Asn Glu Ile Val Glu Gln Glu Lys Lys Tyr Ala Arg
 1745 1750 1755

Cys Tyr Ser
 1760

<210> SEQ ID NO 41
 <211> LENGTH: 1101
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Gln Phe Gln Leu Thr Leu Phe Leu His Leu Gly Trp Leu Ser Tyr
 1 5 10 15

Ser Lys Ala Gln Asp Asp Cys Asn Arg Gly Ala Cys His Pro Thr Thr
 20 25 30

Gly Asp Leu Leu Val Gly Arg Asn Thr Gln Leu Met Ala Ser Ser Thr
 35 40 45

Cys Gly Leu Ser Arg Ala Gln Lys Tyr Cys Ile Leu Ser Tyr Leu Glu
 50 55 60

Gly Glu Gln Lys Cys Phe Ile Cys Asp Ser Arg Phe Pro Tyr Asp Pro
 65 70 75 80

Tyr Asp Gln Pro Asn Ser His Thr Ile Glu Asn Val Ile Val Ser Phe
 85 90 95

Glu Pro Asp Arg Glu Lys Lys Trp Trp Gln Ser Glu Asn Gly Leu Asp
 100 105 110

His Val Ser Ile Arg Leu Asp Leu Glu Ala Leu Phe Arg Phe Ser His
 115 120 125

Leu Ile Leu Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu Val Glu
 130 135 140

Arg Ser Thr Asp Tyr Gly His Asn Trp Lys Val Phe Lys Tyr Phe Ala
 145 150 155 160

Lys Asp Cys Ala Thr Ser Phe Pro Asn Ile Thr Ser Gly Gln Ala Gln
 165 170 175

Gly Val Gly Asp Ile Val Cys Asp Ser Lys Tyr Ser Asp Ile Glu Pro
 180 185 190

Ser Thr Gly Gly Glu Val Val Leu Lys Val Leu Asp Pro Ser Phe Glu
 195 200 205

Ile Glu Asn Pro Tyr Ser Pro Tyr Ile Gln Asp Leu Val Thr Leu Thr
 210 215 220

Asn Leu Arg Ile Asn Phe Thr Lys Leu His Thr Leu Gly Asp Ala Leu
 225 230 235 240

Leu Gly Arg Arg Gln Asn Asp Ser Leu Asp Lys Tyr Tyr Tyr Ala Leu
 245 250 255

Tyr Glu Met Ile Val Arg Gly Ser Cys Phe Cys Asn Gly His Ala Ser
 260 265 270

Glu Cys Arg Pro Met Gln Lys Met Arg Gly Asp Val Phe Ser Pro Pro
 275 280 285

Gly Met Val His Gly Gln Cys Val Cys Gln His Asn Thr Asp Gly Pro
 290 295 300

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Asn Cys Glu Arg Cys Lys Asp Phe Phe Gln Asp Ala Pro Trp Arg Pro
 305 310 315 320

Ala Ala Asp Leu Gln Asp Asn Ala Cys Arg Ser Cys Ser Cys Asn Ser
 325 330 335

His Ser Ser Arg Cys His Phe Asp Met Thr Thr Tyr Leu Ala Ser Gly
 340 345 350

Gly Leu Ser Gly Gly Val Cys Glu Asp Cys Gln His Asn Thr Glu Gly
 355 360 365

Gln His Cys Asp Arg Cys Arg Pro Leu Phe Tyr Arg Asp Pro Leu Lys
 370 375

Thr Ile Ser Asp Pro Tyr Ala Cys Ile Pro Cys Glu Cys Asp Pro Asp
 385 390 395 400

Gly Thr Ile Ser Gly Gly Ile Cys Val Ser His Ser Asp Pro Ala Leu
 405 410 415

Gly Ser Val Ala Gly Gln Cys Leu Cys Lys Glu Asn Val Glu Gly Ala
 420 425 430

Lys Cys Asp Gln Cys Lys Pro Asn His Tyr Gly Leu Ser Ala Thr Asp
 435 440 445

Pro Leu Gly Cys Gln Pro Cys Asp Cys Asn Pro Leu Gly Ser Leu Pro
 450 455 460

Phe Leu Thr Cys Asp Val Asp Thr Gly Gln Cys Leu Cys Leu Ser Tyr
 465 470 475 480

Val Thr Gly Ala His Cys Glu Glu Cys Thr Val Gly Tyr Trp Gly Leu
 485 490 495

Gly Asn His Leu His Gly Cys Ser Pro Cys Asp Cys Asp Ile Gly Gly
 500 505 510

Ala Tyr Ser Asn Val Cys Ser Pro Lys Asn Gly Gln Cys Glu Cys Arg
 515 520 525

Pro His Val Thr Gly Arg Ser Cys Ser Glu Pro Ala Pro Gly Tyr Phe
 530 535 540

Phe Ala Pro Leu Asn Phe Tyr Leu Tyr Glu Ala Glu Glu Ala Thr Thr
 545 550 555 560

Leu Gln Gly Leu Ala Pro Leu Gly Ser Glu Thr Phe Gly Gln Ser Pro
 565 570 575

Ala Val His Val Val Leu Gly Glu Pro Val Pro Gly Asn Pro Val Thr
 580 585 590

Trp Thr Gly Pro Gly Phe Ala Arg Val Leu Pro Gly Ala Gly Leu Arg
 595 600 605

Phe Ala Val Asn Asn Ile Pro Phe Pro Val Asp Phe Thr Ile Ala Ile
 610 615 620

His Tyr Glu Thr Gln Ser Ala Ala Asp Trp Thr Val Gln Ile Val Val
 625 630 635 640

Asn Pro Pro Gly Gly Ser Glu His Cys Ile Pro Lys Thr Leu Gln Ser
 645 650 655

Lys Pro Gln Ser Phe Ala Leu Pro Ala Ala Thr Arg Ile Met Leu Leu
 660 665 670

Pro Thr Pro Ile Cys Leu Glu Pro Asp Val Gln Tyr Ser Ile Asp Val
 675 680 685

Tyr Phe Ser Gln Pro Leu Gln Gly Glu Ser His Ala His Ser His Val
 690 695 700

Leu Val Asp Ser Leu Gly Leu Ile Pro Gln Ile Asn Ser Leu Glu Asn
 705 710 715 720

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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

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Gly Thr Ile Ser Gly Gly Ile Cys Val Ser His Ser Asp Pro Ala Leu
 405 410 415

Gly Ser Val Ala Gly Gln Cys Leu Cys Lys Glu Asn Val Glu Gly Ala
 420 425 430

Lys Cys Asp Gln Cys Lys Pro Asn His Tyr Gly Leu Ser Ala Thr Asp
 435 440 445

Pro Leu Gly Cys Gln Pro Cys Asp Cys Asn Pro Leu Gly Ser Leu Pro
 450 455 460

Phe Leu Thr Cys Asp Val Asp Thr Gly Gln Cys Leu Cys Leu Ser Tyr
 465 470 475 480

Val Thr Gly Ala His Cys Glu Glu Cys Thr Val Gly Tyr Trp Gly Leu
 485 490 495

Gly Asn His Leu His Gly Cys Ser Pro Cys Asp Cys Asp Ile Gly Gly
 500 505 510

Ala Tyr Ser Asn Val Cys Ser Pro Lys Asn Gly Gln Cys Glu Cys Arg
 515 520 525

Pro His Val Thr Gly Arg Ser Cys Ser Glu Pro Ala Pro Gly Tyr Phe
 530 535 540

Phe Ala Pro Leu Asn Phe Tyr Leu Tyr Glu Ala Glu Glu Ala Thr Thr
 545 550 555 560

Leu Gln Gly Leu Ala Pro Leu Gly Ser Glu Thr Phe Gly Gln Ser Pro
 565 570 575

Ala Val His Val Val Leu Gly Glu Pro Val Pro Gly Asn Pro Val Thr
 580 585 590

Trp Thr Gly Pro Gly Phe Ala Arg Val Leu Pro Gly Ala Gly Leu Arg
 595 600 605

Phe Ala Val Asn Asn Ile Pro Phe Pro Val Asp Phe Thr Ile Ala Ile
 610 615 620

His Tyr Glu Thr Gln Ser Ala Ala Asp Trp Thr Val Gln Ile Val Val
 625 630 635 640

Asn Pro Pro Gly Gly Ser Glu His Cys Ile Pro Lys Thr Leu Gln Ser
 645 650 655

Lys Pro Gln Ser Phe Ala Leu Pro Ala Ala Thr Arg Ile Met Leu Leu
 660 665 670

Pro Thr Pro Ile Cys Leu Glu Pro Asp Val Gln Tyr Ser Ile Asp Val
 675 680 685

Tyr Phe Ser Gln Pro Leu Gln Gly Glu Ser His Ala His Ser His Val
 690 695 700

Leu Val Asp Ser Ala Ala Val Gln Trp His Asn Leu Gly Ser Leu Gln
 705 710 715 720

Pro Pro Pro Pro Glu Cys Lys Gln Phe Ser Cys Phe Ser Phe Pro Ser
 725 730 735

Ser Trp Asp Tyr Arg His Pro Pro Pro His Leu Ala Asn Phe Cys Ile
 740 745 750

Phe Ser Arg Asp Gly Val Ser Pro His Trp Pro Gly Trp Ser Gln Thr
 755 760 765

Pro Asp Leu Arg
 770

<210> SEQ ID NO 43
 <211> LENGTH: 1609
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 43

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

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Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro
 420 425 430
 Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp
 435 440 445
 Pro Ser Gly Ser Ile Asp Glu Cys Asn Ile Glu Thr Gly Arg Cys Val
 450 455 460
 Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly
 465 470 475 480
 Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe
 485 490 495
 Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val
 500 505 510
 Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala
 515 520 525
 Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg
 530 535 540
 Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile
 545 550 555 560
 Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn
 565 570 575
 Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala
 580 585 590
 Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu
 595 600 605
 Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val
 610 615 620
 Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr
 625 630 635 640
 Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile
 645 650 655
 Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr
 660 665 670
 Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu
 675 680 685
 Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys
 690 695 700
 Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro
 705 710 715 720
 Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu
 725 730 735
 Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu
 740 745 750
 Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser
 755 760 765
 Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val
 770 775 780
 Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr
 785 790 795 800
 Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu
 805 810 815
 Gly Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp
 820 825 830
 Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu

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Gln	Ala	Ala	Arg	Val	His	Glu	Glu	Ala	Lys	Arg	Ala	Gly	Asp	Lys
1250						1255					1260			
Ala	Val	Glu	Ile	Tyr	Ala	Ser	Val	Ala	Gln	Leu	Ser	Pro	Leu	Asp
1265						1270					1275			
Ser	Glu	Thr	Leu	Glu	Asn	Glu	Ala	Asn	Asn	Ile	Lys	Met	Glu	Ala
1280						1285					1290			
Glu	Asn	Leu	Glu	Gln	Leu	Ile	Asp	Gln	Lys	Leu	Lys	Asp	Tyr	Glu
1295						1300					1305			
Asp	Leu	Arg	Glu	Asp	Met	Arg	Gly	Lys	Glu	Leu	Glu	Val	Lys	Asn
1310						1315					1320			
Leu	Leu	Glu	Lys	Gly	Lys	Thr	Glu	Gln	Gln	Thr	Ala	Asp	Gln	Leu
1325						1330					1335			
Leu	Ala	Arg	Ala	Asp	Ala	Ala	Lys	Ala	Leu	Ala	Glu	Glu	Ala	Ala
1340						1345					1350			
Lys	Lys	Gly	Arg	Asp	Thr	Leu	Gln	Glu	Ala	Asn	Asp	Ile	Leu	Asn
1355						1360					1365			
Asn	Leu	Lys	Asp	Phe	Asp	Arg	Arg	Val	Asn	Asp	Asn	Lys	Thr	Ala
1370						1375					1380			
Ala	Glu	Glu	Ala	Leu	Arg	Lys	Ile	Pro	Ala	Ile	Asn	Gln	Thr	Ile
1385						1390					1395			
Thr	Glu	Ala	Asn	Glu	Lys	Thr	Arg	Glu	Ala	Gln	Gln	Ala	Leu	Gly
1400						1405					1410			
Ser	Ala	Ala	Ala	Asp	Ala	Thr	Glu	Ala	Lys	Asn	Lys	Ala	His	Glu
1415						1420					1425			
Ala	Glu	Arg	Ile	Ala	Ser	Ala	Val	Gln	Lys	Asn	Ala	Thr	Ser	Thr
1430						1435					1440			
Lys	Ala	Glu	Ala	Glu	Arg	Thr	Phe	Ala	Glu	Val	Thr	Asp	Leu	Asp
1445						1450					1455			
Asn	Glu	Val	Asn	Asn	Met	Leu	Lys	Gln	Leu	Gln	Glu	Ala	Glu	Lys
1460						1465					1470			
Glu	Leu	Lys	Arg	Lys	Gln	Asp	Asp	Ala	Asp	Gln	Asp	Met	Met	Met
1475						1480					1485			
Ala	Gly	Met	Ala	Ser	Gln	Ala	Ala	Gln	Glu	Ala	Glu	Ile	Asn	Ala
1490						1495					1500			
Arg	Lys	Ala	Lys	Asn	Ser	Val	Thr	Ser	Leu	Leu	Ser	Ile	Ile	Asn
1505						1510					1515			
Asp	Leu	Leu	Glu	Gln	Leu	Gly	Gln	Leu	Asp	Thr	Val	Asp	Leu	Asn
1520						1525					1530			
Lys	Leu	Asn	Glu	Ile	Glu	Gly	Thr	Leu	Asn	Lys	Ala	Lys	Asp	Glu
1535						1540					1545			
Met	Lys	Val	Ser	Asp	Leu	Asp	Arg	Lys	Val	Ser	Asp	Leu	Glu	Asn
1550						1555					1560			
Glu	Ala	Lys	Lys	Gln	Glu	Ala	Ala	Ile	Met	Asp	Tyr	Asn	Arg	Asp
1565						1570					1575			
Ile	Glu	Glu	Ile	Met	Lys	Asp	Ile	Arg	Asn	Leu	Glu	Asp	Ile	Arg
1580						1585					1590			
Lys	Thr	Leu	Pro	Ser	Gly	Cys	Phe	Asn	Thr	Pro	Ser	Ile	Glu	Lys
1595						1600					1605			

Pro

<210> SEQ ID NO 44

<211> LENGTH: 1193

<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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

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Lys Arg Asp Ser Ala Arg Leu Gly Pro Phe Gly Thr Cys Ile Pro Cys
 405 410 415
 Asn Cys Gln Gly Gly Gly Ala Cys Asp Pro Asp Thr Gly Asp Cys Tyr
 420 425 430
 Ser Gly Asp Glu Asn Pro Asp Ile Glu Cys Ala Asp Cys Pro Leu Gly
 435 440 445
 Phe Tyr Asn Asp Pro His Asp Pro Arg Ser Cys Lys Pro Cys Pro Cys
 450 455 460
 His Asn Gly Phe Ser Cys Ser Val Met Pro Glu Thr Glu Glu Val Val
 465 470 475 480
 Cys Asn Asn Cys Pro Pro Gly Val Thr Gly Ala Arg Cys Glu Leu Cys
 485 490 495
 Ala Asp Gly Tyr Phe Gly Asp Pro Phe Gly Glu His Gly Pro Val Arg
 500 505 510
 Pro Cys Gln Pro Cys Gln Cys Asn Asn Asn Val Asp Pro Ser Ala Ser
 515 520 525
 Gly Asn Cys Asp Arg Leu Thr Gly Arg Cys Leu Lys Cys Ile His Asn
 530 535 540
 Thr Ala Gly Ile Tyr Cys Asp Gln Cys Lys Ala Gly Tyr Phe Gly Asp
 545 550 555 560
 Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Arg Ala Cys Asn Cys Asn
 565 570 575
 Pro Met Gly Ser Glu Pro Val Gly Cys Arg Ser Asp Gly Thr Cys Val
 580 585 590
 Cys Lys Pro Gly Phe Gly Gly Pro Asn Cys Glu His Gly Ala Phe Ser
 595 600 605
 Cys Pro Ala Cys Tyr Asn Gln Val Lys Ile Gln Met Asp Gln Phe Met
 610 615 620
 Gln Gln Leu Gln Arg Met Glu Ala Leu Ile Ser Lys Ala Gln Gly Gly
 625 630 635 640
 Asp Gly Val Val Pro Asp Thr Glu Leu Glu Gly Arg Met Gln Gln Ala
 645 650 655
 Glu Gln Ala Leu Gln Asp Ile Leu Arg Asp Ala Gln Ile Ser Glu Gly
 660 665 670
 Ala Ser Arg Ser Leu Gly Leu Gln Leu Ala Lys Val Arg Ser Gln Glu
 675 680 685
 Asn Ser Tyr Gln Ser Arg Leu Asp Asp Leu Lys Met Thr Val Glu Arg
 690 695 700
 Val Arg Ala Leu Gly Ser Gln Tyr Gln Asn Arg Val Arg Asp Thr His
 705 710 715 720
 Arg Leu Ile Thr Gln Met Gln Leu Ser Leu Ala Glu Ser Glu Ala Ser
 725 730 735
 Leu Gly Asn Thr Asn Ile Pro Ala Ser Asp His Tyr Val Gly Pro Asn
 740 745 750
 Gly Phe Lys Ser Leu Ala Gln Glu Ala Thr Arg Leu Ala Glu Ser His
 755 760 765
 Val Glu Ser Ala Ser Asn Met Glu Gln Leu Thr Arg Glu Thr Glu Asp
 770 775 780
 Tyr Ser Lys Gln Ala Leu Ser Leu Val Arg Lys Ala Leu His Glu Gly
 785 790 795 800
 Val Gly Ser Gly Ser Gly Ser Pro Asp Gly Ala Val Val Gln Gly Leu
 805 810 815
 Val Glu Lys Leu Glu Lys Thr Lys Ser Leu Ala Gln Gln Leu Thr Arg

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820				825				830							
Glu	Ala	Thr	Gln	Ala	Glu	Ile	Glu	Ala	Asp	Arg	Ser	Tyr	Gln	His	Ser
	835						840					845			
Leu	Arg	Leu	Leu	Asp	Ser	Val	Ser	Arg	Leu	Gln	Gly	Val	Ser	Asp	Gln
	850					855					860				
Ser	Phe	Gln	Val	Glu	Glu	Ala	Lys	Arg	Ile	Lys	Gln	Lys	Ala	Asp	Ser
865					870					875					880
Leu	Ser	Ser	Leu	Val	Thr	Arg	His	Met	Asp	Glu	Phe	Lys	Arg	Thr	Gln
			885						890						895
Lys	Asn	Leu	Gly	Asn	Trp	Lys	Glu	Glu	Ala	Gln	Gln	Leu	Leu	Gln	Asn
			900						905					910	
Gly	Lys	Ser	Gly	Arg	Glu	Lys	Ser	Asp	Gln	Leu	Leu	Ser	Arg	Ala	Asn
		915					920						925		
Leu	Ala	Lys	Ser	Arg	Ala	Gln	Glu	Ala	Leu	Ser	Met	Gly	Asn	Ala	Thr
	930					935					940				
Phe	Tyr	Glu	Val	Glu	Ser	Ile	Leu	Lys	Asn	Leu	Arg	Glu	Phe	Asp	Leu
945					950					955					960
Gln	Val	Asp	Asn	Arg	Lys	Ala	Glu	Ala	Glu	Glu	Ala	Met	Lys	Arg	Leu
			965				970								975
Ser	Tyr	Ile	Ser	Gln	Lys	Val	Ser	Asp	Ala	Ser	Asp	Lys	Thr	Gln	Gln
			980						985						990
Ala	Glu	Arg	Ala	Leu	Gly	Ser	Ala	Ala	Ala	Asp	Ala	Gln	Arg	Ala	Lys
		995					1000							1005	
Asn	Gly	Ala	Gly	Glu	Ala	Leu	Glu	Ile	Ser	Ser	Glu	Ile	Glu	Gln	
	1010					1015					1020				
Glu	Ile	Gly	Ser	Leu	Asn	Leu	Glu	Ala	Asn	Val	Thr	Ala	Asp	Gly	
	1025					1030					1035				
Ala	Leu	Ala	Met	Glu	Lys	Gly	Leu	Ala	Ser	Leu	Lys	Ser	Glu	Met	
	1040					1045					1050				
Arg	Glu	Val	Glu	Gly	Glu	Leu	Glu	Arg	Lys	Glu	Leu	Glu	Phe	Asp	
	1055					1060					1065				
Thr	Asn	Met	Asp	Ala	Val	Gln	Met	Val	Ile	Thr	Glu	Ala	Gln	Lys	
	1070					1075					1080				
Val	Asp	Thr	Arg	Ala	Lys	Asn	Ala	Gly	Val	Thr	Ile	Gln	Asp	Thr	
	1085					1090					1095				
Leu	Asn	Thr	Leu	Asp	Gly	Leu	Leu	His	Leu	Met	Asp	Gln	Pro	Leu	
	1100					1105					1110				
Ser	Val	Asp	Glu	Glu	Gly	Leu	Val	Leu	Leu	Glu	Gln	Lys	Leu	Ser	
	1115					1120					1125				
Arg	Ala	Lys	Thr	Gln	Ile	Asn	Ser	Gln	Leu	Arg	Pro	Met	Met	Ser	
	1130					1135					1140				
Glu	Leu	Glu	Glu	Arg	Ala	Arg	Gln	Gln	Arg	Gly	His	Leu	His	Leu	
	1145					1150					1155				
Leu	Glu	Thr	Ser	Ile	Asp	Gly	Ile	Leu	Ala	Asp	Val	Lys	Asn	Leu	
	1160					1165					1170				
Glu	Asn	Ile	Arg	Asp	Asn	Leu	Pro	Pro	Gly	Cys	Tyr	Asn	Thr	Gln	
	1175					1180					1185				
Ala	Leu	Glu	Gln	Gln											
	1190														

<210> SEQ ID NO 45
 <211> LENGTH: 1111
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 45

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

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85					90					95					
Gln	Asp	Glu	Ser	Thr	Trp	Trp	Gln	Ser	Pro	Ser	Met	Ala	Phe	Gly	Val
			100					105					110		
Gln	Tyr	Pro	Thr	Ser	Val	Asn	Ile	Thr	Leu	Arg	Leu	Gly	Lys	Ala	Tyr
		115					120					125			
Glu	Ile	Thr	Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser	Arg	Pro	Glu	Ser
	130					135					140				
Phe	Ala	Ile	Tyr	Lys	Arg	Ser	Arg	Ala	Asp	Gly	Pro	Trp	Glu	Pro	Tyr
	145				150					155					160
Gln	Phe	Tyr	Ser	Ala	Ser	Cys	Gln	Lys	Thr	Tyr	Gly	Arg	Pro	Glu	Gly
				165					170					175	
Gln	Tyr	Leu	Arg	Pro	Gly	Glu	Asp	Glu	Arg	Val	Ala	Phe	Cys	Thr	Ser
			180					185						190	
Glu	Phe	Ser	Asp	Ile	Ser	Pro	Leu	Ser	Gly	Gly	Asn	Val	Ala	Phe	Ser
		195					200				205				
Thr	Leu	Glu	Gly	Arg	Pro	Ser	Ala	Tyr	Asn	Phe	Glu	Glu	Ser	Pro	Gly
	210					215					220				
Leu	Gln	Glu	Trp	Val	Thr	Ser	Thr	Glu	Leu	Leu	Ile	Ser	Leu	Asp	Arg
	225				230				235					240	
Leu	Asn	Thr	Phe	Gly	Asp	Asp	Ile	Phe	Lys	Asp	Pro	Lys	Val	Leu	Gln
			245						250					255	
Ser	Tyr	Tyr	Tyr	Ala	Val	Ser	Asp	Phe	Ser	Val	Gly	Gly	Arg	Cys	Lys
			260					265					270		
Cys	Asn	Gly	His	Ala	Ser	Glu	Cys	Gly	Pro	Asp	Val	Ala	Gly	Gln	Leu
		275					280					285			
Ala	Cys	Arg	Cys	Gln	His	Asn	Thr	Thr	Gly	Thr	Asp	Cys	Glu	Arg	Cys
	290					295					300				
Leu	Pro	Phe	Phe	Gln	Asp	Arg	Pro	Trp	Ala	Arg	Gly	Thr	Ala	Glu	Ala
	305				310					315				320	
Ala	His	Glu	Cys	Leu	Pro	Cys	Asn	Cys	Ser	Gly	Arg	Ser	Glu	Glu	Cys
			325						330					335	
Thr	Phe	Asp	Arg	Glu	Leu	Phe	Arg	Ser	Thr	Gly	His	Gly	Gly	Arg	Cys
			340					345					350		
His	His	Cys	Arg	Asp	His	Thr	Ala	Gly	Pro	His	Cys	Glu	Arg	Cys	Gln
		355					360					365			
Glu	Asn	Phe	Tyr	His	Trp	Asp	Pro	Arg	Met	Pro	Cys	Gln	Pro	Cys	Asp
	370					375					380				
Cys	Gln	Ser	Ala	Gly	Ser	Leu	His	Leu	Gln	Cys	Asp	Asp	Thr	Gly	Thr
	385					390					395			400	
Cys	Ala	Cys	Lys	Pro	Thr	Val	Thr	Gly	Trp	Lys	Cys	Asp	Arg	Cys	Leu
			405						410					415	
Pro	Gly	Phe	His	Ser	Leu	Ser	Glu	Gly	Gly	Cys	Arg	Pro	Cys	Thr	Cys
			420					425					430		
Asn	Pro	Ala	Gly	Ser	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Ser	Gly	Arg	Cys
		435					440						445		
Pro	Cys	Lys	Glu	Asn	Val	Glu	Gly	Asn	Leu	Cys	Asp	Arg	Cys	Arg	Pro
	450					455					460				
Gly	Thr	Phe	Asn	Leu	Gln	Pro	His	Asn	Pro	Ala	Gly	Cys	Ser	Ser	Cys
	465				470					475				480	
Phe	Cys	Tyr	Gly	His	Ser	Lys	Val	Cys	Ala	Ser	Thr	Ala	Gln	Phe	Gln
			485						490					495	
Val	His	His	Ile	Leu	Ser	Asp	Phe	His	Gln	Gly	Ala	Glu	Gly	Trp	Trp
			500					505					510		

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Ala Arg Ser Val Gly Gly Ser Glu His Pro Pro Gln Trp Ser Pro Asn
 515 520 525

Gly Val Leu Leu Ser Pro Glu Asp Glu Glu Glu Leu Thr Ala Pro Glu
 530 535 540

Lys Phe Leu Gly Asp Gln Arg Phe Ser Tyr Gly Gln Pro Leu Ile Leu
 545 550 555 560

Thr Phe Arg Val Pro Pro Gly Asp Ser Pro Leu Pro Val Gln Leu Arg
 565 570 575

Leu Glu Gly Thr Gly Leu Ala Leu Ser Leu Arg His Ser Ser Leu Ser
 580 585 590

Gly Pro Gln Asp Ala Gly His Pro Arg Glu Val Glu Leu Arg Phe His
 595 600 605

Leu Gln Glu Thr Ser Glu Asp Val Ala Pro Pro Leu Pro Pro Phe His
 610 615 620

Phe Gln Arg Leu Leu Ala Asn Leu Thr Ser Leu Arg Leu Arg Val Ser
 625 630 635 640

Pro Gly Pro Ser Pro Ala Gly Pro Val Phe Leu Thr Glu Val Arg Leu
 645 650 655

Thr Ser Ala Arg Pro Gly Leu Ser Pro Pro Ala Ser Trp Val Glu Ile
 660 665 670

Cys Ser Cys Pro Thr Gly Tyr Thr Gly Gln Phe Cys Glu Ser Cys Ala
 675 680 685

Pro Gly Tyr Lys Arg Glu Met Pro Gln Gly Gly Pro Tyr Ala Ser Cys
 690 695 700

Val Pro Cys Thr Cys Asn Gln His Gly Thr Cys Asp Pro Asn Thr Gly
 705 710 715 720

Ile Cys Val Cys Ser His His Thr Glu Gly Pro Ser Cys Glu Arg Cys
 725 730 735

Leu Pro Gly Phe Tyr Gly Asn Pro Phe Ala Gly Gln Ala Asp Asp Cys
 740 745 750

Gln Pro Cys Pro Cys Pro Gly Gln Ser Ala Cys Thr Thr Ile Pro Glu
 755 760 765

Ser Arg Glu Val Val Cys Thr His Cys Pro Pro Gly Gln Arg Gly Arg
 770 775 780

Arg Cys Glu Val Cys Asp Asp Gly Phe Phe Gly Asp Pro Leu Gly Leu
 785 790 795 800

Phe Gly His Pro Gln Pro Cys His Gln Cys Gln Cys Ser Gly Asn Val
 805 810 815

Asp Pro Asn Ala Val Gly Asn Cys Asp Pro Leu Ser Gly His Cys Leu
 820 825 830

Arg Cys Leu His Asn Thr Thr Gly Asp His Cys Glu His Cys Gln Glu
 835 840 845

Gly Phe Tyr Gly Ser Ala Leu Ala Pro Arg Pro Ala Asp Lys Cys Met
 850 855 860

Pro Cys Ser Cys His Pro Gln Gly Ser Val Ser Glu Gln Met Pro Cys
 865 870 875 880

Asp Pro Val Thr Gly Gln Cys Ser Cys Leu Pro His Val Thr Ala Arg
 885 890 895

Asp Cys Ser Arg Cys Tyr Pro Gly Phe Phe Asp Leu Gln Pro Gly Arg
 900 905 910

Gly Cys Arg Ser Cys Lys Cys His Pro Leu Gly Ser Gln Glu Asp Gln
 915 920 925

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Cys His Pro Lys Thr Gly Gln Cys Thr Cys Arg Pro Gly Val Thr Gly
 930 935 940

Gln Ala Cys Asp Arg Cys Gln Leu Gly Phe Phe Gly Phe Ser Ile Lys
 945 950 955 960

Gly Cys Arg Ala Cys Arg Cys Ser Pro Leu Gly Ala Ala Ser Ala Gln
 965 970 975

Cys His Glu Asn Gly Thr Cys Val Cys Arg Pro Gly Phe Glu Gly Tyr
 980 985 990

Lys Cys Asp Arg Cys His Asp Asn Phe Phe Leu Thr Ala Asp Gly Thr
 995 1000 1005

His Cys Gln Gln Cys Pro Ser Cys Tyr Ala Leu Val Lys Glu Glu
 1010 1015 1020

Ala Ala Lys Leu Lys Ala Arg Leu Thr Leu Thr Glu Gly Trp Leu
 1025 1030 1035

Gln Gly Ser Asp Cys Gly Ser Pro Trp Gly Pro Leu Asp Ile Leu
 1040 1045 1050

Leu Gly Glu Ala Pro Arg Gly Asp Val Tyr Gln Gly His His Leu
 1055 1060 1065

Leu Pro Gly Ala Arg Glu Ala Phe Leu Glu Gln Met Met Ser Leu
 1070 1075 1080

Glu Gly Ala Val Lys Ala Ala Arg Glu Gln Leu Gln Arg Leu Asn
 1085 1090 1095

Lys Gly Ala Arg Cys Ala Gln Ala Gly Ser Gln Lys Thr Cys Thr
 1100 1105 1110

Gln Leu Ala Asp Leu Glu Ala Val Leu Glu Ser Ser Glu Glu Glu
 1115 1120 1125

Ile Leu His Ala Ala Ala Ile Leu Ala Ser Leu Glu Ile Pro Gln
 1130 1135 1140

Glu Gly Pro Ser Gln Pro Thr Lys Trp Ser His Leu Ala Thr Glu
 1145 1150 1155

Ala Arg Ala Leu Ala Arg Ser His Arg Asp Thr Ala Thr Lys Ile
 1160 1165 1170

Ala Ala Thr Ala Trp Arg Ala Leu Leu Ala Ser Asn Thr Ser Tyr
 1175 1180 1185

Ala Leu Leu Trp Asn Leu Leu Glu Gly Arg Val Ala Leu Glu Thr
 1190 1195 1200

Gln Arg Asp Leu Glu Asp Arg Tyr Gln Glu Val Gln Ala Ala Gln
 1205 1210 1215

Lys Ala Leu Arg Thr Ala Val Ala Glu Val Leu Pro Glu Ala Glu
 1220 1225 1230

Ser Val Leu Ala Thr Val Gln Gln Val Gly Ala Asp Thr Ala Pro
 1235 1240 1245

Tyr Leu Ala Leu Leu Ala Ser Pro Gly Ala Leu Pro Gln Lys Ser
 1250 1255 1260

Arg Ala Glu Asp Leu Gly Leu Lys Ala Lys Ala Leu Glu Lys Thr
 1265 1270 1275

Val Ala Ser Trp Gln His Met Ala Thr Glu Ala Ala Arg Thr Leu
 1280 1285 1290

Gln Thr Ala Ala Gln Ala Thr Leu Arg Gln Thr Glu Pro Leu Thr
 1295 1300 1305

Lys Leu His Gln Glu Ala Arg Ala Ala Leu Thr Gln Ala Ser Ser
 1310 1315 1320

Ser Val Gln Ala Ala Thr Val Thr Val Met Gly Ala Arg Thr Leu

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1325	1330	1335
Leu Ala Asp Leu Glu Gly Met Lys Leu Gln Phe Pro Arg Pro Lys 1340 1345 1350		
Asp Gln Ala Ala Leu Gln Arg Lys Ala Asp Ser Val Ser Asp Arg 1355 1360 1365		
Leu Leu Ala Asp Thr Arg Lys Lys Thr Lys Gln Ala Glu Arg Met 1370 1375 1380		
Leu Gly Asn Ala Ala Pro Leu Ser Ser Ser Ala Lys Lys Lys Gly 1385 1390 1395		
Arg Glu Ala Glu Val Leu Ala Lys Asp Ser Ala Lys Leu Ala Lys 1400 1405 1410		
Ala Leu Leu Arg Glu Arg Lys Gln Ala His Arg Arg Ala Ser Arg 1415 1420 1425		
Leu Thr Ser Gln Thr Gln Ala Thr Leu Gln Gln Ala Ser Gln Gln 1430 1435 1440		
Val Leu Ala Ser Glu Ala Arg Arg Gln Glu Leu Glu Glu Ala Glu 1445 1450 1455		
Arg Val Gly Ala Gly Leu Ser Glu Met Glu Gln Gln Ile Arg Glu 1460 1465 1470		
Ser Arg Ile Ser Leu Glu Lys Asp Ile Glu Thr Leu Ser Glu Leu 1475 1480 1485		
Leu Ala Arg Leu Gly Ser Leu Asp Thr His Gln Ala Pro Ala Gln 1490 1495 1500		
Ala Leu Asn Glu Thr Gln Trp Ala Leu Glu Arg Leu Arg Leu Gln 1505 1510 1515		
Leu Gly Ser Pro Gly Ser Leu Gln Arg Lys Leu Ser Leu Leu Glu 1520 1525 1530		
Gln Glu Ser Gln Gln Gln Glu Leu Gln Ile Gln Gly Phe Glu Ser 1535 1540 1545		
Asp Leu Ala Glu Ile Arg Ala Asp Lys Gln Asn Leu Glu Ala Ile 1550 1555 1560		
Leu His Ser Leu Pro Glu Asn Cys Ala Ser Trp Gln 1565 1570 1575		

<210> SEQ ID NO 47
 <211> LENGTH: 196
 <212> TYPE: PRT
 <213> ORGANISM: Unknown
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Unknown:
 vWF A3 domain"

<400> SEQUENCE: 47

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

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Thr Ser Glu Met His Gly Ala Arg Pro Gly Ala Ser Lys Ala Val Val
 100 105 110

Ile Leu Val Thr Asp Val Ser Val Asp Ser Val Asp Ala Ala Ala Asp
 115 120 125

Ala Ala Arg Ser Asn Arg Val Thr Val Phe Pro Ile Gly Ile Gly Asp
 130 135 140

Arg Tyr Asp Ala Ala Gln Leu Arg Ile Leu Ala Gly Pro Ala Gly Asp
 145 150 155 160

Ser Asn Val Val Lys Leu Gln Arg Ile Glu Asp Leu Pro Thr Met Val
 165 170 175

Thr Leu Gly Asn Ser Phe Leu His Lys Leu Cys Ser Gly Phe Val Arg
 180 185 190

Ile Cys Thr Gly
 195

<210> SEQ ID NO 48
 <211> LENGTH: 344
 <212> TYPE: PRT
 <213> ORGANISM: Unknown
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Unknown:
 Decorin sequence"

<400> SEQUENCE: 48

Cys Gly Pro Phe Gln Gln Arg Gly Leu Phe Asp Phe Met Leu Glu Asp
 1 5 10 15

Glu Ala Ser Gly Ile Gly Pro Glu Val Pro Asp Asp Arg Asp Phe Glu
 20 25 30

Pro Ser Leu Gly Pro Val Cys Pro Phe Arg Cys Gln Cys His Leu Arg
 35 40 45

Val Val Gln Cys Ser Asp Leu Gly Leu Asp Lys Val Pro Lys Asp Leu
 50 55 60

Pro Pro Asp Thr Thr Leu Leu Asp Leu Gln Asn Asn Lys Ile Thr Glu
 65 70 75 80

Ile Lys Asp Gly Asp Phe Lys Asn Leu Lys Asn Leu His Ala Leu Ile
 85 90 95

Leu Val Asn Asn Lys Ile Ser Lys Val Ser Pro Gly Ala Phe Thr Pro
 100 105 110

Leu Val Lys Leu Glu Arg Leu Tyr Leu Ser Lys Asn Gln Leu Lys Glu
 115 120 125

Leu Pro Glu Lys Met Pro Lys Thr Leu Gln Glu Leu Arg Ala His Glu
 130 135 140

Asn Glu Ile Thr Lys Val Arg Lys Val Thr Phe Asn Gly Leu Asn Gln
 145 150 155 160

Met Ile Val Ile Glu Leu Gly Thr Asn Pro Leu Lys Ser Ser Gly Ile
 165 170 175

Glu Asn Gly Ala Phe Gln Gly Met Lys Lys Leu Ser Tyr Ile Arg Ile
 180 185 190

Ala Asp Thr Asn Ile Thr Ser Ile Pro Gln Gly Leu Pro Pro Ser Leu
 195 200 205

Thr Glu Leu His Leu Asp Gly Asn Lys Ile Ser Arg Val Asp Ala Ala
 210 215 220

Ser Leu Lys Gly Leu Asn Asn Leu Ala Lys Leu Gly Leu Ser Phe Asn
 225 230 235 240

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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 52

Leu Tyr Cys Glu Ile Ala Arg Gly Tyr Ser Leu Lys Arg Lys Val Pro
 1 5 10 15

Asp Gln Ile Arg Ser Arg Lys Ala
 20

<210> SEQ ID NO 53
 <211> LENGTH: 24
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 53

Tyr Ile Gly Leu Lys Asp Ser Lys Ser Pro Ser Glu Leu Ser Ser Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala Cys
 20

<210> SEQ ID NO 54
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 54

Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Arg Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 55
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 55

Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Leu Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 56
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 56

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Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Pro Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 57
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 57

Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Gln Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 58
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 58

Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Trp Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 59
 <211> LENGTH: 23
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 59

Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu Leu Ser Arg Ile
 1 5 10 15

Ala Ser Gln Val Lys Tyr Ala
 20

<210> SEQ ID NO 60
 <211> LENGTH: 24
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"
 <220> FEATURE:
 <221> NAME/KEY: SITE
 <222> LOCATION: (1)..(24)
 <223> OTHER INFORMATION: /note="This sequence may encompass 1-6 'Gly Ser
 Gly Gly' repeating units"

<400> SEQUENCE: 60

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly

-continued

1 5 10 15

Gly Ser Gly Gly Gly Ser Gly Gly
20

<210> SEQ ID NO 61
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 61

Gly Ser Gly Gly Gly Ser Gly Gly
1 5

<210> SEQ ID NO 62
 <211> LENGTH: 215
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 62

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

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

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

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

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

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 63
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

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<220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 63

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

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<210> SEQ ID NO 64
 <211> LENGTH: 221
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 64

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

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-continued

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Gly Ser
210 215 220

<210> SEQ ID NO 65
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 65

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

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

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

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

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

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

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

Thr Val

<210> SEQ ID NO 66
 <211> LENGTH: 39
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 66

Gly Cys Gly Gly Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly
1 5 10 15

Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val
20 25 30

Glu Arg Lys Ala Pro Asp Ala
35

<210> SEQ ID NO 67
 <211> LENGTH: 35
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 67

Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala
1 5 10 15

Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala
20 25 30

Pro Asp Ala
35

-continued

<210> SEQ ID NO 68
 <211> LENGTH: 225
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 68

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

Gly
 225

<210> SEQ ID NO 69
 <211> LENGTH: 168
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 69

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

-continued

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly His Arg Pro Leu Asp
50 55 60

Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile
65 70 75 80

Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln
85 90 95

Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Gly Ser Gly Gly
100 105 110

Gly Ser Gly Gly Gly His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala
115 120 125

Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg
130 135 140

Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys
145 150 155 160

Ala Pro Asp Ala Gly Gly Gly Thr
165

<210> SEQ ID NO 70
<211> LENGTH: 168
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 70

Gly His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg
1 5 10 15

Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala
20 25 30

Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala Pro Asp Ala
35 40 45

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly His Arg Pro Leu Asp
50 55 60

Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile
65 70 75 80

Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln
85 90 95

Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Gly Ser Gly Gly
100 105 110

Gly Ser Gly Gly Gly His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala
115 120 125

Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg
130 135 140

Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys
145 150 155 160

Ala Pro Asp Ala Gly Gly Gly Thr Gly
165

<210> SEQ ID NO 71
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

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<400> SEQUENCE: 71

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

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Lys Ser Leu Pro Thr Asn Ser Phe Val Gly Cys Leu Lys Asn Phe Gln
 420 425 430
 Leu Asp Ser Lys Pro Leu Tyr Thr Pro Ser Ser Ser Phe Gly Val Ser
 435 440 445
 Ser Cys Thr Gly
 450

<210> SEQ ID NO 72
 <211> LENGTH: 391
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 72

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Ile Gly Phe Pro
 85 90 95
 Gln Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Cys Gly Ala Gly Gly Gly Ser Gly Gly Gly
 210 215 220
 His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro
 225 230 235 240
 Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys
 245 250 255
 Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly
 260 265 270
 Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly His Arg Pro Leu Asp Lys
 275 280 285
 Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser
 290 295 300

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Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys
 305 310 315 320

Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Gly Ser Gly Gly Gly
 325 330 335

Ser Gly Gly Gly His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala Pro
 340 345 350

Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala
 355 360 365

Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala
 370 375 380

Pro Asp Ala Gly Gly Gly Thr
 385 390

<210> SEQ ID NO 73
 <211> LENGTH: 395
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 73

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

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

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

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

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

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

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

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Gly Ser Gly Gly Gly
 210 215 220

Ser Gly Gly Gly His Arg Pro Leu Asp Lys Lys Arg Glu Glu Ala Pro
 225 230 235 240

Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala
 245 250 255

Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala

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<210> SEQ ID NO 77
 <211> LENGTH: 25
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 77

Lys Lys Arg Lys Leu Val Ala Leu Thr Asp Phe Leu Gly Ile Cys Gly
 1 5 10 15
 Ser Glu Asn Asp Gly Arg Lys Lys Lys
 20 25

<210> SEQ ID NO 78
 <211> LENGTH: 25
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 78

Leu Val Arg Ala Lys Leu Thr Asp Lys Phe Leu Gly Lys Arg Ile Gly
 1 5 10 15
 Ser Lys Glu Cys Asn Lys Asp Lys Gly
 20 25

<210> SEQ ID NO 79
 <211> LENGTH: 25
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

<400> SEQUENCE: 79

Ala Leu Leu Leu Gly Ile Gly Arg Asp Phe Asn Lys Lys Lys Arg Lys
 1 5 10 15
 Lys Lys Ser Glu Val Thr Asp Gly Cys
 20 25

<210> SEQ ID NO 80
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic 6xHis tag"

<400> SEQUENCE: 80

His His His His His His
 1 5

<210> SEQ ID NO 81
 <211> LENGTH: 4
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic peptide"

-continued

<400> SEQUENCE: 81

Gly Gly Ser Gly

1

The invention claimed is:

1. A polypeptide comprising a growth factor binding domain comprising 25-100 contiguous amino acids of SEQ ID NO: 13 and wherein the 25-100 contiguous amino acids include SEQ ID NO: 1, and wherein the polypeptide is attached to a transglutaminase-reactive peptide having the amino acid sequence of SEQ ID NO:12.

2. The polypeptide of claim 1, wherein the polypeptide is linked to one or more additional peptides, wherein each additional polypeptide has an amino acid sequence that is at least 80% identical to one of SEQ ID NOs:1-7, 13-15, 49-50, or 66-70, or a fragment thereof.

3. The polypeptide of claim 2, wherein the polypeptides are separated by one or more linkers.

4. The polypeptide of claim 1, wherein the polypeptide is attached to a collagen binding peptide.

5. The polypeptide of claim 1, wherein the polypeptide is attached to a cell adhesion moiety.

6. The polypeptide of claim 1, wherein the polypeptide is attached to a tag or a functional moiety.

7. The polypeptide of claim 1, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:8.

8. The polypeptide of claim 1, wherein the growth factor binding domain consists of SEQ ID NO:1.

9. The polypeptide of claim 1, wherein the growth factor binding domain comprising 25-50 contiguous amino acids of SEQ ID NO:13 and wherein the 25-50 contiguous amino acids include SEQ ID NO:1.

10. The polypeptide of claim 1, wherein the growth factor binding domain comprising 25-40 contiguous amino acids of SEQ ID NO:13 and wherein the 25-40 contiguous amino acids include SEQ ID NO:1.

11. A composition comprising the polypeptide of claim 1.

12. A biomaterial scaffold comprising the polypeptide of claim 1.

13. A biomaterial scaffold comprising the polypeptide of claim 1, wherein the polypeptide is covalently linked to fibrin, and wherein the biomaterial scaffold further comprises exogenously added Vascular Endothelial Growth Factor (VEGF) and Platelet-derived Growth Factor (PDGF).

14. An implant comprising the polypeptide of claim 1.

15. A method for regenerating tissue in a subject in need thereof, the method comprising administering to the subject the biomaterial of claim 12.

16. A method for facilitating wound or tissue healing in a subject in need thereof, the method comprising administering the biomaterial of claim 12 to the subject.

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