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(54) METHODS AND COMPOSITIONS FOR THE TREATMENT OF WOUNDS

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

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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.

Specification includes a Sequence Listing.

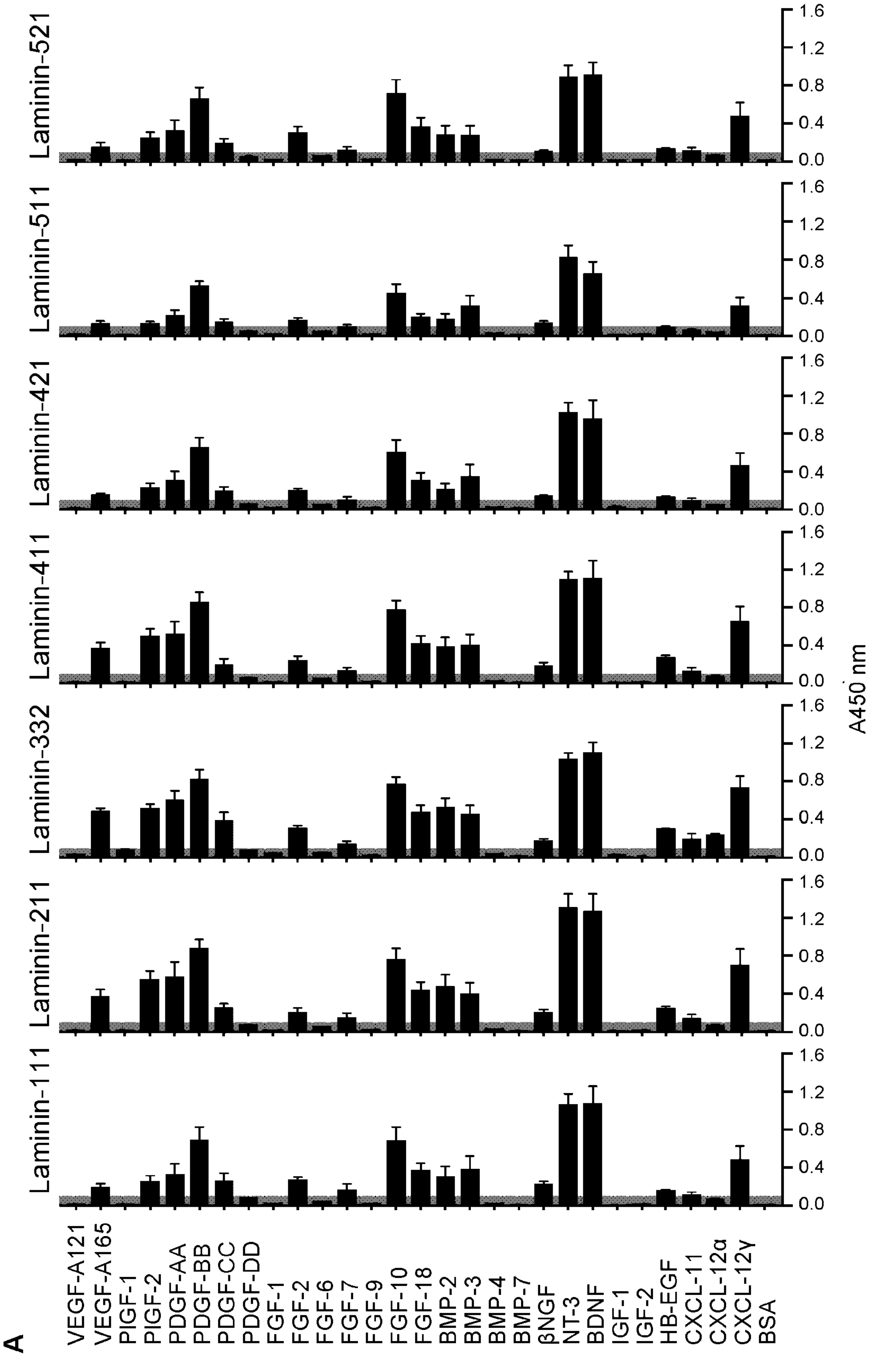

A
Laminin-111
Laminin-211
Laminin-332
Laminin-411
Laminin-421
Laminin-511
Laminin-521
VEGF-A121
VEGF-A165
PIGF-1
PIGF-2
PDGF-AA
PDGF-BB
PDGF-CC
PDGF-DD
FGF-1
FGF-2
FGF-6
FGF-7
FGF-9
FGF-10
FGF-18
BMP-2
BMP-3
BMP-4
BMP-7
βNGF
NT-3
BDNF
IGF-1
IGF-2
HB-EGF
CXCL-11
CXCL-12α
CXCL-12γ
BSA
0.0
0.4
0.8
1.2
1.6
A450 nm

FIG. 1A

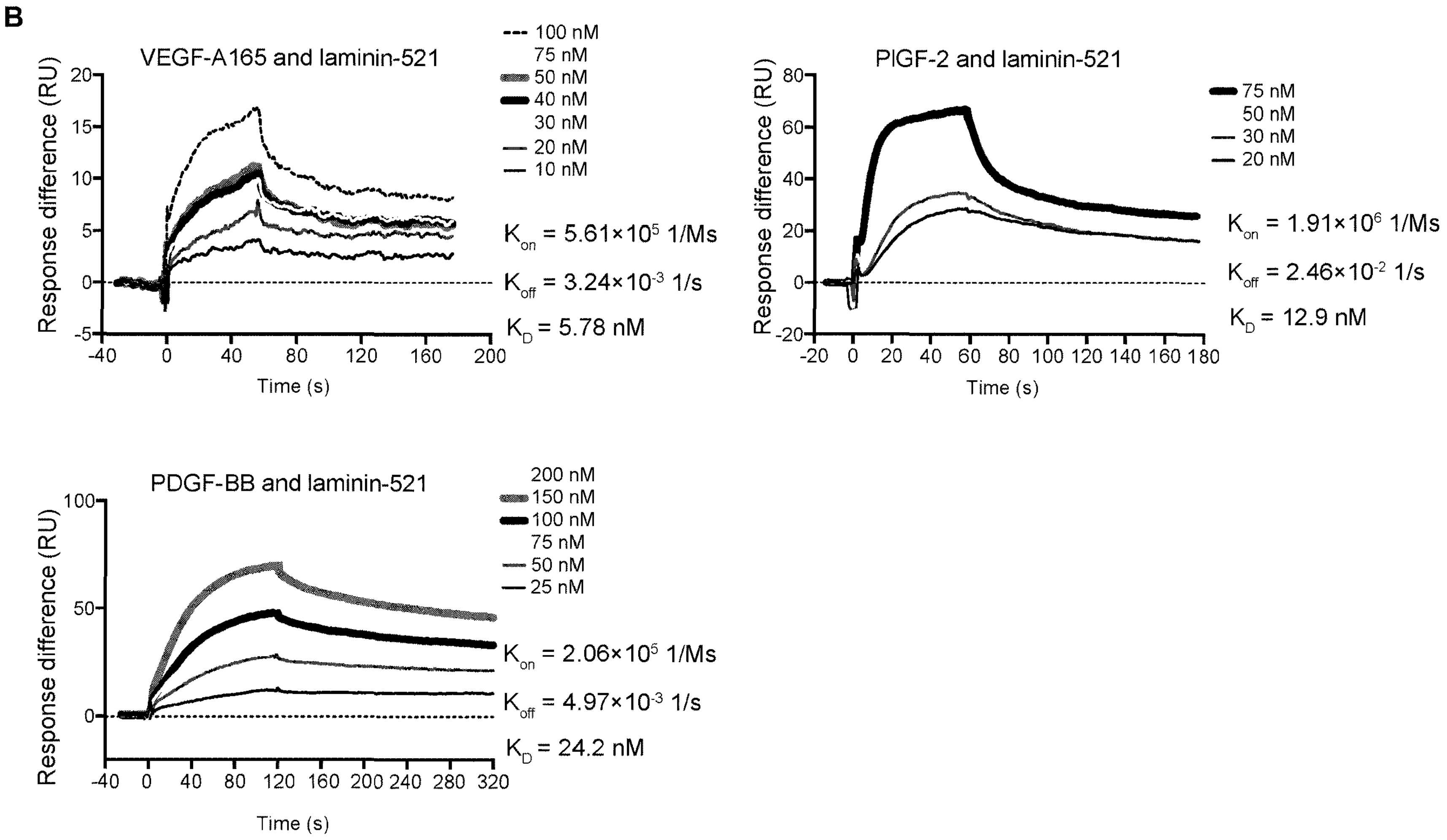

B
VEGF-A165 and laminin-521
Response difference (RU)
20
15
10
5
0
-5
-40
0
40
80
120
160
200
Time (s)
100 nM
75 nM
50 nM
40 nM
30 nM
20 nM
10 nM
K_{on} = 5.61×10^5 1/Ms
K_{off} = 3.24×10^{-3} 1/s
K_D = 5.78 nM
PlGF-2 and laminin-521
Response difference (RU)
80
60
40
20
0
-20
-20
0
20
40
60
80
100
120
140
160
180
Time (s)
75 nM
50 nM
30 nM
20 nM
K_{on} = 1.91×10^6 1/Ms
K_{off} = 2.46×10^{-2} 1/s
K_D = 12.9 nM
PDGF-BB and laminin-521
Response difference (RU)
100
50
0
-40
0
40
80
120
160
200
240
280
320
Time (s)
200 nM
150 nM
100 nM
75 nM
50 nM
25 nM
K_{on} = 2.06×10^5 1/Ms
K_{off} = 4.97×10^{-3} 1/s
K_D = 24.2 nM

FIG. 1B

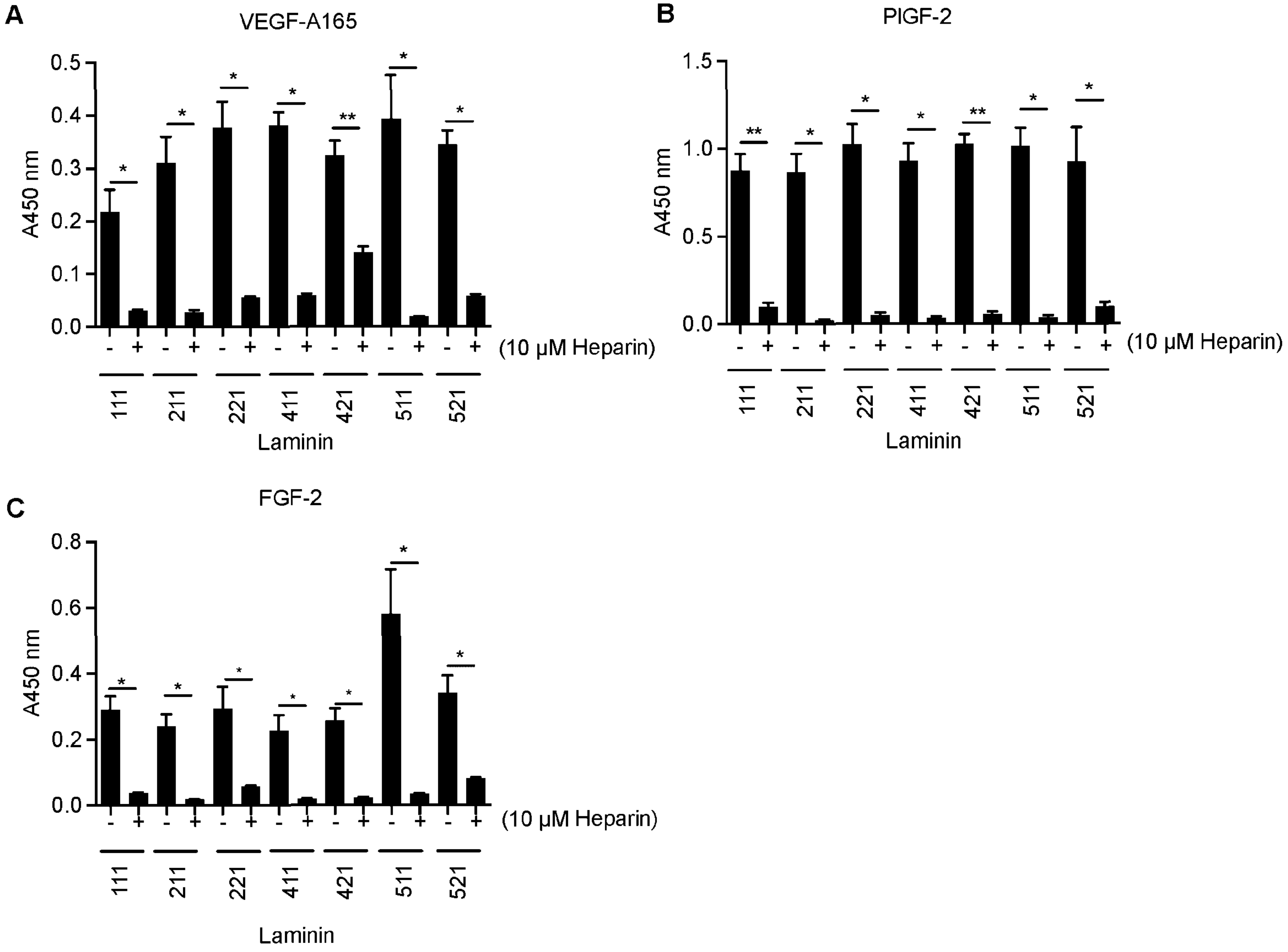

A
VEGF-A165
A450 nm
0.0
0.1
0.2
0.3
0.4
0.5
*
*
*
*
**
*
*
- + - + - + - + - + - + - +
(10 µM Heparin)
111
211
221
411
421
511
521
Laminin
B
PlGF-2
A450 nm
0.0
0.5
1.0
1.5
**
*
*
*
**
*
*
- + - + - + - + - + - + - +
(10 µM Heparin)
111
211
221
411
421
511
521
Laminin
C
FGF-2
A450 nm
0.0
0.2
0.4
0.6
0.8
*
*
*
*
*
*
*
- + - + - + - + - + - + - +
(10 µM Heparin)
111
211
221
411
421
511
521
Laminin

FIG. 2A-C

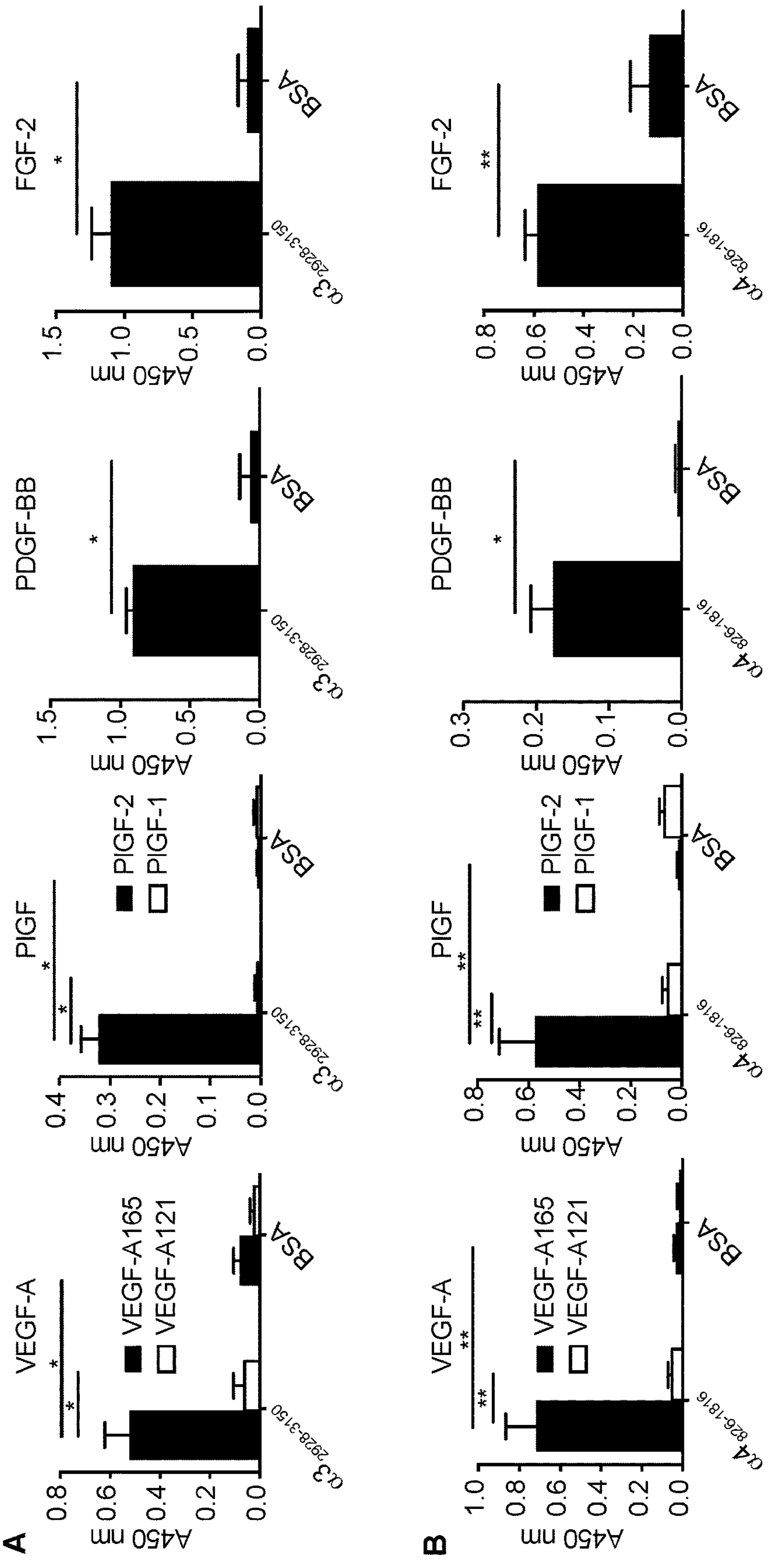

A
B
VEGF-A
PlGF
PDGF-BB
FGF-2
VEGF-A165
VEGF-A121
PlGF-2
PlGF-1
A450 nm
0.0
0.2
0.4
0.6
0.8
1.0
0.1
0.3
0.5
1.5
*
**
α3 2928-3150
α4 826-1816
BSA

FIG. 3A-B

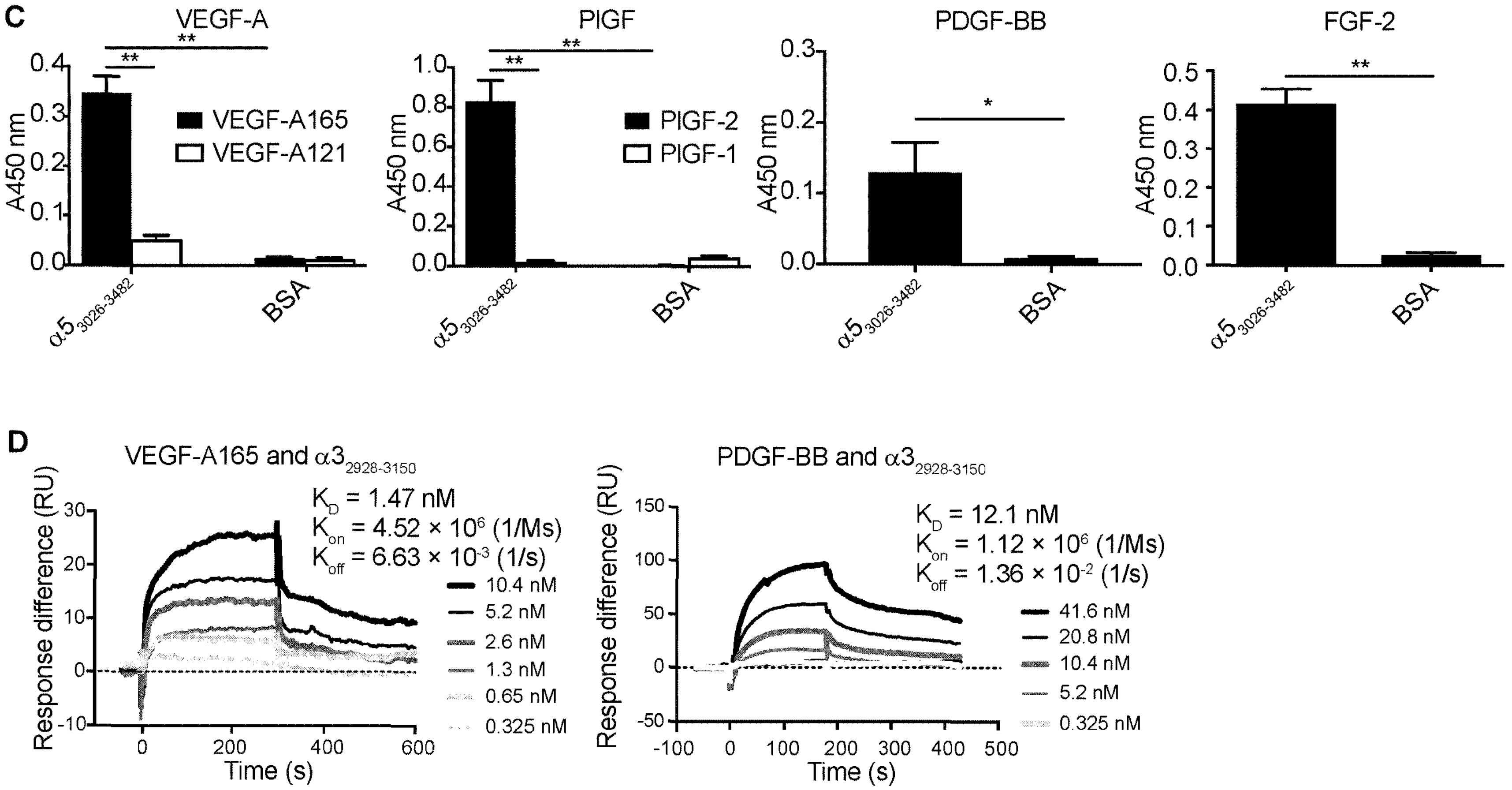

C
VEGF-A
**
**
A450 nm
0.4
0.3
0.2
0.1
0.0
VEGF-A165
VEGF-A121
α5 3026-3482
BSA
PIGF
**
**
1.0
0.8
0.6
0.4
0.2
0.0
PIGF-2
PIGF-1
PDGF-BB
*
0.3
0.2
0.1
0.0
FGF-2
**
0.5
D
VEGF-A165 and α3 2928-3150
Response difference (RU)
30
20
10
0
-10
Time (s)
0
200
400
600
K_D = 1.47 nM
K_on = 4.52 × 10^6 (1/Ms)
K_off = 6.63 × 10^-3 (1/s)
10.4 nM
5.2 nM
2.6 nM
1.3 nM
0.65 nM
0.325 nM
PDGF-BB and α3 2928-3150
150
100
50
-50
-100
300
500
K_D = 12.1 nM
K_on = 1.12 × 10^6 (1/Ms)
K_off = 1.36 × 10^-2 (1/s)
41.6 nM
20.8 nM
10.4 nM
5.2 nM
0.325 nM

FIG. 3C-D

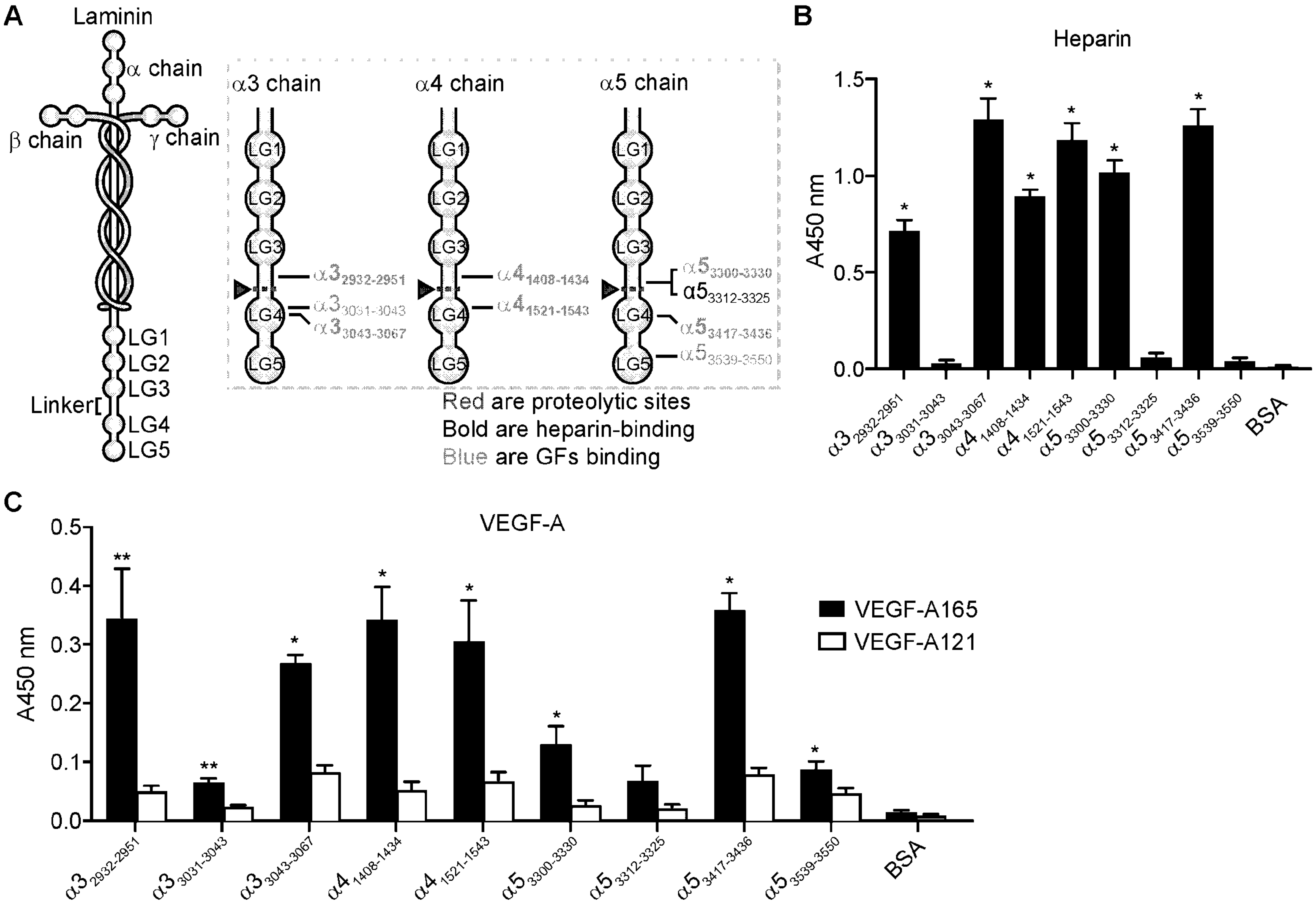

A
Laminin
α chain
β chain
γ chain
LG1
LG2
LG3
Linker
LG4
LG5
α3 chain
α4 chain
α5 chain
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
Red are proteolytic sites
Bold are heparin-binding
Blue are GFs binding
B
Heparin
A450 nm
1.5
1.0
0.5
0.0
BSA
C
VEGF-A
0.5
0.4
0.3
0.2
0.1
0.0
VEGF-A165
VEGF-A121
*
**

FIG. 4A-C

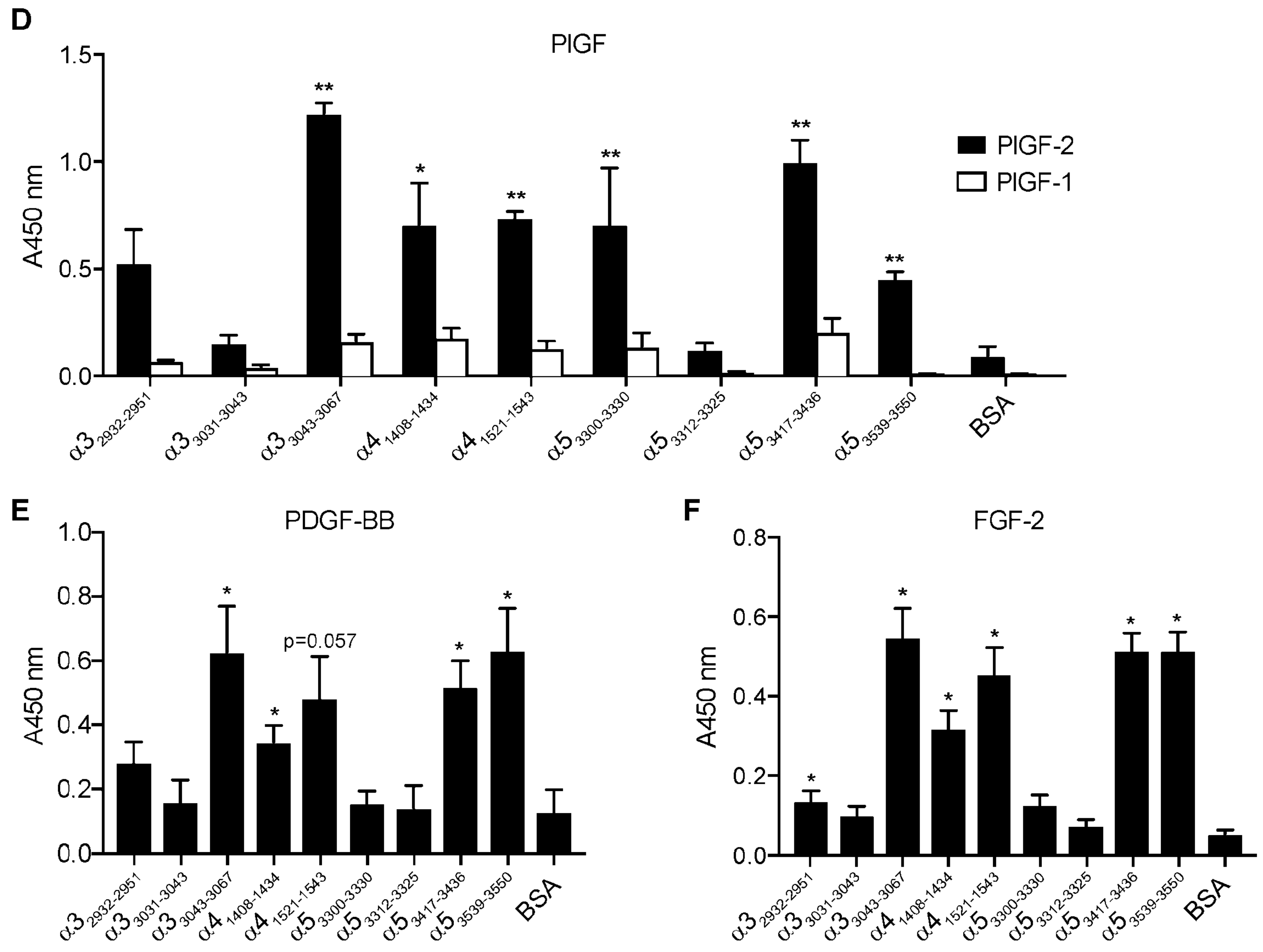

D
PIGF
A450 nm
1.5
1.0
0.5
0.0
**
*
**
**
**
**
PIGF-2
PIGF-1
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
BSA
E
PDGF-BB
A450 nm
1.0
0.8
0.6
0.4
0.2
0.0
*
*
p=0.057
*
*
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
BSA
F
FGF-2
A450 nm
0.8
0.6
0.4
0.2
0.0
*
*
*
*
*
*
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
BSA

FIG. 4D-F

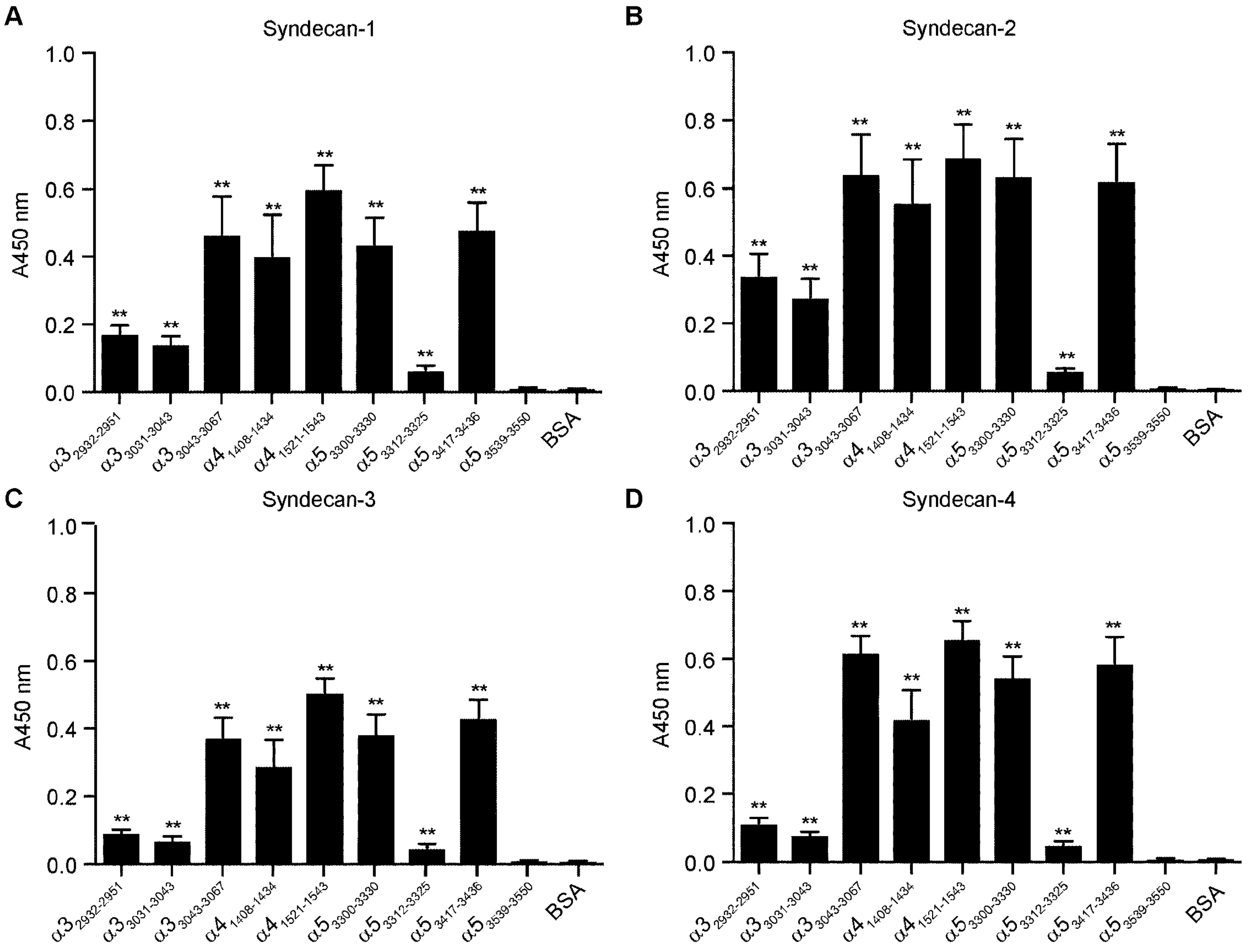

A
Syndecan-1
B
Syndecan-2
C
Syndecan-3
D
Syndecan-4
A450 nm
1.0
0.8
0.6
0.4
0.2
0.0
**
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
BSA

FIG. 5A-D

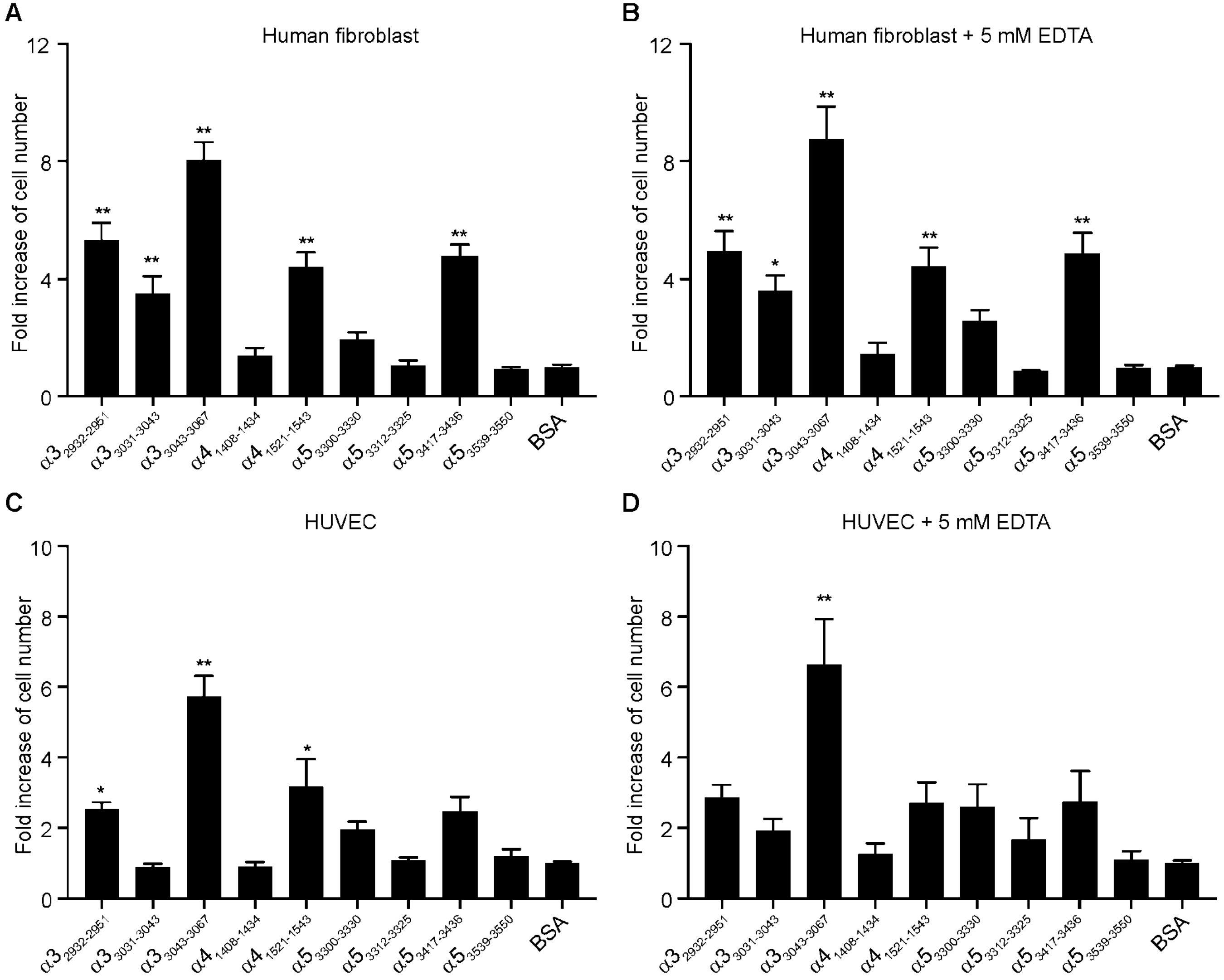

A
Human fibroblast
B
Human fibroblast + 5 mM EDTA
C
HUVEC
D
HUVEC + 5 mM EDTA
Fold increase of cell number
0
4
8
12
2
6
10
**
*
α3 2932-2951
α3 3031-3043
α3 3043-3067
α4 1408-1434
α4 1521-1543
α5 3300-3330
α5 3312-3325
α5 3417-3436
α5 3539-3550
BSA

FIG. 6A-D

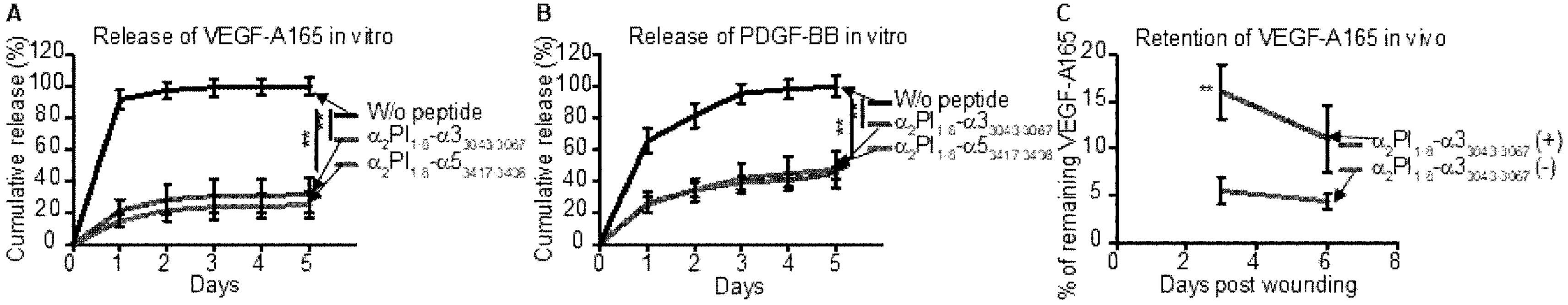

A
Release of VEGF-A165 in vitro
Cumulative release (%)
120
100
80
60
40
20
0
0
1
2
3
4
5
Days
**
**
W/o peptide
α_2PI_{1-8}-$\alpha3_{3043-3067}$
α_2PI_{1-8}-$\alpha5_{3417-3436}$
B
Release of PDGF-BB in vitro
Cumulative release (%)
120
100
80
60
40
20
0
0
1
2
3
4
5
Days
**
**
W/o peptide
α_2PI_{1-8}-$\alpha3_{3043-3067}$
α_2PI_{1-8}-$\alpha5_{3417-3436}$
C
Retention of VEGF-A165 in vivo
% of remaining VEGF-A165
20
15
10
5
0
0
2
4
6
8
Days post wounding
**
α_2PI_{1-8}-$\alpha3_{3043-3067}$ (+)
α_2PI_{1-8}-$\alpha3_{3043-3067}$ (-)

FIG. 7A-C

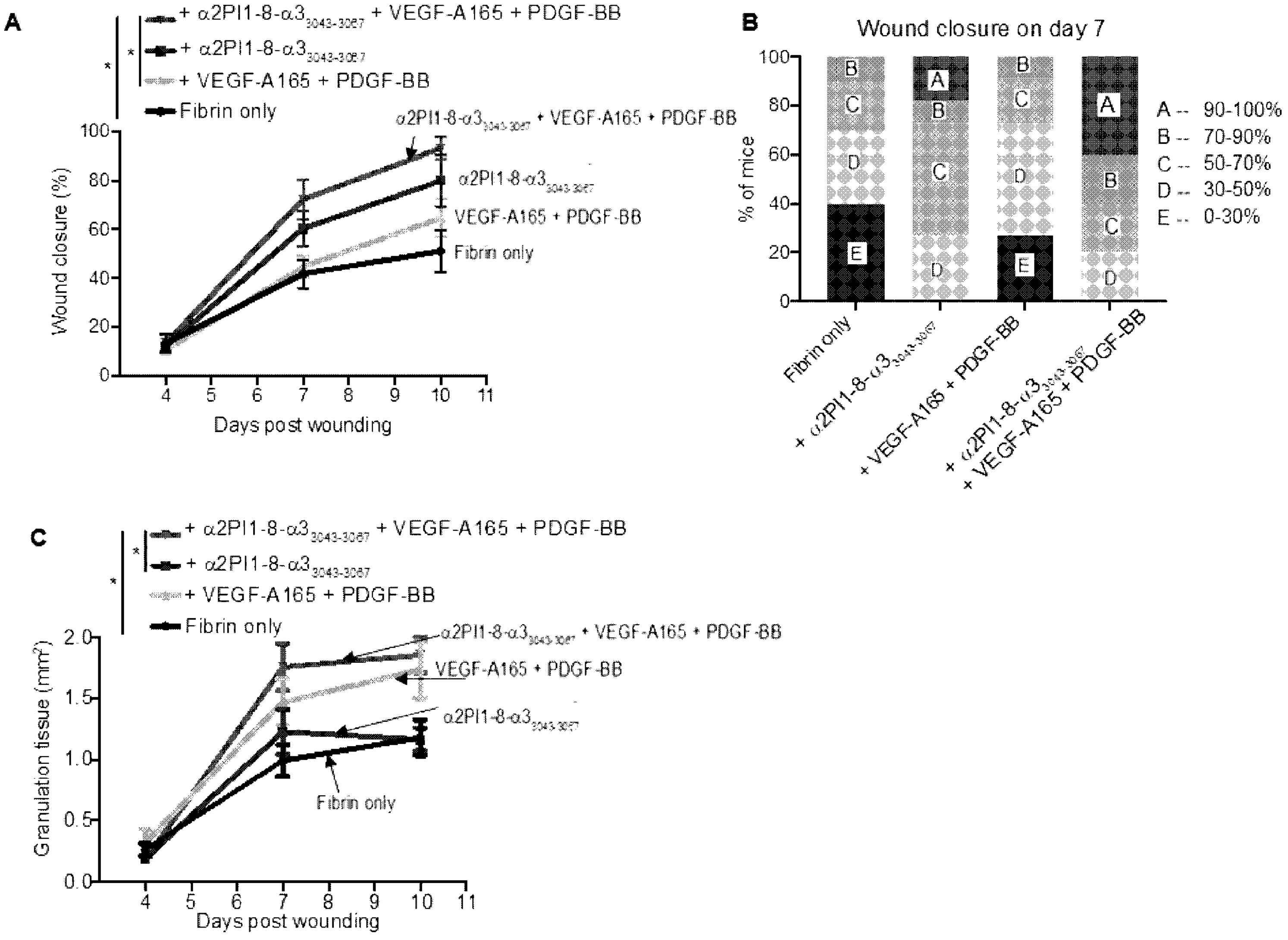

A
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇ + VEGF-A165 + PDGF-BB
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇
+ VEGF-A165 + PDGF-BB
Fibrin only
*
*
Wound closure (%)
100
80
60
40
20
0
4
5
6
7
8
9
10
11
Days post wounding
α2PI1-8-α3₃₀₄₃₋₃₀₆₇ + VEGF-A165 + PDGF-BB
α2PI1-8-α3₃₀₄₃₋₃₀₆₇
VEGF-A165 + PDGF-BB
Fibrin only
B
Wound closure on day 7
% of mice
100
80
60
40
20
0
A
B
C
D
E
A -- 90-100%
B -- 70-90%
C -- 50-70%
D -- 30-50%
E -- 0-30%
Fibrin only
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇
+ VEGF-A165 + PDGF-BB
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇
+ VEGF-A165 + PDGF-BB
C
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇ + VEGF-A165 + PDGF-BB
+ α2PI1-8-α3₃₀₄₃₋₃₀₆₇
+ VEGF-A165 + PDGF-BB
Fibrin only
*
*
Granulation tissue (mm²)
2.0
1.5
1.0
0.5
0.0
4
5
6
7
8
9
10
11
Days post wounding
α2PI1-8-α3₃₀₄₃₋₃₀₆₇ + VEGF-A165 + PDGF-BB
VEGF-A165 + PDGF-BB
α2PI1-8-α3₃₀₄₃₋₃₀₆₇
Fibrin only

FIG. 8A-C

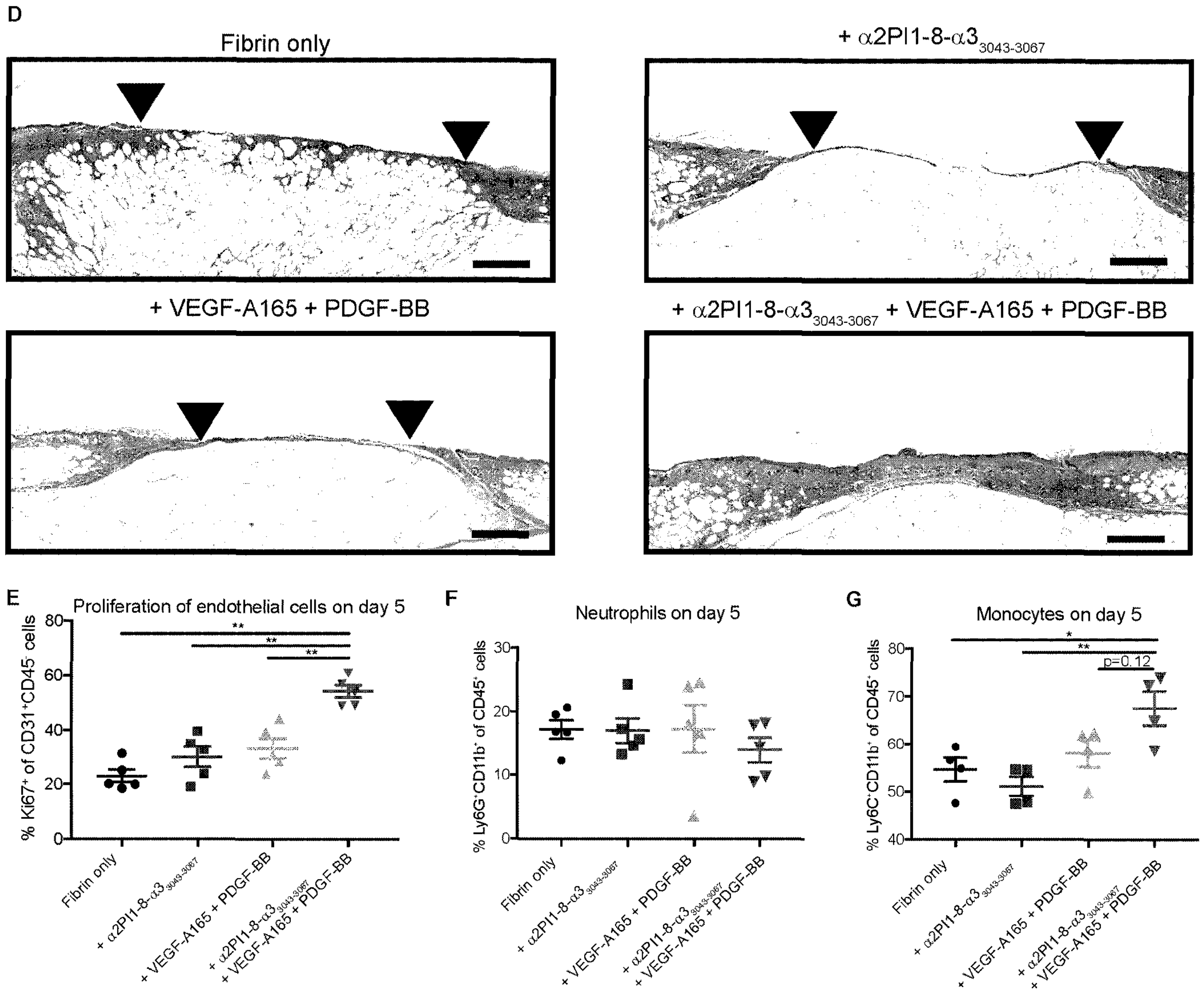

D
Fibrin only
+ α2PI1-8-α3$_{3043-3067}$
+ VEGF-A165 + PDGF-BB
+ α2PI1-8-α3$_{3043-3067}$ + VEGF-A165 + PDGF-BB
E
Proliferation of endothelial cells on day 5
% Ki67$^+$ of CD31$^+$CD45$^-$ cells
0
20
40
60
80
**
**
**
F
Neutrophils on day 5
% Ly6G$^+$CD11b$^+$ of CD45$^+$ cells
0
10
20
30
G
Monocytes on day 5
% Ly6C$^+$CD11b$^+$ of CD45$^+$ cells
40
50
60
70
80
*
**
p=0.12
Fibrin only
+ α2PI1-8-α3$_{3043-3067}$
+ VEGF-A165 + PDGF-BB
+ α2PI1-8-α3$_{3043-3067}$ + VEGF-A165 + PDGF-BB

FIG. 8D-G

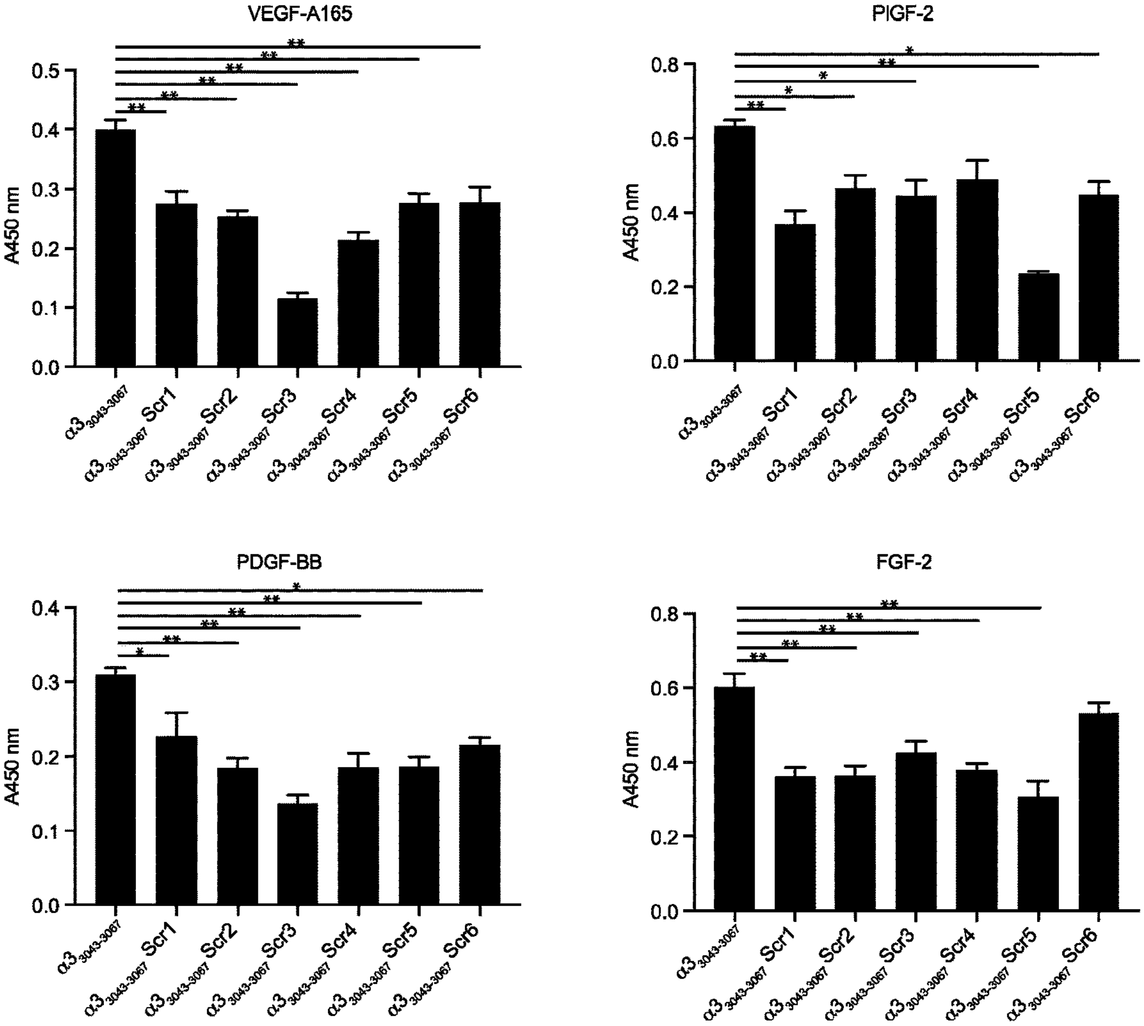

VEGF-A165
PlGF-2
PDGF-BB
FGF-2
A450 nm
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.8
*
**
α3 3043-3067
α3 3043-3067 Scr1
α3 3043-3067 Scr2
α3 3043-3067 Scr3
α3 3043-3067 Scr4
α3 3043-3067 Scr5
α3 3043-3067 Scr6

FIG. 9

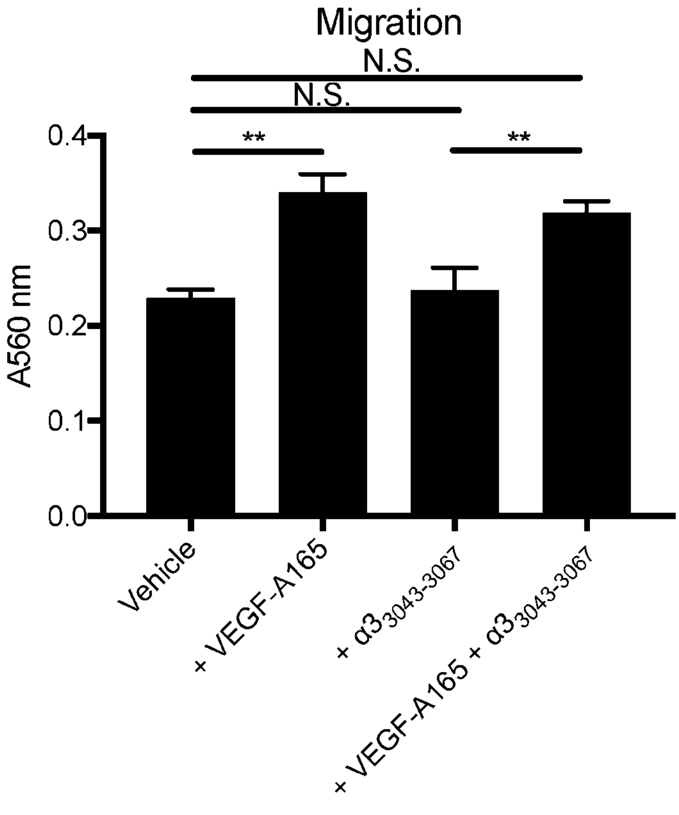

Migration
N.S.
N.S.
**
**
A560 nm
0.4
0.3
0.2
0.1
0.0
Vehicle
+ VEGF-A165
+ α3 3043-3067
+ VEGF-A165 + α3 3043-3067

FIG. 10

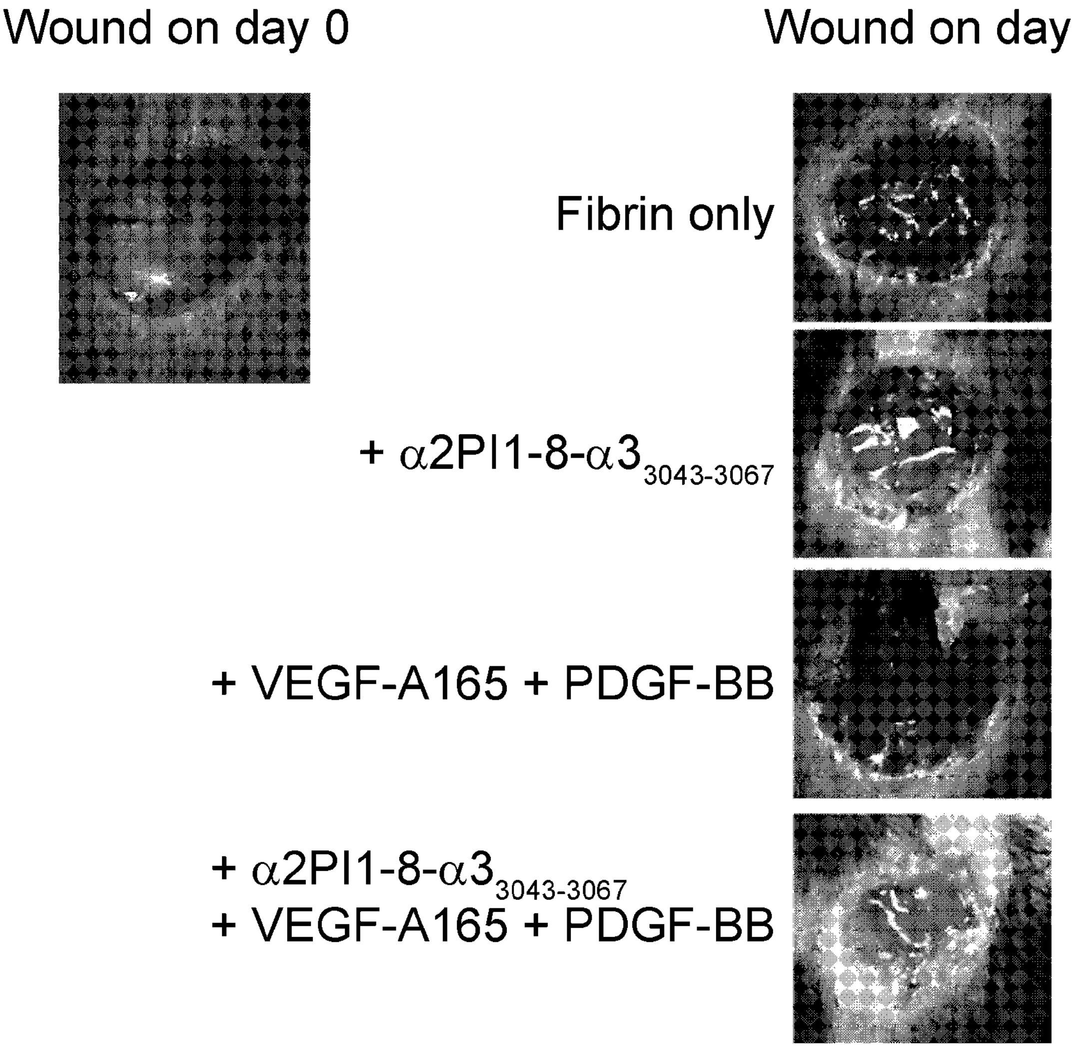

Wound on day 0
Wound on day 7
Fibrin only
+ α2PI1-8-α3$_{3043-3067}$
+ VEGF-A165 + PDGF-BB
+ α2PI1-8-α3$_{3043-3067}$
+ VEGF-A165 + PDGF-BB

FIG. 11

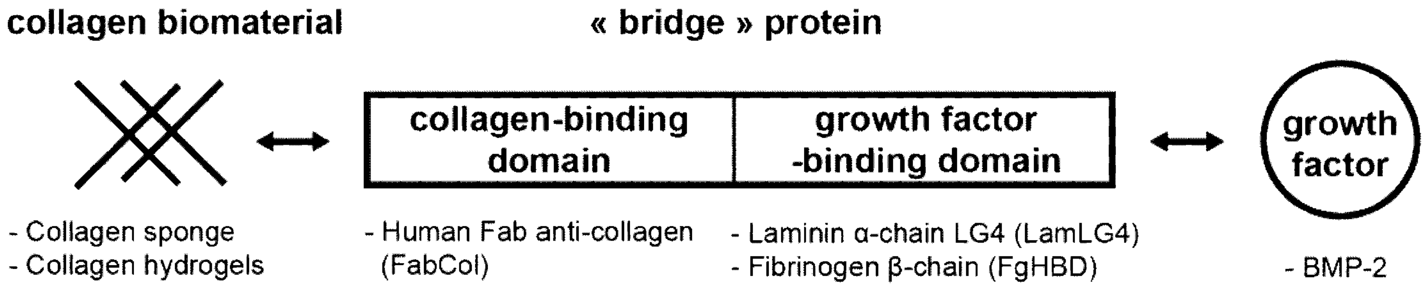
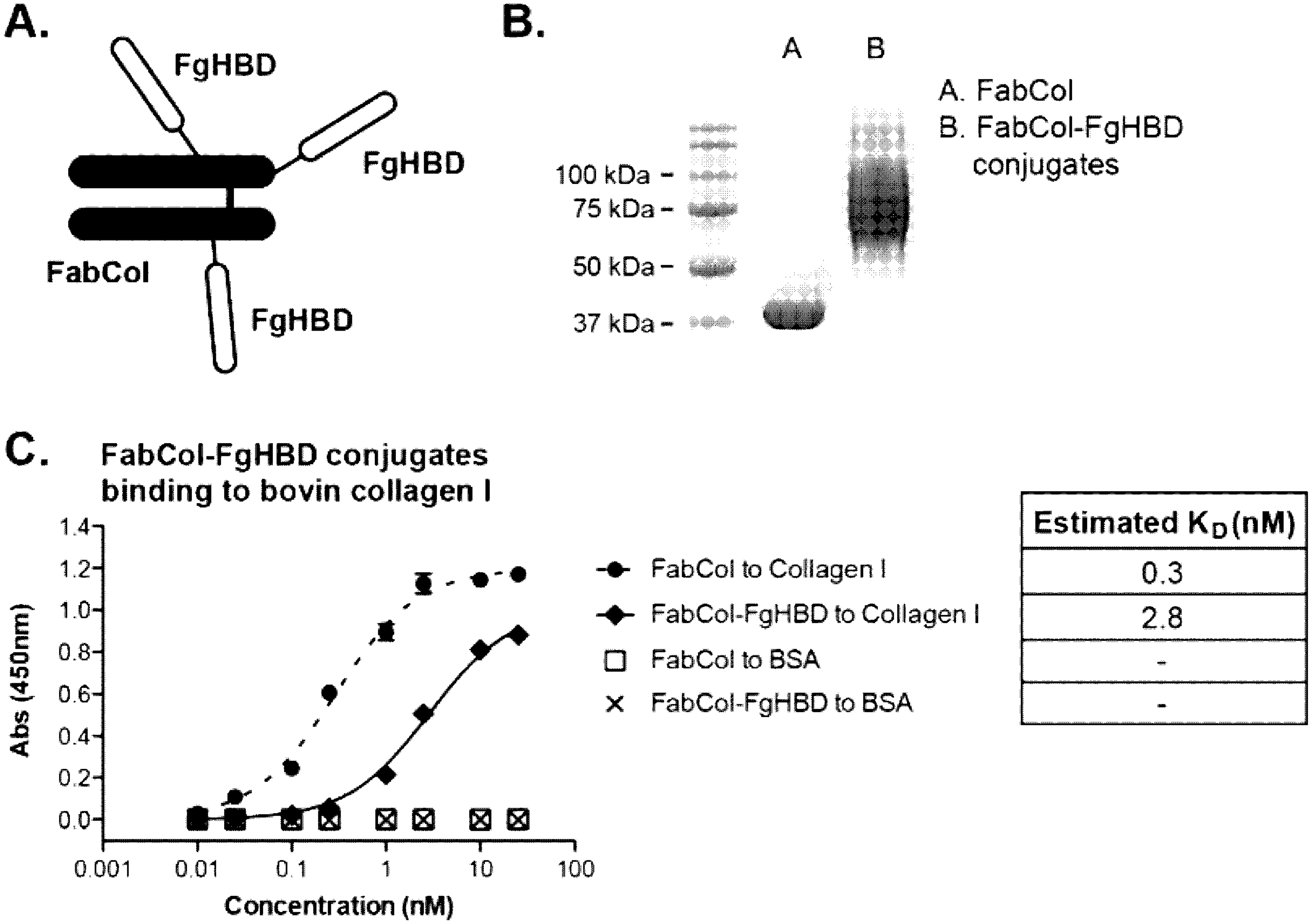

collagen biomaterial
« bridge » protein
collagen-binding domain
growth factor -binding domain
growth factor
- Collagen sponge
- Collagen hydrogels
- Human Fab anti-collagen (FabCol)
- Laminin α-chain LG4 (LamLG4)
- Fibrinogen β-chain (FgHBD)
- BMP-2

FIG. 12



Estimated K_D (nM)
0.3
2.8
-
-

FIG. 13A-C

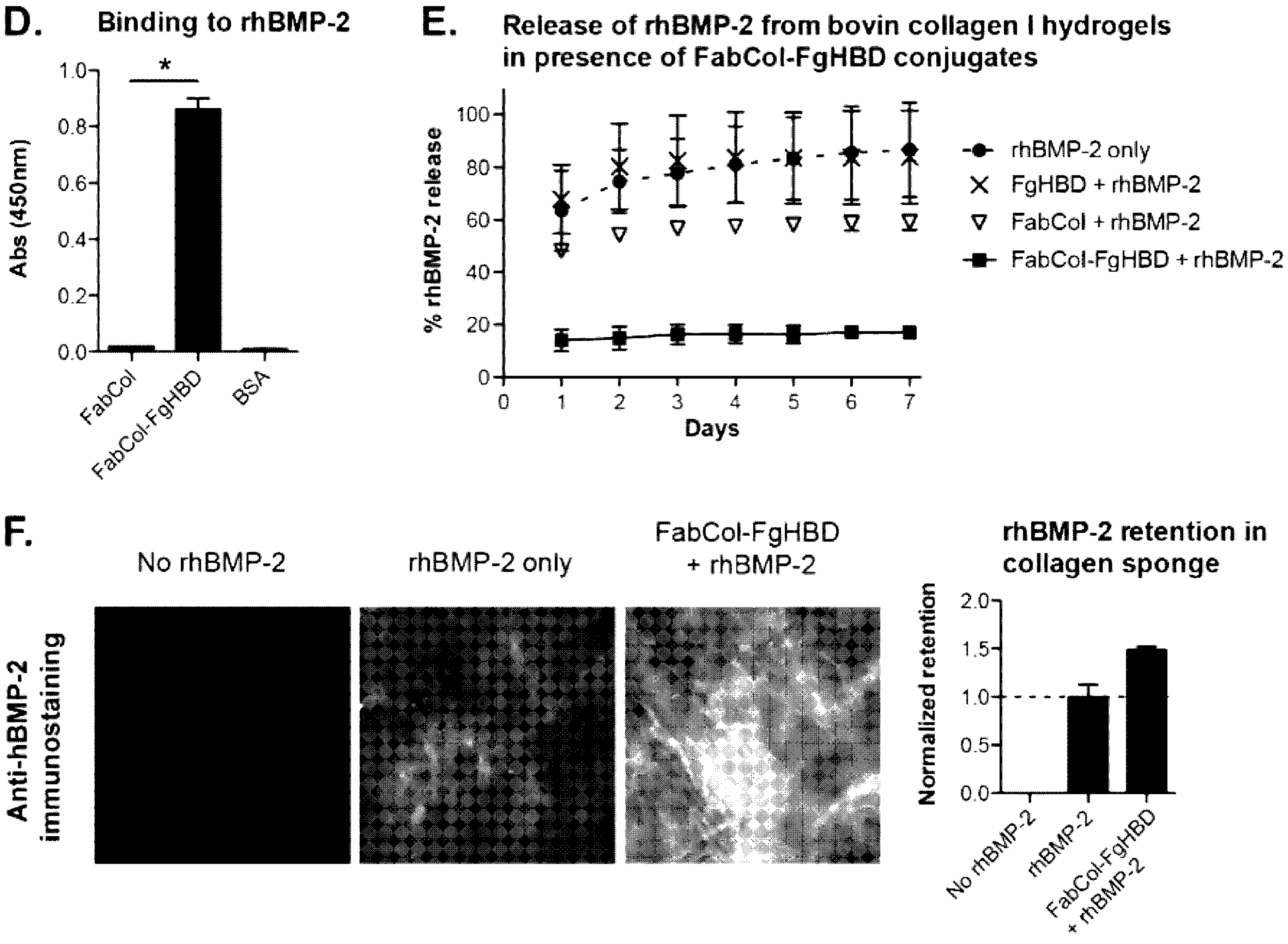
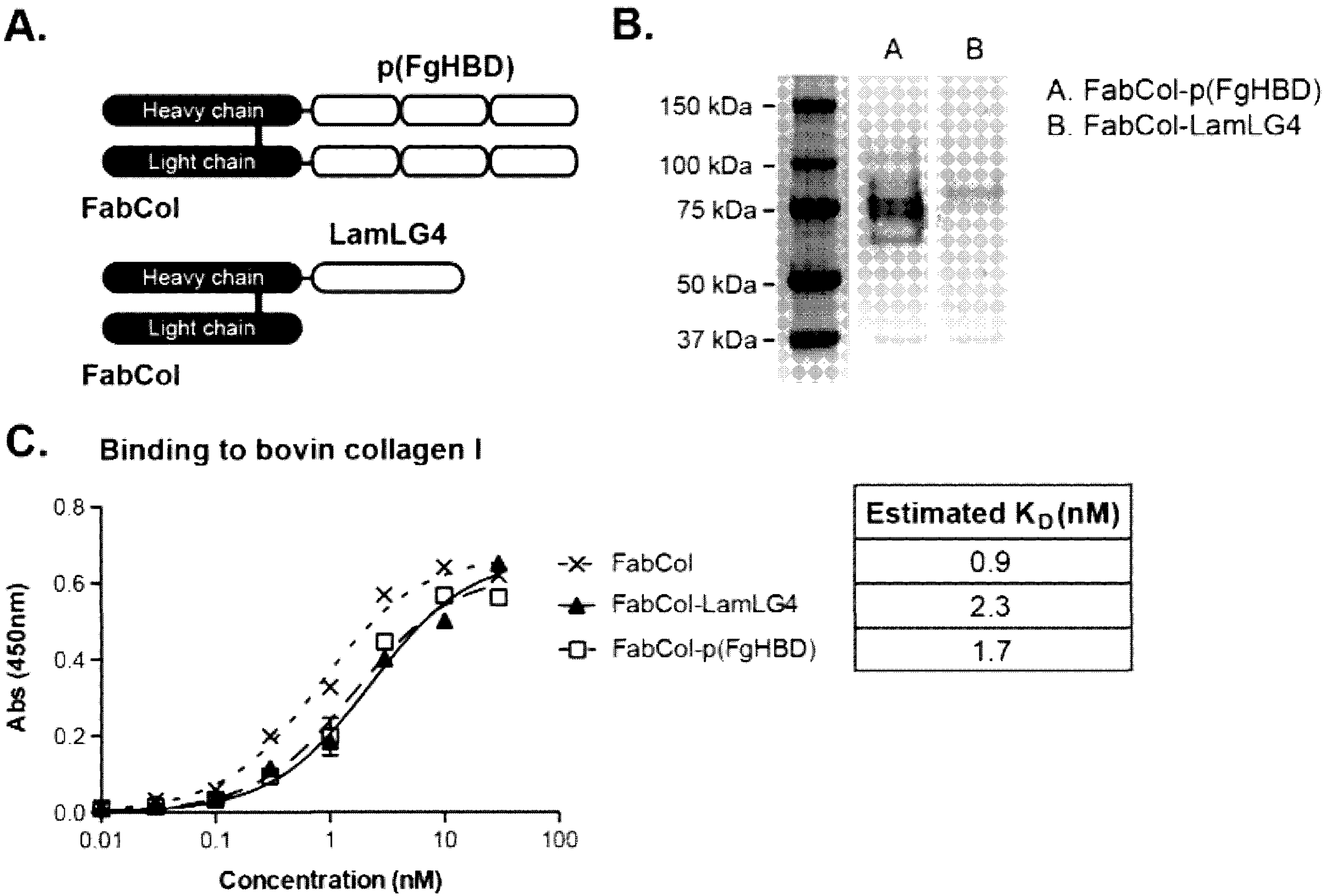

D.
Binding to rhBMP-2
Abs (450nm)
1.0
0.8
0.6
0.4
0.2
0.0
*
FabCol
FabCol-FgHBD
BSA
E.
Release of rhBMP-2 from bovin collagen I hydrogels in presence of FabCol-FgHBD conjugates
% rhBMP-2 release
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Days
rhBMP-2 only
FgHBD + rhBMP-2
FabCol + rhBMP-2
FabCol-FgHBD + rhBMP-2
F.
No rhBMP-2
rhBMP-2 only
FabCol-FgHBD + rhBMP-2
Anti-hBMP-2 immunostaining
rhBMP-2 retention in collagen sponge
Normalized retention
2.0
1.5
1.0
0.5
0.0
No rhBMP-2
rhBMP-2
FabCol-FgHBD + rhBMP-2

FIG. 13D-F



Estimated K_D(nM)
0.9
2.3
1.7

FIG. 14A-C

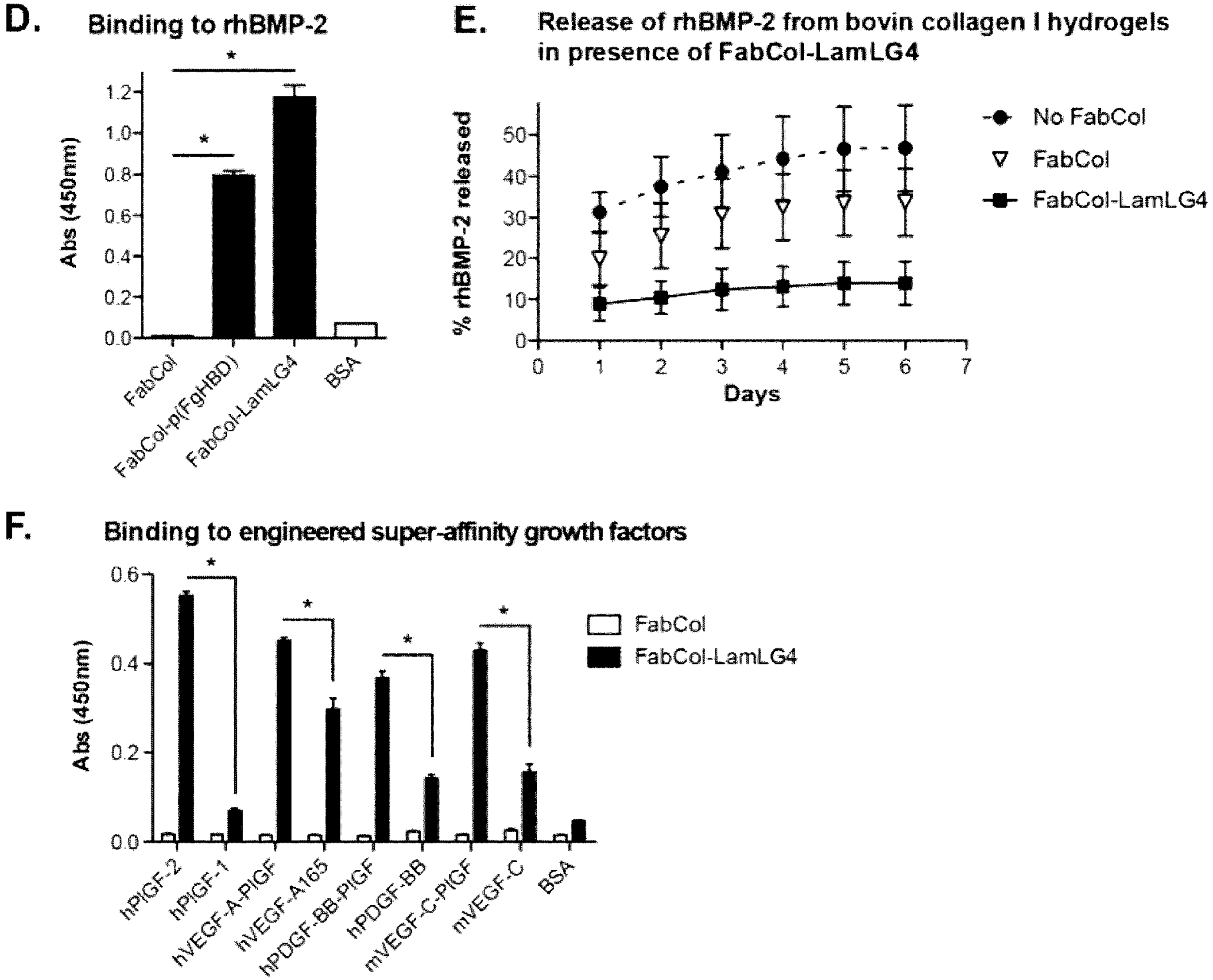

D.
Binding to rhBMP-2
Abs (450nm)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
*
*
FabCol
FabCol-p(FgHBD)
FabCol-LamLG4
BSA
E.
Release of rhBMP-2 from bovin collagen I hydrogels in presence of FabCol-LamLG4
% rhBMP-2 released
0
10
20
30
40
50
Days
0
1
2
3
4
5
6
7
No FabCol
FabCol
FabCol-LamLG4
F.
Binding to engineered super-affinity growth factors
Abs (450nm)
0.0
0.2
0.4
0.6
*
*
*
*
FabCol
FabCol-LamLG4
hPlGF-2
hPlGF-1
hVEGF-A-PlGF
hVEGF-A165
hPDGF-BB-PlGF
hPDGF-BB
mVEGF-C-PlGF
mVEGF-C
BSA

FIG. 14D-F

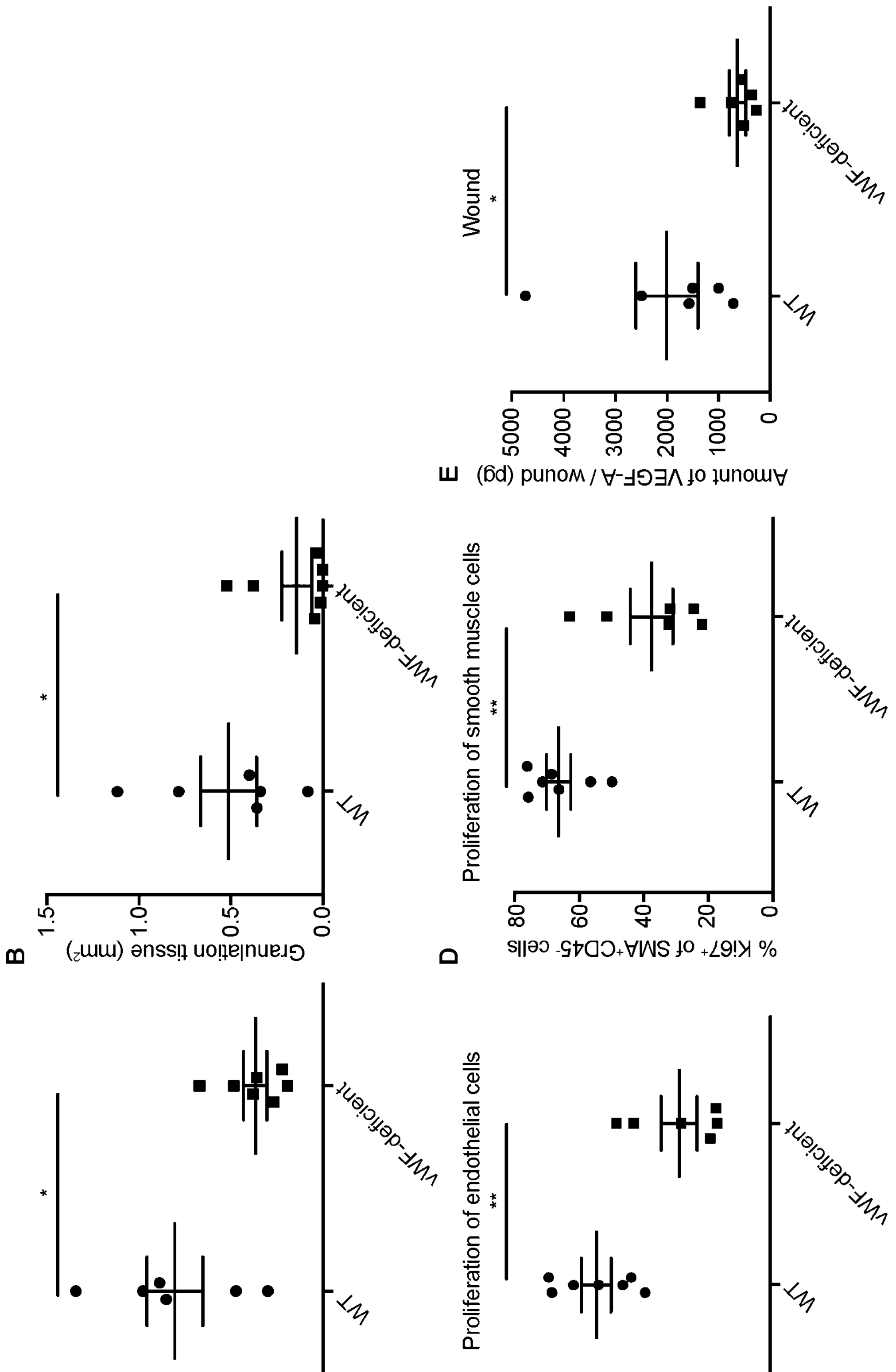

A
Wound closure (%)
40
30
20
10
0
*
WT
vWF-deficient
B
Granulation tissue (mm^2)
1.5
1.0
0.5
0.0
*
WT
vWF-deficient
C
Proliferation of endothelial cells
% Ki67$^+$ of CD31$^+$CD45$^-$ cells
80
60
40
20
0
**
WT
vWF-deficient
D
Proliferation of smooth muscle cells
% Ki67$^+$ of SMA$^+$CD45$^-$ cells
80
60
40
20
0
**
WT
vWF-deficient
E
Wound
Amount of VEGF-A / wound (pg)
5000
4000
3000
2000
1000
0
*
WT
vWF-deficient

FIG. 15A-E

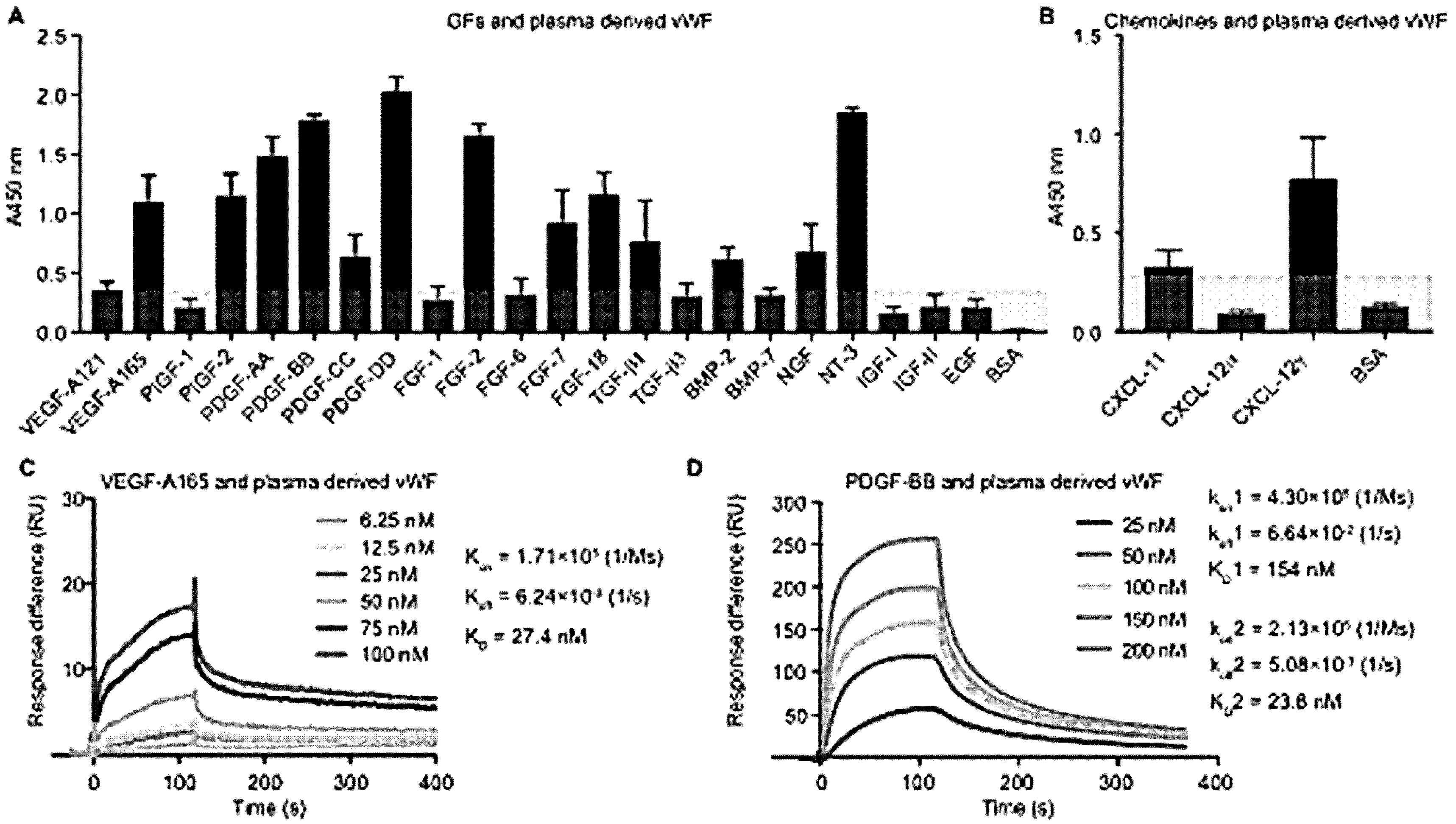

A
GFs and plasma derived vWF
A450 nm
2.5
2.0
1.5
1.0
0.5
0.0
VEGF-A121
VEGF-A165
PIGF-1
PIGF-2
PDGF-AA
PDGF-BB
PDGF-CC
PDGF-DD
FGF-1
FGF-2
FGF-6
FGF-7
FGF-18
TGF-β1
TGF-β3
BMP-2
BMP-7
NGF
NT-3
IGF-I
IGF-II
EGF
BSA
B
Chemokines and plasma derived vWF
A450 nm
1.5
1.0
0.5
0.0
CXCL-11
CXCL-12α
CXCL-12γ
BSA
C
VEGF-A165 and plasma derived vWF
Response difference (RU)
30
20
10
0
100
200
300
400
Time (s)
6.25 nM
12.5 nM
25 nM
50 nM
75 nM
100 nM
$K_{on} = 1.71 \times 10^{5}$ (1/Ms)
$K_{off} = 6.24 \times 10^{-3}$ (1/s)
$K_D = 27.4$ nM
D
PDGF-BB and plasma derived vWF
Response difference (RU)
300
250
200
150
100
50
0
100
200
300
400
Time (s)
25 nM
50 nM
100 nM
150 nM
200 nM
$k_{a}1 = 4.30 \times 10^{5}$ (1/Ms)
$k_{d}1 = 6.64 \times 10^{-2}$ (1/s)
$K_D1 = 154$ nM
$k_{a}2 = 2.13 \times 10^{5}$ (1/Ms)
$k_{d}2 = 5.08 \times 10^{-3}$ (1/s)
$K_D2 = 23.8$ nM

FIG. 16A-D

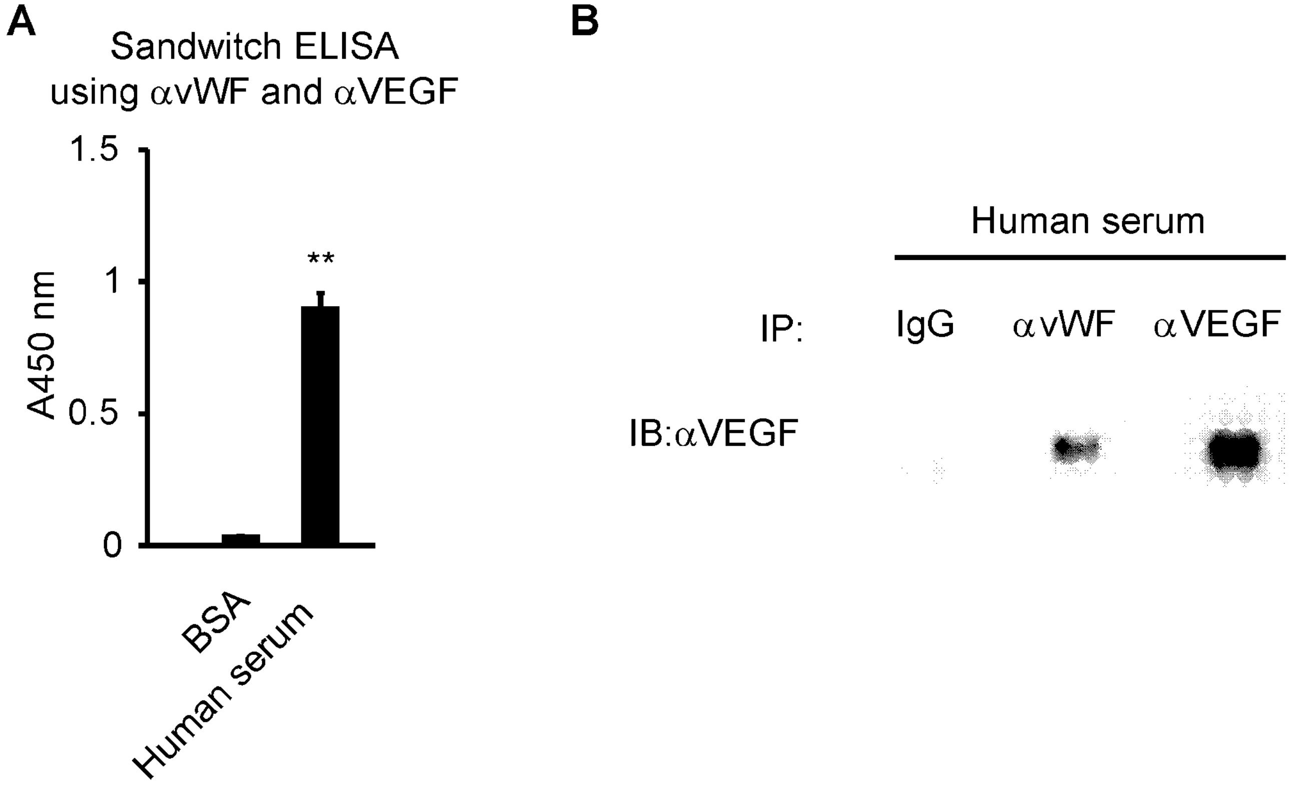

A
Sandwitch ELISA
using αvWF and αVEGF
A450 nm
1.5
1
0.5
0
**
BSA
Human serum
B
Human serum
IP:
IgG
αvWF
αVEGF
IB:αVEGF

FIG. 17A-B

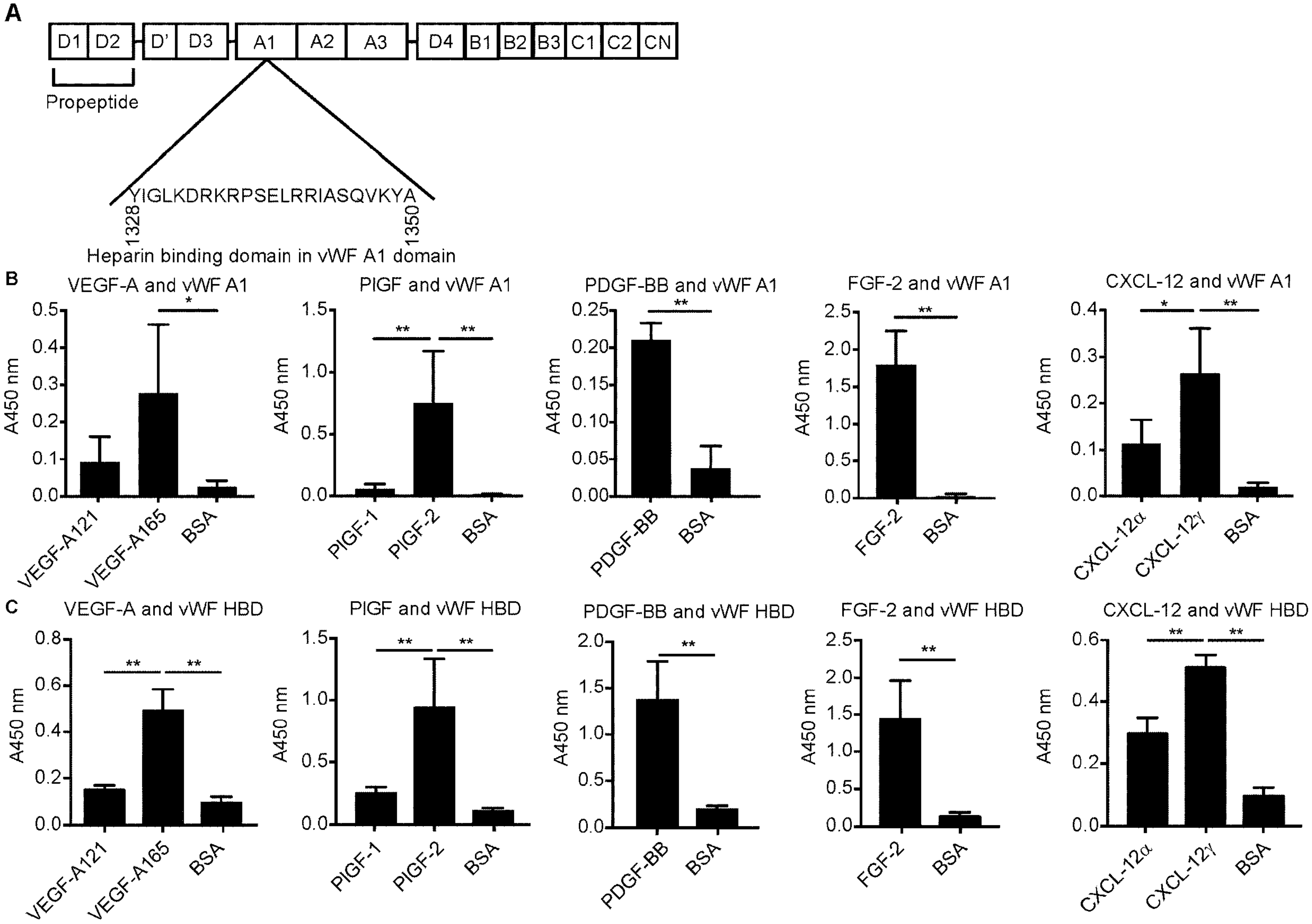

A
D1
D2
D'
D3
A1
A2
A3
D4
B1
B2
B3
C1
C2
CN
Propeptide
YIGLKDRKRPSELRRIASQVKYA
1328
1350
Heparin binding domain in vWF A1 domain
B
VEGF-A and vWF A1
A450 nm
0.0
0.1
0.2
0.3
0.4
0.5
*
VEGF-A121
VEGF-A165
BSA
PIGF and vWF A1
A450 nm
0.0
0.5
1.0
1.5
**
**
PIGF-1
PIGF-2
BSA
PDGF-BB and vWF A1
A450 nm
0.00
0.05
0.10
0.15
0.20
0.25
**
PDGF-BB
BSA
FGF-2 and vWF A1
A450 nm
0.0
0.5
1.0
1.5
2.0
2.5
**
FGF-2
BSA
CXCL-12 and vWF A1
A450 nm
0.0
0.1
0.2
0.3
0.4
*
**
CXCL-12α
CXCL-12γ
BSA
C
VEGF-A and vWF HBD
A450 nm
0.0
0.2
0.4
0.6
0.8
**
**
VEGF-A121
VEGF-A165
BSA
PIGF and vWF HBD
A450 nm
0.0
0.5
1.0
1.5
**
**
PIGF-1
PIGF-2
BSA
PDGF-BB and vWF HBD
A450 nm
0.0
0.5
1.0
1.5
2.0
**
PDGF-BB
BSA
FGF-2 and vWF HBD
A450 nm
0.0
0.5
1.0
1.5
2.0
2.5
**
FGF-2
BSA
CXCL-12 and vWF HBD
A450 nm
0.0
0.2
0.4
0.6
**
**
CXCL-12α
CXCL-12γ
BSA

FIG. 18A-C

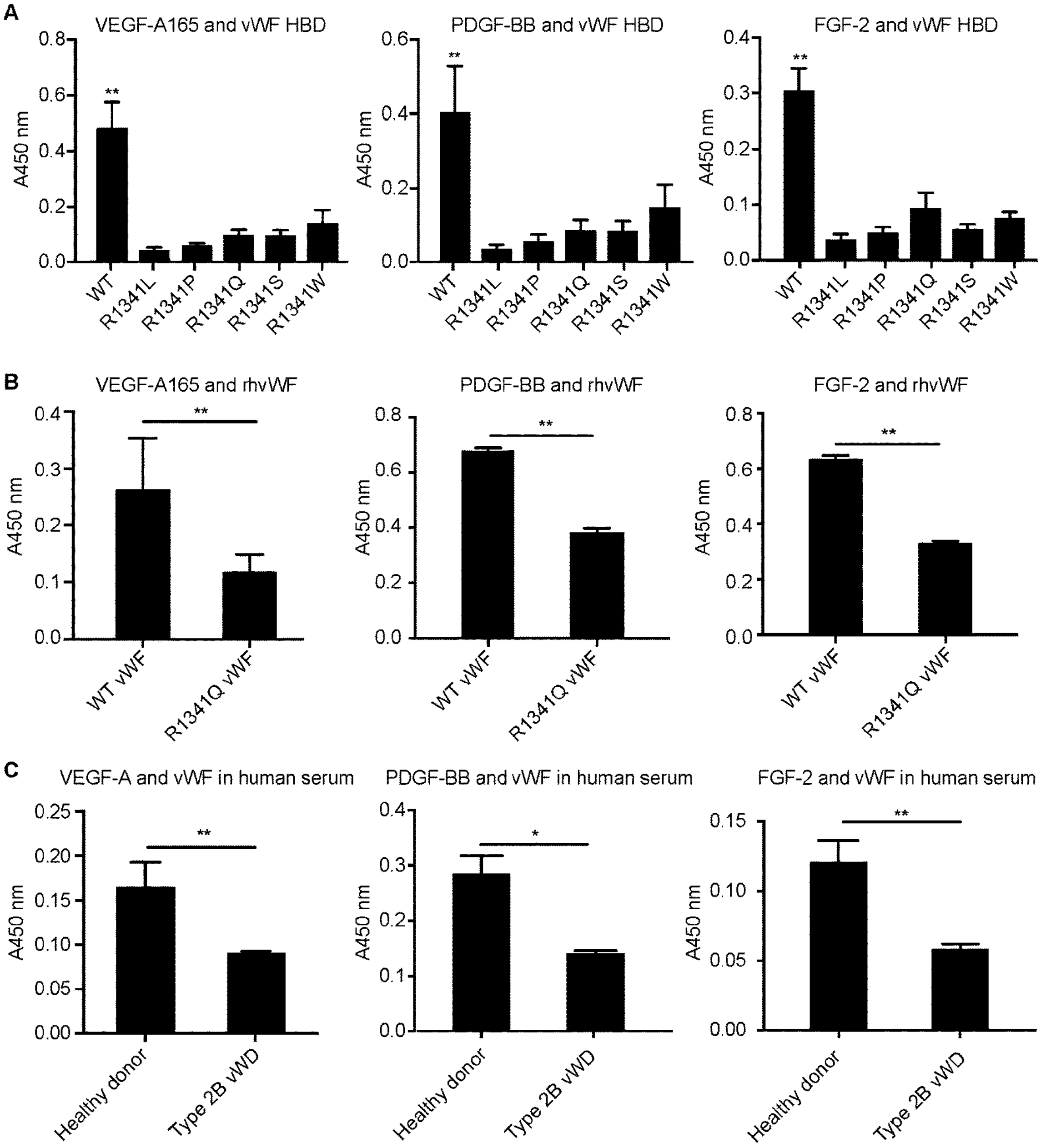

A
VEGF-A165 and vWF HBD
PDGF-BB and vWF HBD
FGF-2 and vWF HBD
A450 nm
0.8
0.6
0.4
0.2
0.0
0.3
0.1
**
WT
R1341L
R1341P
R1341Q
R1341S
R1341W
B
VEGF-A165 and rhvWF
PDGF-BB and rhvWF
FGF-2 and rhvWF
WT vWF
R1341Q vWF
C
VEGF-A and vWF in human serum
PDGF-BB and vWF in human serum
FGF-2 and vWF in human serum
0.25
0.20
0.15
0.10
0.05
0.00
*
Healthy donor
Type 2B vWD

FIG. 19A-C

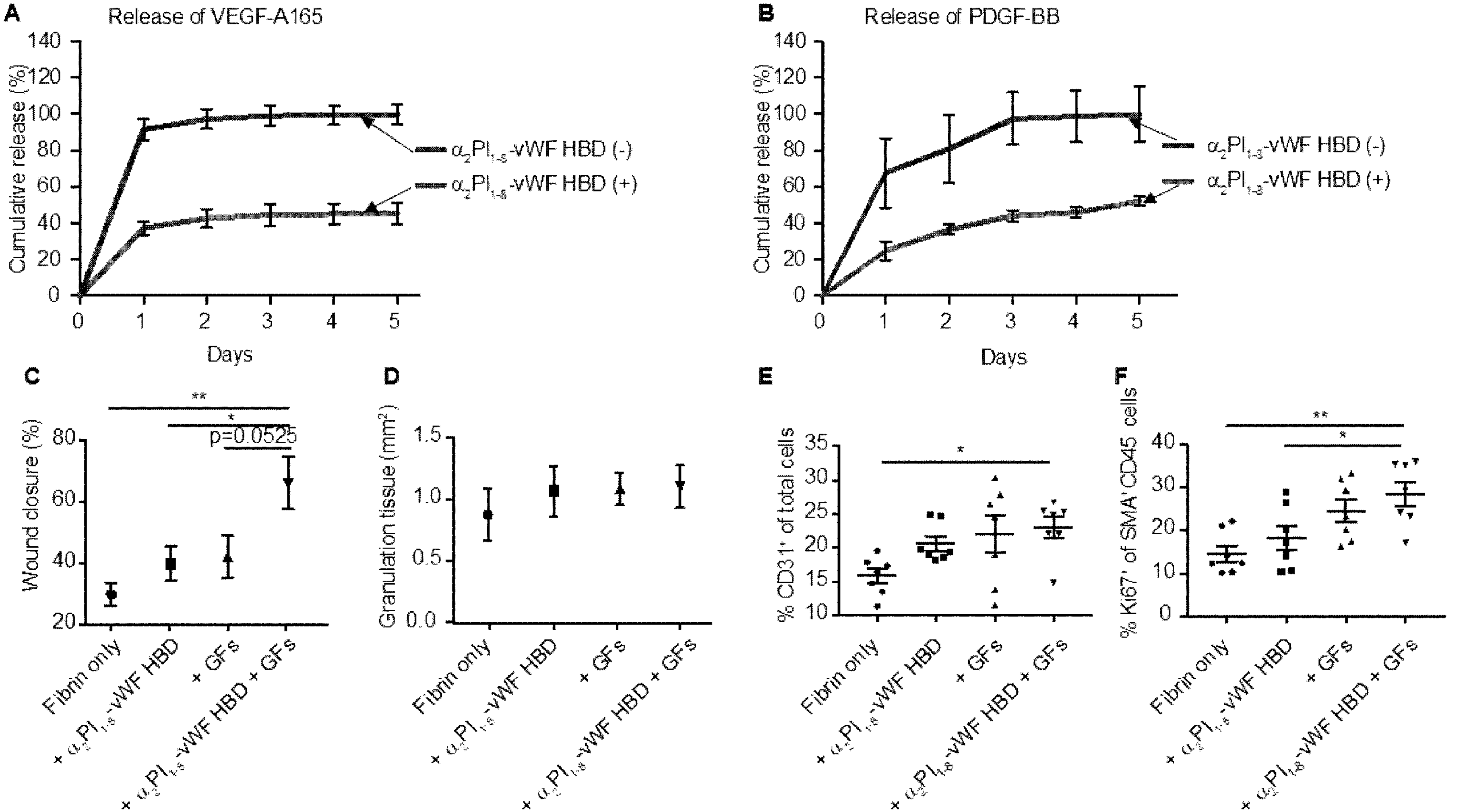

A
Release of VEGF-A165
Cumulative release (%)
140
120
100
80
60
40
20
0
Days
0
1
2
3
4
5
α2PI1-8-vWF HBD (-)
α2PI1-8-vWF HBD (+)
B
Release of PDGF-BB
Cumulative release (%)
140
120
100
80
60
40
20
0
Days
0
1
2
3
4
5
α2PI1-8-vWF HBD (-)
α2PI1-8-vWF HBD (+)
C
Wound closure (%)
80
60
40
20
**
*
p=0.0525
Fibrin only
+ α2PI1-8-vWF HBD
+ GFs
+ α2PI1-8-vWF HBD + GFs
D
Granulation tissue (mm2)
1.5
1.0
0.5
0.0
Fibrin only
+ α2PI1-8-vWF HBD
+ GFs
+ α2PI1-8-vWF HBD + GFs
E
% CD31+ of total cells
35
30
25
20
15
10
*
Fibrin only
+ α2PI1-8-vWF HBD
+ GFs
+ α2PI1-8-vWF HBD + GFs
F
% Ki67+ of SMA+CD45- cells
40
30
20
10
0
**
*
Fibrin only
+ α2PI1-8-vWF HBD
+ GFs
+ α2PI1-8-vWF HBD + GFs

FIG. 20A-F

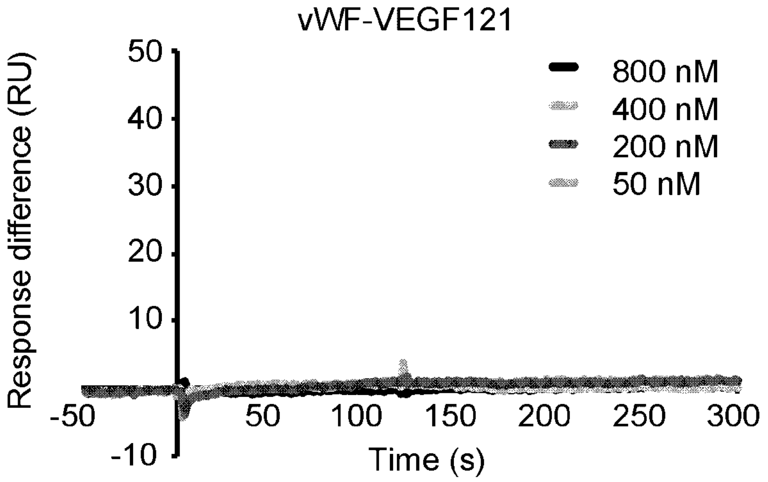

vWF-VEGF121
Response difference (RU)
50
40
30
20
10
-10
-50
50
100
150
200
250
300
Time (s)
800 nM
400 nM
200 nM
50 nM

FIG. 21

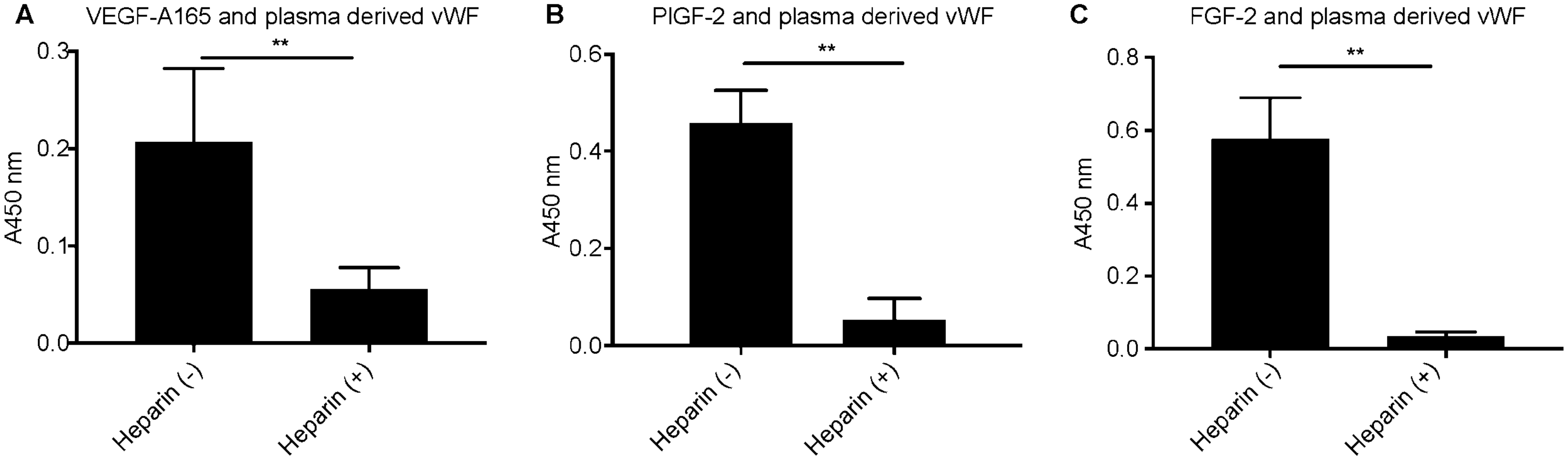

A
VEGF-A165 and plasma derived vWF
A450 nm
0.3
0.2
0.1
0.0
**
Heparin (-)
Heparin (+)
B
PIGF-2 and plasma derived vWF
A450 nm
0.6
0.4
0.2
0.0
**
Heparin (-)
Heparin (+)
C
FGF-2 and plasma derived vWF
A450 nm
0.8
0.6
0.4
0.2
0.0
**
Heparin (-)
Heparin (+)

FIG. 22A-C

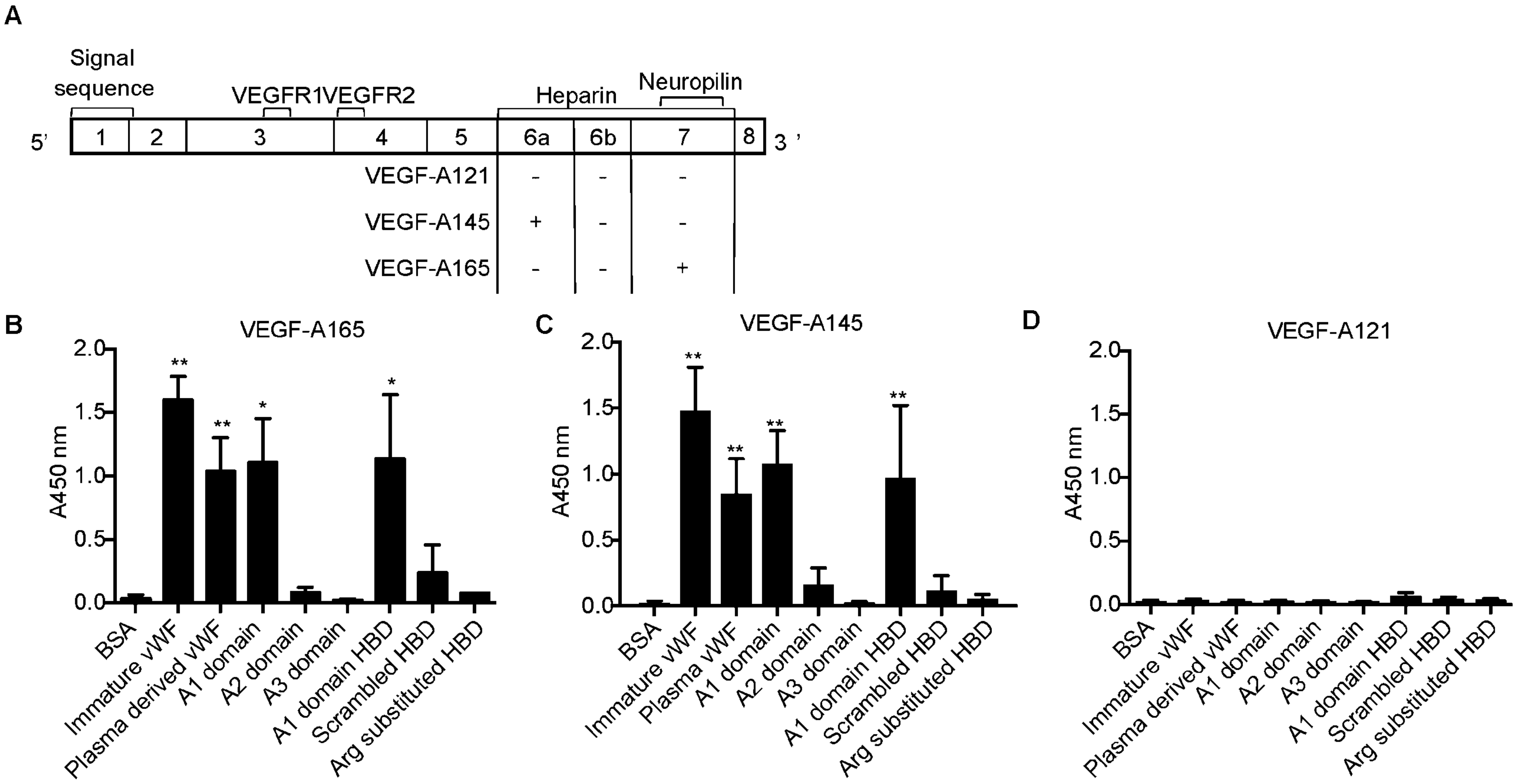

A
Signal sequence
VEGFR1
VEGFR2
Heparin
Neuropilin
5'
1
2
3
4
5
6a
6b
7
8
3 '
VEGF-A121 - - -
VEGF-A145 + - -
VEGF-A165 - - +
B
VEGF-A165
A450 nm
0.0
0.5
1.0
1.5
2.0
**
**
*
*
BSA
Immature vWF
Plasma derived vWF
A1 domain
A2 domain
A3 domain
A1 domain HBD
Scrambled HBD
Arg substituted HBD
C
VEGF-A145
A450 nm
0.0
0.5
1.0
1.5
2.0
**
**
**
**
BSA
Immature vWF
Plasma vWF
A1 domain
A2 domain
A3 domain
A1 domain HBD
Scrambled HBD
Arg substituted HBD
D
VEGF-A121
A450 nm
0.0
0.5
1.0
1.5
2.0
BSA
Immature vWF
Plasma derived vWF
A1 domain
A2 domain
A3 domain
A1 domain HBD
Scrambled HBD
Arg substituted HBD

FIG. 23A-D

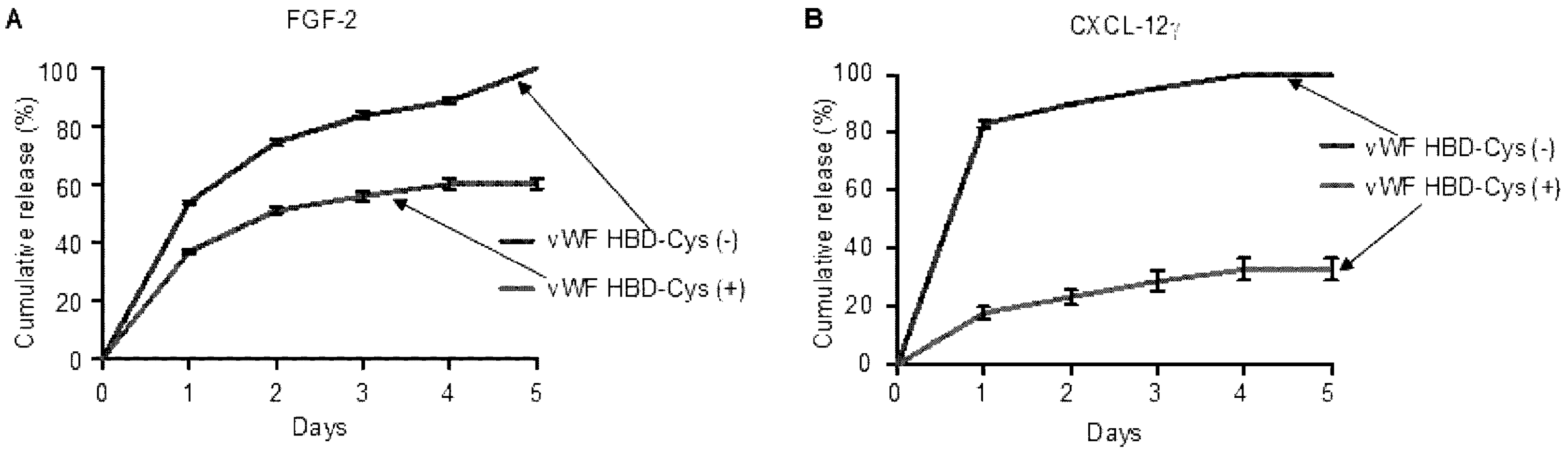

A
FGF-2
Cumulative release (%)
100
80
60
40
20
0
0
1
2
3
4
5
Days
vWF HBD-Cys (-)
vWF HBD-Cys (+)
B
CXCL-12γ
Cumulative release (%)
100
80
60
40
20
0
0
1
2
3
4
5
Days
vWF HBD-Cys (-)
vWF HBD-Cys (+)

FIG. 24A-B

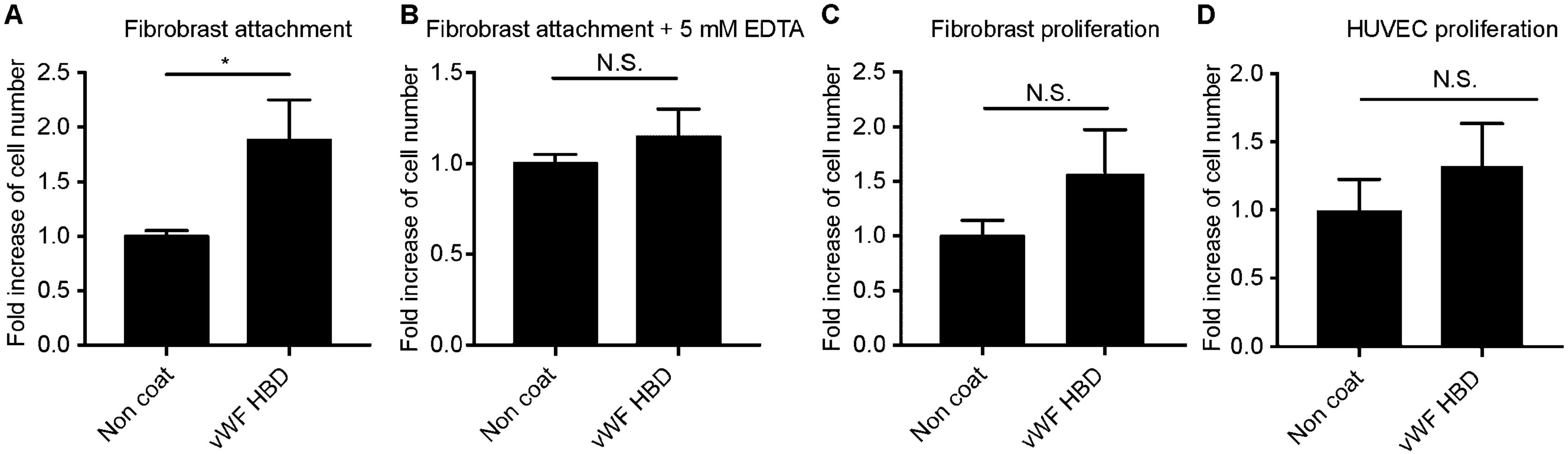

A
Fibrobrast attachment
Fold increase of cell number
2.5
2.0
1.5
1.0
0.5
0.0
*
Non coat
vWF HBD
B
Fibrobrast attachment + 5 mM EDTA
Fold increase of cell number
1.5
1.0
0.5
0.0
N.S.
Non coat
vWF HBD
C
Fibrobrast proliferation
Fold increase of cell number
2.5
2.0
1.5
1.0
0.5
0.0
N.S.
Non coat
vWF HBD
D
HUVEC proliferation
Fold increase of cell number
2.0
1.5
1.0
0.5
0.0
N.S.
Non coat
vWF HBD

FIG. 25A-D

METHODS AND COMPOSITIONS FOR THE TREATMENT OF WOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application 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

[0002] 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

[0003] 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

[0004] 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

[0005] 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.

[0006] 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.

[0007] 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).

[0008] 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 α2-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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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, PlGF, PDGF, FGF, and BMP. In some embodiments, the growth factor comprises one or more of VEGF-A 165, PlGF2, 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 PlGF or from PlGF2. 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.

[0021] 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, PlGF, PDGF, FGF and BMP. In some embodiments, the growth factor comprises one or more of VEGF-A 165, PlGF2, PDGF-BB, FGF-2 and BMP-2. In some embodiments, the composition comprises one or more growth factors or cytokines described herein.

[0022] 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 α2 plasmin inhibitor peptide (α_2PI_{1-8}). 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.

[0023] In some embodiments, the dose of a growth factor is adminstered according to a dosage amount and schedule described herein.

[0024] 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) μg/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, μg, 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 μg/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.

[0025] 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, μg, 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 μg/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.

[0026] 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) μg/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, μg, 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 μg/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.

[0027] In some embodiments, with respect to PlGF or specifically PlGF2, 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) μg/kg body weight. In some embodiments, with respect to PlGF or specifically PlGF2, 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 PlGF or specifically PlGF2, 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 μg/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.

[0028] 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) μg/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 μg/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.

[0029] 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.

[0030] 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).

[0031] 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.

[0032] 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.

[0033] 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.

[0034] Yet further aspects relate to a method for treating angiodysplasia 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 angiodysplasia. In some embodiments, the subject is one that has reduced high molecular weight multimers (HMWM) of the vWF protein.

[0035] 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.

[0036] 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 mm^2. 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 mm^2, or any derivable range therein.

[0037] 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 GPIbα. 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.

[0038] 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.

[0039] The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product or synthetic amino acid polymer.

[0040] 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.

[0041] It is contemplated that the methods and compositions include exclusion of any of the embodiments described herein.

[0042] The terms "a" and "an" are defined as one or more unless this disclosure explicitly requires otherwise.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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

[0047] 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.

[0048] FIGS. **1**A-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.

[0049] FIGS. **2**A-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 μg/mL laminin and further incubated with a 1 μg/mL (A) VEGF-A165, (B) PlGF-2, or (C) FGF-2 solution in the absence or presence of excess (10 μM) heparin. Bound GFs were detected using a specific antibody for each GF (n=4, mean±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.

[0050] FIGS. **3**A-D. GFs bind to recombinant LG domain protein derived from laminin α3, α4 and α5 chains. Affinity of GFs against recombinant laminin LG domains. ELISA plates were coated with 1 μg/mL (A) $\alpha3_{2928\text{-}3150}$, (B) $\alpha4_{826\text{-}1816}$, or (C) $\alpha5_{3026\text{-}3482}$ and further incubated with 1 μg/mL of VEGF-A165, VEGF-A121, PlGF-2, PlGF-1, PDGF-BB, or FGF-2 solution. Bound GFs were detected using a specific antibody for each GF (n=4, mean±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 $\alpha3_{2928\text{-}3150}$ against VEGF-A165 and PDGF-BB were measured by SPR. A SPR chip was functionalized with the laminin $\alpha3_{2928\text{-}3150}$ 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.

[0051] FIGS. **4**A-F. GFs bind to chemically synthesized laminin HBD peptides derived from the LG domain of laminin α3, α4, and α5 chains. (A) The location of laminin-derived peptides in the LG domain of laminin α3, α4, and α5 chains. (B-F) Affinity of heparin and GFs against chemically synthesized peptides derived from the LG domain of laminin α3, α4, and α5 chains. ELISA plates were coated with 10 μg/mL laminin peptide and further incubated with (B) biotinylated heparin, (C) VEGF-A165 and VEGF-A121, (D) PlGF-2 and PlGF-1, (E) PDGF-BB, or (F) FGF-2. Concentrations were 1 μg/mL for GFs and 10 μg/mL for heparin. Bound heparin was detected with streptavidin, and bound GFs with a specific antibody for each GF (n=4, mean±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.

[0052] FIGS. **5**A-D. Chemically synthesized peptides derived from the LG domain of laminin α3, α4 and α5 chains bind to syndecans. Affinity of syndecans to chemically synthesized peptides derived from the laminin α3, α4 and α5 LG domains. ELISA plates were coated with 10 μg/mL laminin peptide and further incubated with 1 μg/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±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.

[0053] FIGS. **6**A-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 μg/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±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.

[0054] FIGS. **7**A-C. GF retention in fibrin matrices is enhanced by incorporating laminin HBD peptide. (A,B) GF retention in fibrin matrix. $\alpha_2PI_{1\text{-}8}$-$\alpha3_{3043\text{-}3067}$ or $\alpha_2PI_{1\text{-}8}$-$\alpha5_{3417\text{-}3436}$ 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±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 $\alpha_2PI_{1\text{-}8}$-$\alpha3_{3043\text{-}3067}$ 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±SEM. Student's t-test; $^{**}p<0.01$.

[0055] FIGS. **8**A-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_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide, fibrin containing admixed GFs, and fibrin functionalized with α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide containing GFs. After 4, 7, and 10 days, (A-B) wound closure and (C) granulation tissue area were evaluated by histology (means±SEM, day 4: n=6, day 7: fibrin only and α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide+GFs, n=10; other treatment groups, n=11, day 10: α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide, n=8, α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 μm. (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±SEM). $^*P<0.05$, $^{**}P<0.01$, ANOVA with Tukey's test.

[0056] 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 $\alpha3_{3043-3062}$. ELISA plates were coated with 10 μg/mL laminin peptide and further incubated with VEGF-A165, PlGF-2, PDGF-BB, or FGF-2. Concentrations were 1 μg/mL for GFs. Bound GF was detected with a specific antibody for each GF (n=4, mean±SEM). Statistical analyses were done using one-way ANOVA. $^*p<0.05$, $^{**}p<0.01$. Sequence of the peptides are described in Table 2.

[0057] 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 μM of $\alpha3_{3043-3067}$ 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. (means±SEM, n=4). Statistical analyses were done using one-way ANOVA. $^{**}P<0.01$

[0058] 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide, fibrin containing admixed GFs, and fibrin functionalized with α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide containing GFs. Representative pictures of wounds after 0 and 7 days are presented.

[0059] FIG. **12**. Bipartite «bridge» proteins composed of a growth factor-binding domain linked to a collagen I-binding domain.

[0060] FIGS. **13**A-F. Conjugation of a collagen-binding domain FabCol to a growth factor-binding domain FgHBD.

[0061] FIGS. **14**A-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.

[0062] FIGS. **15**A-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. (means±SEM). Proliferation of (C) CD31+CD45− endothelial cells and (D) SMA+CD45− SMCs assessed by Ki67+ marker determined using flow cytometry (means±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.

[0063] FIGS. **16**A-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, mean±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 (2000 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.

[0064] FIGS. **17**A-B. vWF binds to VEGF-A in human serum. (A) ELISA plates were coated with 10 μg/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, mean±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. Representative image of 3 human serum. Statistical analyses were done using Student's t-test. $^{**}p<0.01$.

[0065] FIGS. **18**A-C. The HBD within the A1 domain of vWF mediates GF binding. (A) The location of the A1 domain and HBD within vWF. FIG. **18**A discloses SEQ ID NO: 50. (B-C) Affinity of VEGF-A, PlGF, 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 μg/mL recombinant vWF A1 domain protein or 10 μg/mL vWF A1 HBD peptide and further incubated with a 1 μg/mL VEGF-A, PlGF, PDGF-BB, FGF-2, or CXCL-12 solution. Bound GFs were detected using a specific antibody for each GF (n=4, mean±SD). Statistical analyses were done using ANOVA with Tukey's test or Student's t-test. $^*p<0.05$, $^{**}p<0.01$.

[0066] FIGS. **19**A-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, mean±SD). (B) Binding of VEGF-A165, PDGF-BB, and FGF-2 to recombinant human (rh)vWF with R1341Q substitution. (n=4, mean±SD). (C) Binding of VEGF-A165, PDGF-BB, and FGF-2 to vWF in healthy donor or type 2B vWD patient serum (n=3, mean+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.

[0067] FIGS. **20**A-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; mean±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 □$_2$PI$_{1-8}$-vWF HBD only, fibrin containing GFs only, and fibrin functionalized with □$_2$PI$_{1-8}$-vWF HBD containing GFs. (C) After 7 d, wound closure and (D) granulation tissue area were evaluated by histomorphometry. (means±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 (means±SEM). *p<0.05, **p<0.01, ANOVA with Tukey's test.

[0068] 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 nM). Curves represent the responses (in RU) to vWF obtained.

[0069] FIGS. **22**A-C. Excess heparin inhibits GF binding to vWF. Inhibition of GF binding to vWF by excess heparin. ELISA plates were coated with 10 μg/mL vWF and further incubated with a 1 μg/mL (A) VEGF-A165, (B) PlGF-2, or (C) FGF-2 solution containing 10 μM heparin. Bound GFs were detected using a specific antibody for each GF (n=4, mean±SD).

[0070] FIGS. **23**A-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 μg/mL, each). Bound VEGF-A was detected using a specific antibody for VEGF-A (n=4, mean±SD). Statistical comparisons were done using ANOVA with Tukey's test compared with BSA control. **p<0.01.

[0071] FIGS. **24**A-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-12γ over 5 d. (n=3; mean±SEM). All data points for vWF HBD were statistically significant compared to controls without vWF HBD (p<0.01, Student's t-test)

[0072] FIGS. **25**A-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 μg/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±SD). (C) 1000 cells/well human lung fibroblasts or (D) 1000 cells/well human umbilical vein endothelial cells (HUVEC) were cultured on 1 μg/mL vWF HBD pre-coated 96-well tissue culture plates. Cell numbers were quantified after 72 hrs using a CyQUANT assay (n=4, mean±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

[0073] Lamin and von Willebrand (vWF) peptides that bind certain growth factors are useful in would healing and tissue repair.

[0074] 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 CXCL12γ, 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.

[0075] 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 Ibα (GPIbα 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

[0076] Embodiments of the disclosure relate to laminin peptides and von Willebrand factor peptides that bind to growth factors.

[0077] 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.

[0078] 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 α6β1, α7β1 and α6β4 integrins and syndecan. The laminin α3, α4, and α5 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

[0079] 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 MFCKLVEHVPGRPVRNPQCRICDGNSANPRERHPISHAIDGTNNWWQ SPSIQNGREYHWVTITLDLRQVFQVAYVIIKAANAPRPGNWILERSLDG TTFSPWQYYAVSDSECLSRYNITPRRGPPTYRADDEVICTSYYSRLVPL EHGEIHTSLINGRPSADDLSPKLLEFTSARYIRLRLQRIRTLNADLMTLS HREPKELDPIVTRRYYYSIKDISVGGMCICYGHASSCPWDETTKKLQC QCEHNTCGESCNRCCPGYHQQPWRPGTVSSGNTCEACNCHNKAKDC YYDESVAKQKKSLNTAGQFRGGGVCINCLQNTMGINCETCIDGYYRP HKVSPYEDEPCRPCNCDPVGSLSSVCIKDDLHSDLHNGKQPGQCPCKE GYTGEKCDRCQLGYKDYPTCVSCGCNPVGSASDEPCTGPCVCKENVE GKACDRCKPGFYNLKEKNPRGCSECFCFGVSDVCSSLSWPVGQVNSM SGWLVTDLISPRKIPSQQDALGGRHQVSINNTAVMQRLAPKYYWAAP EAYLGNKLTAFGGFLKYTVSYDIPVETVDSNLMSHADVIIKGNGLTLS TQAEGLSLQPYEEYLNVVRLVPENFQDFHSKRQ1DRDQLMTVLANVT HLLIRANYNSAKMALYRLESVSLDIASSNAIDLVVAADVEHCECPQGY TGTSCESCLSGYYRVDGILFGGICQPCECHGHAAECNVHGVCIACAHN TTGVHCEQCLPGFYGEPSRGTPGDCQPCACPLTIASNNFSPTCHLNDGD EVVCDWCAPGYSGAWCERCADGYYGNPTVPGESCVPCDCSGNVDPS EAGHCDSVTGECLKCLGNTDGAHCERCADGFYGDAVTAKNCRACEC HVKGSHSAVCHLETGLCDCKPNVTGQQCDQCLHGYYGLDSGHGCRP CNCSVAGSVSDGCTDEGQCHCVPGVAGKRCDRCAHGFYAYQDGSCT PCDCPHTQNTCDPETGECVCPPHTQGVKCEECEDGHWGYDAEVGCQ ACNCSLVGSTHHRCDVVTGHCQCKSKFGGRACDQCSLGYRDFPDCVP CDCDLRGTSGDACNLEQGLCGCVEETGACPCKENVFGPQCNECREGT FALRADNPLGCSPCFCSGLSHLCSELEDYVRTPVTLGSDQPLLRVVSQS NLRGTTEGVYYQAPDFLLDAATVRQHIRAEPFYWRLPQQFQGDQLMA YGGKLKYSVAFYSLDGVGTSNFEPQVLIKGGRIRKQVIYMDAPAPENG VRQEQEVAMRENFWKYFNSVSEKPVTREDFMSVLSDIEYILIKASYGQ GLQQSRISDISMEVGRKAEKLHPEEEVASLLENCVCPPGTVGFSCQDC APGYHRGKLPAGSDRGPRPLVAPCVPCSCNNHSDTCDPNTGKCLNCG DNTAGDHCDVCTSGYYGKVTGSASDCALCACPHSPPASFSPTCVLEG DHDFRCDACLLGYEGKHCERCSSSYYGNPQTPGGSCQKCDCNPHGSV HGDCDRTSGQCVCRLGASGLRCDECEPRHILMETDCVSCDDECVGVL LNDLDEIGDAVLSLNLTGIIPVPYGILSNLENTTKYLQESLLKENMQKD LGKIKLEGVAEETDNLQKKLTRMLASTQKVNRATERIFKESQDLAIAIE RLQMSITEIMEKTTLNQTLDEDFLLPNSTLQNMQQNGTSLLEIMQIRDF TQLHQNATLELKAAEDLLSQIQENYQKPLEELEVLKEAASHVLSKHNN ELKAAEALVREAEAKMQESNHLLLMVNANLREFSDKKLHVQEEQNL TSELIVQGRGLIDAAAAQTDAVQDALEHLEDHQDKLLLWSAKIRHHID DLVMHMSQRNAVDLVYRAEDHAAEFQRLADVLYSGLENIRNVSLNA TSAAYVHYNIQSLIEESEELARDAHRTVTETSLLSESLVSNGKAAVQRS SRFLKEGNNLSRKLPGIALELSELRNKTNRFQENAVEITRQTNESLLILR AIPKGIRDKGAKTKELATSASQSAVSTLRDVAGLSQELLNTSASLSRVN TTLRETHQLLQDSTMATLLAGRKVKDVEIQANLLFDRLKPLKMLEEN LSRNLSEIKLLISQARKQAASIKVAVSADRDCIRAYQPQISSTNYNTLTL NVKTQEPDNLLFYLGSSTASDFLAVEMRRGRVAFLWDLGSGSTRLEFP

-continued

Human Laminin	Sequence
	DEPIDDNRWHSIHVAREGNIGSLSVKEMSSNQKSPTKTSKSPGTANVLD VNNSTLMFVGGLGGQIKKSPAVKVTHFKGCLGEAFLNGKSIGLWNYIE REGKCRGCFGSSQNEDPSEHFDGSGYSVVEKSLPATVTQIIMLENTESP NGLLLYLGSYGTKDFLSIELFRGRVKVMTDLGSGPITLLTDRRYNNGT WYKIAFQRNRKQGVLAVIDAYNTSNKETKQGETPGASSDLNRLDKDPI YVGGLPRSRVVRRGVTTKSFVGCIKNLEISRSTFDLLRNSYGVRKGCLL EPIRSVSFLKGGYIELPPKSLSPESEWLVTFATTNSSGIILAALGGDVEKR GDREEAHVPFFSVMLIGGNIEVHVNPGDGTGLRKALLHAPTGTCSDGQ AHSISLVRNRRIITVQLDENNPVEMKLGTLVESRTINVSNLYVGGIPEGE GTSLLTMRRSEHGCIKNLIENLELLDENSAVGHEQVDLDTCWLSERPK LAPDAEDSKLLPEPRAFPEQCVVDAALEYVPGAHQEGLTQNSHEILPEN QSAVRKKLSVELSIRTFASSGLIYYMAHQNQADYAVLQLHGGRLHFM FDLGKGRTKVSHPALLSDGKWHTVKTDYVKRKGFITVDGRESPMVTV VGDGTMLDVEGLFYLGGLPSQYQARKIGNITHSIPACIGDVTVNSKQL DKDSPVSAFTVNRCYAVAQEGTYFDGSGYAALVKEGYKVQSDVNITL EFRTSSQNGVLLGISTAKVDAIGLELVDGKVLFHVNNGAGRITAAYEP KTATVLCDGKWHTLQANKSKHRITLIVDGNAVGAESPHTQSTSVDTN NPIYVGGYPAGVKQKCLRSQTSFRGCLRKLALIKSPQVQSEDESRAFEL HGVFLHSCPGTES
laminin subunit alpha-2 isoform a precursor (LAMA2-isoform a); SEQ ID NO: 26	MPGAAGVLLLLLLSGGLGGVQAQRPQQQRQSQAHQQRGLFPAVLNL ASNALITTNATCGEKGPEMYCKLVEHVPGQPVRNPQCRICNQNSSNPN QRHPITNAIDGKNTWWQSPSIKNGIEYHYVTITLDLQQVFQIAYVIVKA ANSPRPGNWILERSLDDVEYKPWQYHAVTDTECLTLYNIYPRTGPPSY AKDDEVICTSFYSKIHPLENGEIHISLINGRPSADDPSPELLEFTSARYIRL RFQRIRTLNADLMMFAHKDPREIDPIVTRRYYYSVKDISVGGMCICYG HARACPLDPATNKSRCECEHNTCGDSCDQCCPGFHQKPWRAGTFLTK TECEACNCHGKAEECYYDENVARRNLSLNIRGKYIGGGVCINCTQNT AGINCETCTDGFFRPKGVSPNYPRPCQPCHCDPIGSLNEVCVKDEKHA RRGLAPGSCHCKTGFGGVSCDRCARGYTGYPDCKACNCSGLGSKNED PCFGPCICKENVEGGDCSRCKSGFFNLQEDNWKGCDECFCSGVSNRCQ SSYWTYGKIQDMSGWYLTDLPGRIRVAPQQDDLDSPQQISISNAEARQ ALPHSYYWSAPAPYLGNKLPAVGGQLTFTISYDLEEEEEDTERVLQLM IILEGNDLSISTAQDEVYLHPSEEHTNVLLLKEESFTIHGTHFPVRRKEF MTVLANLKRVLLQITYSFGMDAIFRLSSVNLESAVSYPTDGSIAAAVE VCQCPPGYTGSSCESCWPRHRRVNGTIFGGICEPCQCFGHAESCDDVT GECLNCKDHTGGPYCDKCLPGFYGEPTKGTSEDCQPCACPLNIPSNNF SPTCHLDRSLGLICDGCPVGYTGPRCERCAEGYFGQPSVPGGSCQPCQ CNDNLDFSIPGSCDSLSGSCLICKPGTTGRYCELCADGYFGDAVDAKN CQPCRCNAGGSFSEVCHSQTGQCECRANVQGQRCDKCKAGTFGLQSA RGCVPCNCNSFGSKSFDCEESGQCWCQPGVTGKKCDRCAHGYFNFQE GGCTACECSHLGNNCDPKTGRCICPPNTIGEKCSKCAPNTWGHSITTG CKACNCSTVGSLDFQCNVNTGQCNCHPKFSGAKCTECSRGHWNYPRC NLCDCFLPGTDATTCDSETKKCSCSDQTGQCTCKVNVEGIHCDRCRPG KFGLDAKNPLGCSSCYCFGTTTQCSEAKGLIRTWVTLKAEQTILPLVD EALQHTTTKGIVFQHPEIVAHMDLMREDLHLEPFYWKLPEQFEGKKL MAYGGKLKYAIYFEAREETGFSTYNPQVIIRGGTPTHARIIVRHMAAPL IGQLTRHEIEMTEKEWKYYGDDPRVHRTVTREDFLDILYDIHYILIKAT YGNFMRQSRISEISMEVAEQGRGTTMTPPADLIEKCDCPLGYSGLSCEA CLPGFYRLRSQPGGRTPGPTLGTCVPCQCNGHSSLCDPETSICQNCQHH TAGDFCERCALGYYGIVKGLPNDCQQCACPLISSSNNFSPSCVAEGLD DYRCTACPRGYEGQYCERCAPGYTGSPGNPGGSCQECECDPYGSLPVP CDPVTGFCTCRPGATGRKCDGCKHWHAREGWECVFCGDECTGLLLG DLARLEQMVMSINLTGPLPAPYKMLYGLENIVITQELKHLLSPQRAPER LIQLAEGNLNTLVTEMNELLTRATKVTADGEQTGQDAERTNTRAKSL GEFIKELARDAEAVNEKAIKLNETLGTRDEAFERNLEGLQKEIDQMIKE LRRKNLETQKEIAEDELVAAEALLKKVKKLFGESRGENEEMEKDLRE KLADYKNKVDDAWDLLREATDKIREANRLFAVNQKNMTALEKKKEA VESGKRQIENTLKEGNDILDEANRLADEINSIIDYVEDIQTKLPPMSEEL NDKIDDLSQEIKDRKLAEKVSQAESHAAQLNDSSAVLDGILDEAKNISF NATAAFKAYSNIKDYIDEAEKVAKEAKDLAHEATKLATGPRGLLKED AKGCLQKSFRILNEAKKLANDVKENEDHLNGLKTRIENADARNGDLL RTLNDTLGKLSAIPNDTAAKLQAVKDKARQANDTAKDVLAQITELHQ NLDGLKKNYNKLADSVAKTNAVVKDPSKNKIIADADATVKNLEQEA DRLIDKLKPIKELEDNLKKNISEIKELINQARKQANSIKVSVSSGGDCIR TYKPEIKKGSYNNIVVNVKTAVADNLLFYLGSAKFIDFLAIEMRKGKV SFLWDVGSGVGRVEYPDLTIDDSYWYRIVASRTGRNGTISVRALDGPK ASIVPSTHHSTSPPGYTILDVDANAMLFVGGLTGKLKKADAVRVITFT GCMGETYFDNKPIGLWNFREKEGDCKGCTVSPQVEDSEGTIQFDGEG YALVSRPIRWYPNISTVMFKFRTFSSSALLMYLATRDLRDFMSVELTD GHIKVSYDLGSGMASVVSNQNHNDGKWKSFTLSRIQKQANISIVDIDT NQEENIATSSSGNNFGLDLKADDKIYFGGLPTLRNLSMKARPEVNLKK YSGCLKDIEISRTPYNILSSPDYVGVTKGCSLENVYTVSFPKPGFVELSP

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Human Laminin	Sequence
	VPIDVGTEINLSFSTKNESGIILLGSGGTPAPPRRKRRQTGQAYYVILLNRGRLEVHLSTGARTMRKIVIRPEPNLFHDGREHSVHVERTRGIFTVQVDENRRYMQNLTVEQPIEVKKLFVGGAPPEFQPSPLRNIPPFEGCIWNLVINSVPMDFARPVSFKNADIGRCAHQKLREDEDGAAPAEIVIQPEPVPTPAFPTPTPVLTHGPCAAESEPALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHTMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTKGTGKPLEVNFAKALELRGVQPVSCPAN
laminin subunit alpha-2 isoform b precursor (LAMA2-isoform b); SEQ ID NO: 27	MPGAAGVLLLLLLSGGLGGVQAQRPQQQRQSQAHQQRGLFPAVLNLASNALITTNATCGEKGPEMYCKLVEHVPGQPVRNPQCRICNQNSSNPNQRHPITNAIDGKNTWWQSPSIKNGIEYHYVTITLDLQQVFQIAYVIVKAANSPRPGNWILERSLDDVEYKPWQYHAVTDTECLTLYNIYPRTGPPSYAKDDEVICTSFYSKIHPLENGEIHISLINGRPSADDPSPELLEFTSARYIRLRFQRIRTLNADLMMFAHKDPREIDPIVTRRYYYSVKDISVGGMCICYGHARACPLDPATNKSRCECEHNTCGDSCDQCCPGFHQKPWRAGTFLTKTECEACNCHGKAEECYYDENVARRNLSLNIRGKYIGGGVCINCTQNTAGINCETCTDGFFRPKGVSPNYPRPCQPCHCDPIGSLNEVCVKDEKHARRGLAPGSCHCKTGFGGVSCDRCARGYTGYPDCKACNCSGLGSKNEDPCFGPCICKENVEGGDCSRCKSGFFNLQEDNWKGCDECFCSGVSNRCQSSYWTYGKIQDMSGWYLTDLPGRIRVAPQQDDLDSPQQISISNAEARQALPHSYYWSAPAPYLGNKLPAVGGQLTFTISYDLEEEEEDTERVLQLMIILEGNDLSISTAQDEVYLHPSEEHTNVLLLKEESFTIHGTHFPVRRKEFMTVLANLKRVLLQITYSFGMDAIFRLSSVNLESAVSYPTDGSIAAAVEVCQCPPGYTGSSCESCWPRHRRVNGTIFGGICEPCQCFGHAESCDDVTGECLNCKDHTGGPYCDKCLPGFYGEPTKGTSEDCQPCACPLNIPSNNFSPTCHLDRSLGLICDGCPVGYTGPRCERCAEGYFGQPSVPGGSCQPCQCNDNLDFSIPGSCDSLSGSCLICKPGTTGRYCELCADGYFGDAVDAKNCQPCRCNAGGSFSEVCHSQTGQCECRANVQGQRCDKCKAGTFGLQSARGCVPCNCNSFGSKSFDCEESGQCWCQPGVTGKKCDRCAHGYFNFQEGGCTACECSHLGNNCDPKTGRCICPPNTIGEKCSKCAPNTWGHSITTGCKACNCSTVGSLDFQCNVNTGQCNCHPKFSGAKCTECSRGHWNYPRCNLCDCFLPGTDATTCDSETKKCSCSDQTGQCTCKVNVEGIHCDRCRPGKFGLDAKNPLGCSSCYCFGTTTQCSEAKGLIRTWVTLKAEQTILPLVDEALQHTTTKGIVFQHPEIVAHMDLMREDLHLEPFYWKLPEQFEGKKLMAYGGKLKYAIYFEAREETGFSTYNPQVIIRGGTPTHARIIVRHMAAPLIGQLTRHEIEMTEKEWKYYGDDPRVHRTVTREDFLDILYDIHYILIKATYGNFMRQSRISEISMEVAEQGRGTTMTPPADLIEKCDCPLGYSGLSCEACLPGFYRLRSQPGGRTPGPTLGTCVPCQCNGHSSLCDPETSICQNCQHHTAGDFCERCALGYYGIVKGLPNDCQQCACPLISSSNNFSPSCVAEGLDDYRCTACPRGYEGQYCERCAPGYTGSPGNPGGSCQECECDPYGSLPVPCDPVTGFCTCRPGATGRKCDGCKHWHAREGWECVFCGDECTGLLLGDLARLEQMVMSINLTGPLPAPYKMLYGLENMTQELKHLLSPQRAPERLIQLAEGNLNTLVTEMNELLTRATKVTADGEQTGQDAERTNTRAKSLGEFIKELARDAEAVNEKAIKLNETLGTRDEAFERNLEGLQKEIDQMIKELRRKNLETQKEIAEDELVAAEALLKKVKKLFGESRGENEEMEKDLREKLADYKNKVDDAWDLLREATDKIREANRLFAVNQKNMTALEKKKEAVESGKRQIENTLKEGNDILDEANRLADEINSIIDYVEDIQTKLPPMSEELNDKIDDLSQEIKDRKLAEKVSQAESHAAQLNDSSAVLDGILDEAKNISFNATAAFKAYSNIKDYIDEAEKVAKEAKDLAHEATKLATGPRGLLKEDAKGCLQKSFRILNEAKKLANDVKENEDHLNGLKTRIENADARNGDLLRTLNDTLGKLSAIPNDTAAKLQAVKDKARQANDTAKDVLAQITELHQNLDGLKKNYNKLADSVAKTNAVVKDPSKNKIIADADATVKNLEQEADRLIDKLKPIKELEDNLKKNISEIKELINQARKQANSIKVSVSSGGDCIRTYKPEIKKGSYNNIVVNVKTAVADNLLFYLGSAKFIDFLAIEMRKGKVSFLWDVGSGVGRVEYPDLTIDDSYWYRIVASRTGRNGTISVRALDGPKASIVPSTHHSTSPPGYTILDVDANAMLFVGGLTGKLKKADAVRVITFTGCMGETYFDNKPIGLWNFREKEGDCKGCTVSPQVIEDSEGTIQFDGEGYALVSRPIRWYPNISTVMEKERTFSSSALLMYLATRDLRDFMSVELTDGHIKVSYDLGSGMASVVSNQNHNDGKWKSFTLSRIQKQANISIVDIDTNQEENIATSSSGNNFGLDLKADDKIYFGGLPTLRNLRPEVNLKKYSGCLKDIEISRTPYNILSSPDYVGVTKGCSLENVYTVSFPKPGEVELSPVPIDVGTEINLSFSTKNESGIILLGSGGTPAPPRRKRRQTGQAYYVILLNRGRLEVHLSTGARTMRKIVIRPEPNLFHDGREHSVHVERTRGIFTVQVDENRRYMQNLTVEQPIEVKKLFVGGAPPEFQPSPLRNIPPFEGCIWNLVINSVPMDFARPVSFKNADIGRCAHQKLREDEDGAAPAEIVIQPEPVPTPAFPTPTPVLTHGPCAAESEPALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHTMIPT

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Human Laminin	Sequence
	KINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVG GLPINYTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFAN AQRGTYFDGTGFAKAVGGEKVGLDLLVEFEERTTTTGVLLGISSQKM DGMGIEMIDEKLMFHVDNGAGRFTAVYDAGVPGHLCDGQWHKVTA NKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGL TTSIPERGCIRSLKLTKGTGKPLEVNFAKALELRGVQPVSCPAN
laminin subunit alpha-3 isoform 1 precursor (LAMA3-isoform 1); SEQ ID NO: 28	MAAAARPRGRALGPVLPPTPLLLLVLRVLPACGATARDPGAAAGLSL HPTYFNLAEAARIWATATCGERGPGEGRPQPELYCKLVGGPTAPGSGH TIQGQFCDYCNSEDPRKAHPVTNAIDGSERWWQSPPLSSGTQYNRVNL TLDLGQLFHVAYILIKFANSPRPDLWVLERSVDFGSTYSPWQYFAHSK VDCLKEFGREANMAVTRDDDVLCVTEYSRIVPLENGEVVVSLINGRPG AKNFTFSHTLREFTKATNIRLRFLRTNTLLGHLISKAQRDPTVTRRYYY SIKDISIGGQCVCNGHAEVCNINNPEKLFRCECQHHTCGETCDRCCTGY NQRRWRPAAWEQSHECEACNCHGHASNCYYDPDVERQQASLNTQGI YAGGGVCINCQHNTAGVNCEQCAKGYYRPYGVPVDAPDGCIPCSCDP EHADGCEQGSGRCHCKPNFHGDNCEKCAIGYYNFPFCLRIPIFPVSTPS SEDPVAGDIKGCDCNLEGVLPEICDAHGRCLCRPGVEGPRCDTCRSGF YSFPICQACWCSALGSYQMPCSSVTGQCECRPGVTGQRCDRCLSGAY DFPHCQGSSSACDPAGTINSNLGYCQCKLHVEGPTCSRCKLLYWNLD KENPSGCSECKCHKAGTVSGTGECRQGDGDCHCKSHVGGDSCDTCED GYFALEKSNYFGCQGCQCDIGGALSSMCSGPSGVCQCREHVVGKVCQ RPENNYYFPDLHHMKYEIEDGSTPNGRDLRFGFDPLAFPEFSWRGYAQ MTSVQNDVRITLNVGKSSGSLFRVILRYVNPGTEAVSGHITIYPSWGAA QSKEIIFLPSKEPAFVTVPGNGFADPFSITPGIWVACIKAEGVLLDYLVL LPRDYYEASVLQLPVTEPCAYAGPPQENCLLYQHLPVTRFPCTLACEA RHFLLDGEPRPVAVRQPTPAHPVMVDLSGREVELHLRLRIPQVGHYVV VVEYSTEAAQLFVVDVNVKSSGSVLAGQVNIYSCNYSVLCRSAVIDH MSRIAMYELLADADIQLKGHMARFLLHQVCIIPIEEFSAEYVRPQVHCI ASYGRFVNQSATCVSLAHETPPTALILDVLSGRPFPHLPQQSSPSVDVL PGVTLKAPQNQVTLRGRVPHLGRYVFVIHFYQAAHPTFPAQVSVDGG WPRAGSFHASFCPHVLGCRDQVIAEGQIEFDISEPEVAATVKVPEGKSL VLVRVLVVPAENYDYQILHKKSMDKSLEFITNCGKNSFYLDPQTASRF CKNSARSLVAFYHKGALPCECHPTGATGPHCSPEGGQCPCQPNVIGRQ CTRCATGHYGFPRCKPCSCGRRLCEEMTGQCRCPPRTVRPQCEVCETH SFSFHPMAGCEGCNCSRRGTIEAAMPECDRDSGQCRCKPRITGRQCDR CASGFYRFPECVPCNCNRDGTEPGVCDPGTGACLCKENVEGTECNVC REGSFHLDPANLKGCTSCFCFGVNNQCHSSHKRRTKFVDMLGWHLET ADRVDIPVSFNPGSNSMVADLQELPATIHSASWVAPTSYLGDKVSSYG GYLTYQAKSFGLPGDMVLLEKKPDVQLTGQHMSIIYEETNTPRPDRLH HGRVHVVEGNFRHASSRAPVSREELMTVLSRLADVRIQGLYFTETQRL TLSEVGLEEASDTGSGRIALAVEICACPPAYAGDSCQGCSPGYYRDHK GLYTGRCVPCNCNGHSNQCQDGSGICVNCQHNTAGEHCERCQEGYY GNAVHGSCRACPCPHTNSFATGCVVNGGDVRCSCKAGYTGTQCERC APGYFGNPQKFGGSCQPCSCNSNGQLGSCHPLTGDCINQEPKDSSPAE ECDDCDSCVMTLLNDLATMGEQLRLVKSQLQGLSASAGLLEQMRHM ETQAKDLRNQLLNYRSAISNHGSKIEGLERELTDLNQEFETLQEKAQV NSRKAQTLNNNVNRATQSAKELDVKIKNVIRNVHILLKQISGTDGEGN NVPSGDFSREWAEAQRMMRELRNRNFGKHLREAEADKRESQLLLNRI RTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRARLQEAAAQAKQA NGLNQENERALGAIQRQVKEINSLQSDFTKYLTTADSSLLQTNIALQL MEKSQKEYEKLAASLNEARQELSDKVRELSRSAGKTSLVEEAEKHAR SLQELAKQLEEIKRNASGDELVRCAVDAATAYENILNAIKAAEDAANR AASASESALQTVIKEDLPRKAKTLSSNSDKLLNEAKMTQKKLKQEVSP ALNNLQQTLNIVTVQKEVIDTNLTTLRDGLHGIQRGDIDAMISSAKSM VRKANDITDEVLDGLNPIQTDVERIKDTYGRTQNEDFKKALTDADNSV NKLTNKLPDLWRKIESINQQLLPLGNISDNMDRIRELIQQARDAASKVA VPMRFNGKSGVEVRLPNDLEDLKGYTSLSLFLQRPNSRENGGTENMF VMYLGNKDASRDYIGMAVVDGQLTCVYNLGDREAELQVDQILTKSE TKEAVMDRVKFQRIYQFARLNYTKGATSSKPETPGVYDMDGRNSNTL LNLDPENVVFYVGGYPPDFKLPSRLSFPPYKGCIELDDLNENVLSLYNF KKTFNLNTTEVEPCRRRKEESDKNYFEGTGYARVPTQPHAPIPTFGQTI QTTVDRGLLFFAENGDRFISLNIEDGKLMVRYKLNSELPKERGVGDAI NNGRDHSIQIKIGKLQKRMWINVDVQNTIIDGEVFDFSTYYLGGIPIAIR ERFNISTPAFRGCMKNLKKTSGVVRLNDTVGVTKKCSEDWKLVRSAS FSRGGQLSFTDLGLPPTDHLQASFGFQTFQPSGILLDHQTWTRNLQVTL EDGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNSGLRLLIDDQLLR NSKRLKHISSSRQSLRLGGSNFEGCISNVFVQRLSLSPEVLDLTSNSLKR DVSLGGCSLNKPPFLMLLKGSTRFNKTKTFRINQLLQDTPVASPRSVK VWQDACSPLPKTQANHGALQFGDIPTSHLLFKLPQELLKPRSQFAVDM QTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCN DGKWHTVVFGHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPP SGKPKSLPTNSFVGCLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFS

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Human Laminin	Sequence
	EEGGHVVLAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHLCVYLEA GKVTASMDSGAGGTSTSVTPKQSLCDGQWHSVAVTIKQHILHLELDT DSSYTAGQIPFPPASTQEPLHLGGAPANLTTLRIPVWKSFFGCLRNIHV NHIPVPVTEALEVQGPVSLNGCPDQ
laminin subunit alpha-3 isoform 2 precursor (LAMA3-isoform 2); SEQ ID NO: 29	MPPAVRRSACSMGWLWIFGAALGQCLGYSSQQQRVPFLQPPGQSQLQ ASYVEFRPSQGCSPGYYRDHKGLYTGRCVPCNCNGHSNQCQDGSGIC VNCQHNTAGEHCERCQEGYYGNAVHGSCRACPCPHTNSFATGCVVN GGDVRCSCKAGYTGTQCERCAPGYFGNPQKFGGSCQPCSCNSNGQLG SCHPLTGDCINQEPKDSSPAEECDDCDSCVMTLLNDLATMGEQLRLVK SQLQGLSASAGLLEQMRHMETQAKDLRNQLLNYRSAISNHGSKIEGLE RELTDLNQEFETLQEKAQVNSRKAQTLNNNVNRATQSAKELDVKIKN VIRNVHILLKQISGTDGEGNNVPSGDFSREWAEAQRMMRELRNRNFG KHLREAEADKRESQLLLNRIRTWQKTHQGENNGLANSIRDSLNEYEA KLSDLRARLQEAAAQAKQANGLNQENERALGAIQRQVKEINSLQSDF TKYLTTADSSLLQTNIALQLMEKSQKEYEKLAASLNEARQELSDKVRE LSRSAGKTSLVEEAEKHARSLQELAKQLEEIKRNASGDELVRCAVDAA TAYENILNAIKAAEDAANRAASASESALQTVIKEDLPRKAKTLSSNSD KLLNEAKMTQKKLKQEVSPALNNLQQTLNIVTVQKEVIDTNLTTLRD GLHGIQRGDIDANTISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDTY GRTQNEDFKKALTDADNSVNKLTNKLPDLWRKIESINQQLLPLGNISD NMDRIRELIQQARDAASKVAVPMRFNGKSGVEVRLPNDLEDLKGYTS LSLFLQRPNSRENGGTENMFVMYLGNKDASRDYIGMAVVDGQLTCV YNLGDREAELQVDQILTKSETKEAVMDRVKFQRIYQFARLNYTKGAT SSKPETPGVYDMDGRNSNTLLNLDPENVVFYVGGYPPDFKLPSRLSFP PYKGCIELDDLNENVLSLYNFKKTFNLNTTEVEPCRRRKEESDKNYFE GTGYARVPTQPHAPIPTFGQTIQTTVDRGLLFFAENGDRFISLNIEDGKL MVRYKLNSELPKERGVGDAINNGRDHSIQIKIGKLQKRMWINVDVQN TIIDGEVFDFSTYYLGGIPIAIRERFNISTPAFRGCMKNLKKTSGVVRLN DTVGVTKKCSEDWKLVRSASFSRGGQLSFTDLGLPPTDHLQASFGFQT FQPSGILLDHQTWTRNLQVTLEDGYIELSTSDSGGPIFKSPQTYMDGLL HYVSVISDNSGLRLLIDDQLLRNSKRLKHISSSRQSLRLGGSNFEGCISN VFVQRLSLSPEVLDLTSNSLKRDVSLGGCSLNKPPFLMLLKGSTRFNKT KTFRINQLLQDTPVASPRSVKVWQDACSPLPKTQANHGALQFGDIPTS HLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGR LVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDGEKGRLVVDGLRA REGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDSKPLY TPSSSFGVSSCLGGPLEKGIYFSEEGGHVVLAHSVLLGPEFKLVFSIRPR SLTGILIHIGSQPGKHLCVYLEAGKVTASMDSGAGGTSTSVTPKQSLCD GQWHSVAVTIKQHILHLELDTDSSYTAGQIPFPPASTQEPLHLGGAPAN LTTLRIPVWKSFFGCLRNIHVNHIPVPVTEALEVQGPVSLNGCPDQ
laminin subunit alpha-3 isoform 3precursor (LAMA3-isoform 3); SEQ ID NO: 30	MAAAARPRGRALGPVLPPTPLLLLVLRVLPACGATARDPGAAAGLSL HPTYFNLAEAARIWATATCGERGPGEGRPQPELYCKLVGGPTAPGSGH TIQGQFCDYCNSEDPRKAHPVTNAIDGSERWWQSPPLSSGTQYNRVNL TLDLGQLFHVAYILIKFANSPRPDLWVLERSVDFGSTYSPWQYFAHSK VDCLKEFGREANMAVTRDDDVLCVTEYSRIVPLENGEVVVSLINGRPG AKNFTFSHTLREFTKATNIRLRFLRTNTLLGHLISKAQRDPTVTRRYYY SIKDISIGGQCVCNGHAEVCNINNPEKLFRCECQHHTCGETCDRCCTGY NQRRWRPAAWEQSHECEACNCHGHASNCYYDPDVERQQASLNTQGI YAGGGVCINCQHNTAGVNCEQCAKGYYRPYGVPVDAPDGCIPCSCDP EHADGCEQGSGRCHCKPNFHGDNCEKCAIGYYNFPFCLRIPIFPVSTPS SEDPVAGDIKGCDCNLEGVLPEICDAHGRCLCRPGVEGPRCDTCRSGF YSFPICQACWCSALGSYQMPCSSVTGQCECRPGVTGQRCDRCLSGAY DFPHCQGSSSACDPAGTINSNLGYCQCKLHVEGPTCSRCKLLYWNLD KENPSGCSECKCHKAGTVSGTGECRQGDGDCHCKSHVGGDSCDTCED GYFALEKSNYFGCQGCQCDIGGALSSMCSGPSGVCQCREHVVGKVCQ RPENNYYFPDLHHMKYEIEDGSTPNGRDLRFGFDPLAFPEFSWRGYAQ MTSVQNDVRITLNVGKSSGSLFRVILRYVNPGTEAVSGHITIYPSWGAA QSKEIIFLPSKEPAFVTVPGNGFADPFSITPGIWVACIKAEGVLLDYLVL LPRDYYEASVLQLPVTEPCAYAGPPQENCLLYQHLPVTRFPCTLACEA RHFLLDGEPRPVAVRQPTPAHPVMVDLSGREVELHLRLRIPQVGHYVV VVEYSTEAAQLFVVDVNVKSSGSVLAGQVNIYSCNYSVLCRSAVIDH MSRIAMYELLADADIQLKGHMARFLLHQVCIIPIEEFSAEYVRPQVHCI ASYGRFVNQSATCVSLAHETPPTALILDVLSGRPFPHLPQQSSPSVDVL PGVTLKAPQNQVTLRGRVPHLGRYVFVIHFYQAAHPTFPAQVSVDGG WPRAGSFHASFCPHVLGCRDQVIAEGQIEFDISEPEVAATVKVPEGKSL VLVRVLVVPAENYDYQILHKKSMDKSLEFITNCGKNSFYLDPQTASRF CKNSARSLVAFYHKGALPCECHPTGATGPHCSPEGGQCPCQPNVIGRQ CTRCATGHYGFPRCKPCSCGRRLCEEMTGQCRCPPRTVRPQCEVCETH SFSFHPMAGCEGCNCSRRGTIEAAMPECDRDSGQCRCKPRITGRQCDR CASGFYRFPECVPCNCNRDGTEPGVCDPGTGACLCKENVEGTECNVC REGSFHLDPANLKGCTSCFCFGVNNQCHSSHKRRTKFVDMLGWHLET

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Human Laminin	Sequence
	ADRVDIPVSFNPGSNSMVADLQELPATIHSASWVAPTSYLGDKVSSYG GYLTYQAKSFGLPGDMVLLEKKPDVQLTGQHMSIIYEETNTPRPDRLH HGRVHVVEGNFRHASSRAPVSREELMTVLSRLADVRIQGLYFTETQRL TLSEVGLEEASDTGSGRIALAVEICACPPAYAGDSCQGCSPGYYRDHK GLYTGRCVPCNCNGHSNQCQDGSGICVNCQHNTAGEHCERCQEGYY GNAVHGSCRACPCPHTNSFATGCVVNGGDVRCSCKAGYTGTQCERC APGYFGNPQKFGGSCQPCSCNSNGQLGSCHPLTGDCINQEPKDSSPAE ECDDCDSCVMTLLNDLATMGEQLRLVKSQLQGLSASAGLLEQMRHM ETQAKDLRNQLLNYRSAISNHGSKIEGLERELTDLNQEFETLQEKAQV NSRKAQTLNNNVNRATQSAKELDVKIKNVIRNVHMLNRIRTWQKTHQ GENNGLANSIRDSLNEYEAKLSDLRARLQEAAAQAKQANGLNQENER ALGAIQRQVKEINSLQSDFTKYLTTADSSLLQTNIALQLMEKSQKEYEK LAASLNEARQELSDKVRELSRSAGKTSLVEEAEKHARSLQELAKQLEE IKRNASGDELVRCAVDAATAYENILNAIKAAEDAANRAASASESALQT VIKEDLPRKAKTLSSNSDKLLNEAKMTQKKLKQEVSPALNNLQQTLNI VTVQKEVIDTNLTTLRDGLHGIQRGDIDAMISSAKSMVRKANDITDEV LDGLNPIQTDVERIKDTYGRTQNEDFKKALTDADNSVNKLTNKLPDL WRKIESINQQLLPLGNISDNMDRIRELIQQARDAASKVAVPMRENGKS GVEVRLPNDLEDLKGYTSLSLFLQRPNSRENGGTENMFVMYLGNKDA SRDYIGMAVVDGQLTCVYNLGDREAELQVDQILTKSETKEAVMDRV KFQRIYQFARLNYTKGATSSKPETPGVYDMDGRNSNTLLNLDPENVVF YVGGYPPDFKLPSRLSFPPYKGCIELDDLNENVLSLYNFKKTFNLNTTE VEPCRRRKEESDKNYFEGTGYARVPTQPHAPIPTFGQTIQTTVDRGLLF FAENGDRFISLNIEDGKLMVRYKLNSELPKERGVGDAINNGRDHSIQIK IGKLQKRMWINVDVQNTIIDGEVEDFSTYYLGGIPIAIRERFNISTPAFR GCMKNLKKTSGVVRLNDTVGVTKKCSEDWKLVRSASFSRGGQLSFT DLGLPPTDHLQASFGFQTFQPSGILLDHQTWTRNLQVTLEDGYIELSTS DSGGPIFKSPQTYMDGLLHYVSVISDNSGLRLLIDDQLLRNSKRLKHIS SSRQSLRLGGSNFEGCISNVFVQRLSLSPEVLDLTSNSLKRDVSLGGCS LNKPPFLMLLKGSTRFNKTKTFRINQLLQDTPVASPRSVKVWQDACSP LPKTQANHGALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGL VFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTV VFGHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLP TNSFVGCLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVV LAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHLCVYLEAGKVTASM DSGAGGTSTSVTPKQSLCDGQWHSVAVTIKQHILHLELDTDSSYTAGQ IPFPPASTQEPLHLGGAPANLTTLRIPVWKSFFGCLRNIHVNHIPVPVTE ALEVQGPVSLNGCPDQ
laminin subunit alpha-3 isoform 4 precursor (LAMA3-isoform 4); SEQ ID NO: 31	MPPAVRRSACSMGWLWIFGAALGQCLGYSSQQQRVPFLQPPGQSQLQ ASYVEFRPSQGCSPGYYRDHKGLYTGRCVPCNCNGHSNQCQDGSGIC VNCQHNTAGEHCERCQEGYYGNAVHGSCRACPCPHTNSFATGCVVN GGDVRCSCKAGYTGTQCERCAPGYFGNPQKFGGSCQPCSCNSNGQLG SCHPLTGDCINQEPKDSSPAEECDDCDSCVMTLLNDLATMGEQLRLVK SQLQGLSASAGLLEQMRHMETQAKDLRNQLLNYRSAISNHGSKIEGLE RELTDLNQEFETLQEKAQVNSRKAQTLNNNVNRATQSAKELDVKIKN VIRNVHMLNRIRTWQKTHQGENNGLANSIRDSLNEYEAKLSDLRARL QEAAAQAKQANGLNQENERALGAIQRQVKEINSLQSDFTKYLTTADS SLLQTNIALQLMEKSQKEYEKLAASLNEARQELSDKVRELSRSAGKTS LVEEAEKHARSLQELAKQLEEIKRNASGDELVRCAVDAATAYENILNA IKAAEDAANRAASASESALQTVIKEDLPRKAKTLSSNSDKLLNEAKMT QKKLKQEVSPALNNLQQTLNIVTVQKEVIDTNLTTLRDGLHGIQRGDI DAMISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDTYGRTQNEDFK KALTDADNSVNKLTNKLPDLWRKIESINQQLLPLGNISDNMDRIRELIQ QARDAASKVAVPMRFNGKSGVEVRLPNDLEDLKGYTSLSLFLQRPNS RENGGTENNIFVMYLGNKDASRDYIGMAVVDGQLTCVYNLGDREAEL QVDQILTKSETKEAVMDRVKFQRIYQFARLNYTKGATSSKPETPGVYD MDGRNSNTLLNLDPENVVFYVGGYPPDFKLPSRLSFPPYKGCIELDDL NENVLSLYNFKKTFNLNTTEVEPCRRRKEESDKNYFEGTGYARVPTQP HAPIPTFGQTIQTTVDRGLLFFAENGDRFISLNIEDGKLMVRYKLNSELP KERGVGDAINNGRDHSIQIKIGKLQKRMWINVDVQNTIIDGEVFDFSTY YLGGIPIAIRERFNISTPAFRGCMKNLKKTSGVVRLNDTVGVTKKCSED WKLVRSASFSRGGQLSFTDLGLPPTDHLQASFGFQTFQPSGILLDHQT WTRNLQVTLEDGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNSGL RLLIDDQLLRNSKRLKHISSSRQSLRLGGSNFEGCISNVFVQRLSLSPEV LDLTSNSLKRDVSLGGCSLNKPPFLMLLKGSTRFNKTKTFRINQLLQDT PVASPRSVKVWQDACSPLPKTQANHGALQFGDIPTSHLLFKLPQELLK

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Human Laminin	Sequence
	PRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVVLAHSVLLGPEFKLVFSIRPRSLTGILIHIGSQPGKHLCVYLEAGKVTASMDSGAGGTSTSVTPKQSLCDGQWHSVAVTIKQHILHLELDTDSSYTAGQIPFPPASTQEPLHLGGAPANLTTLRIPVWKSFFGCLRNIFIVNHIPVPVTEALEVQGPVSLNGCPDQ
laminin subunit alpha-3 isoform 5 precursor (LAMA3-isoform 5); SEQ ID NO: 32	MAAAARPRGRALGPVLPPTPLLLLVLRVLPACGATARDPGAAAGLSLHPTYFNLAEAARIWATATCGERGPGEGRPQPELYCKLVGGPTAPGSGHTIQGQFCDYCNSEDPRKAHPVTNAIDGSERWWQSPPLSSGTQYNRVNLTLDLGQLFHVAYILIKFANSPRPDLWVLERSVDFGSTYSPWQYFAHSKVDCLKEFGREANMAVTRDDDVLCVTEYSRIVPLENGEVVVSLINGRPGAKNFTFSHTLREFTKATNIRLRFLRTNTLLGHLISKAQRDPTVTRRYYYSIKDISIGGQCVCNGHAEVCNINNPEKLFRCECQHHTCGETCDRCCTGYNQRRWRPAAWEQSHECEACNCHGHASNCYYDPDVERQQASLNTQGIYAGGGVCINCQHNTAGVNCEQCAKGYYRPYGVPVDAPDGCIRKFHFKLVYLSLCVLPQRSHQANFGSVNNFLHALSLQSISCARYVTSVTYTVSLNFGFIACKWK
laminin subunit alpha-4 isoform 1 precursor (LAMA4-isoform 1); SEQ ID NO: 33	MALSSAWRSVLPLWLLWSAACSRAASGDDNAFPFDIEGSSAVGRQDPPETSEPRVALGRLPPAAEKCNAGFFHTLSGECVPCDCNGNSNECLDGSGYCVHCQRNTTGEHCEKCLDGYIGDSIRGAPQFCQPCPCPLPHLANFAESCYRKNGAVRCICNENYAGPNCERCAPGYYGNPLLIGSTCKKCDCSGNSDPNLIFEDCDEVTGQCRNCLRNTTGFKCERCAPGYYGDARIAKNCAVCNCGGGPCDSVTGECLEEGFEPPTGMDCPTISCDKCVWDLTDDLRLAALSIEEGKSGVLSVSSGAAAHRHVNEINATIYLLKTKLSERENQYALRKIQINNAENTMKSLLSDVEELVEKENQASRKGQLVQKESMDTINHASQLVEQAHDMRDKIQEINNKMLYYGEEHELSPKEISEKLVLAQKMLEEIRSRQPFFTQRELVDEEADEAYELLSQAESWQRLHNETRTLFPVVLEQLDDYNAKLSDLQEALDQALNYVRDAEDMNRATAARQRDHEKQQERVREQMEVVNMSLSTSADSLTTPRLTLSELDDIIKNASGIYAEIDGAKSELQVKLSNLSNLSHDLVQEAIDHAQDLQQEANELSRKLHSSDMNGLVQKALDASNVYENIVNYVSEANETAEFALNTTDRIYDAVSGIDTQIIYHKDESENLLNQARELQAKAESSSDEAVADTSRRVGGALARKSALKTRLSDAVKQLQAAERGDAQQRLGQSRLITEEANRTTMEVQQATAPMANNLTNWSQNLQHFDSSAYNTAVNSARDAVRNLTEVVPQLLDQLRTVEQKRPASNVSASIQRIRELIAQTRSVASKIQVSMMFDGQSAVEVHSRTSMDDLKAFTSLSLYMKPPVKRPELTETADQFILYLGSKNAKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSSWPAYFSIVKIERVGKHGKVFLTVPSLSSTAEEKFIKKGEFSGDDSLLDLDPEDTVFYVGGVPSNFKLPTSLNLPGFVGCLELATLNNDVISLYNFKHIYNMDPSTSVPCARDKLAFTQSRAASYFFDGSGYAVVRDITRRGKFGQVTRFDIEVRTPADNGLILLMVNGSMFFRLEMRNGYLHVFYDFGFSGGPVHLEDTLKKAQINDAKYHEISIIYHNDKKMILVVDRRHVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMKGFQFQKKDFNLLEQTETLGVGYGCPEDSLISRRAYFNGQSFIASIQKISFFDGFEGGFNFRTLQPNGLLFYYASGSDVFSISLDNGTVIMDVKGIKVQSVDKQYNDGLSHFVISSVSPTRYELIVDKSRVGSKNPTKGKIEQTQASEKKFYFGGSPISAQYANFTGCISNAYFTRVDRDVEVEDFQRYTEKVHTSLYECPIESSPLFLLHKKGKNLSKPKASQNKKGGKSKDAPSWDPVALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDVIFIRERSSGRLVIDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCLSNLQLNGASITSASQTFSVTPCFEGPMETGTYFSTEGGYVVLDESFNIGLKFEIAFEVRPRSSSGTLVHGHSVNGEYLNVHMKNGQVIVKVNNGIRDFSTSVTPKQSLCDGRWHRITVIRDSNVVQLDVDSEVNHVVGPLNPKPIDHREPVFVGGVPESLLTPRLAPSKPFTGCIRHFVIDGHPVSFSKAALVSGAVSINSCPAA
laminin subunit alpha-4 isoform 2 precursor (LAMA4-isoform 2); SEQ ID NO: 34	MALSSAWRSVLPLWLLWSAACSRAASGDDNAFPFDIEGSSAVGRQDPPETSEPRVALGRLPPAAEKCNAGFFHTLSGECVPCDCNGNSNECLDGSGYCVHCQRNTTGEHCEKCLDGYIGDSIRGAPQFCQPCPCPLPHLANFAESCYRKNGAVRCICNENYAGPNCERCAPGYYGNPLLIGSTCKKCDCSGNSDPNLIFEDCDEVTGQCRNCLRNTTGFKCERCAPGYYGDARIAKNCAVCNCGGGPCDSVTGECLEEGFEPPTGCDKCVWDLTDDLRLAALSIEEGKSGVLSVSSGAAAHRHVNEINATIYLLKTKLSERENQYALRKIQINNAENTMKSLLSDVEELVEKENQASRKGQLVQKESMDTINHASQLVEQAHDMRDKIQEINNKMLYYGEEHELSPKEISEKLVLAQKMLEEIRSRQPFFTQRELVDEEADEAYELLSQAESWQRLHNETRTLFPVVLEQLDDYNAKLSDLQEALDQALNYVRDAEDMNRATAARQRDHEKQQERVREQMEVVNMSLSTSADSLTTPRLTLSELDDIIKNASGIYAEIDGAKSELQVKLSNLSNLSHDLVQEAIDHAQDLQQEANELSRKLHSSDMNGLVQKALDASNVYENIVNYVSEANETAEFALNTTDRIYDAVSGIDTQIIYHKDESENLLNQAR

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Human Laminin	Sequence
	ELQAKAESSSDEAVADTSRRVGGALARKSALKTRLSDAVKQLQAAERGDAQQRLGQSRLITEEANRTTMEVQQATAPMANNLTNWSQNLQHFDSSAYNTAVNSARDAVRNLTEVVPQLLDQLRTVEQKRPASNVSASIQRIRELIAQTRSVASKIQVSMMFDGQSAVEVHSRTSMDDLKAFTSLSLYMKPPVKRPELTETADQFILYLGSKNAKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSSWPAYFSIVKIERVGKHGKVFLTVPSLSSTAEEKFIKKGEFSGDDSLLDLDPEDTVFYVGGVPSNFKLPTSLNLPGFVGCLELATLNNDVISLYNFKHIYNMDPSTSVPCARDKLAFTQSRAASYFFDGSGYAVVRDITRRGKFGQVTRFDIEVRTPADNGLILLMVNGSMFFRLEMRNGYLHVFYDFGFSGGPVHLEDTLKKAQINDAKYHEISIIYHNDKKMILVVDRRHVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMKGFQFQKKDFNLLEQTETLGVGYGCPEDSLISRRAYFNGQSFIASIQKISFFDGFEGGFNFRTLQPNGLLFYYASGSDVFSISLDNGTVIMDVKGIKVQSVDKQYNDGLSHFVISSVSPTRYELIVDKSRVGSKNPTKGKIEQTQASEKKFYFGGSPISAQYANFTGCISNAYFTRVDRDVEVEDFQRYTEKVHTSLYECPIESSPLFLLHKKGKNLSKPKASQNKKGGKSKDAPSWDPVALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDVIFIRERSSGRLVIDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCLSNLQLNGASITSASQTFSVTPCFEGPMETGTYFSTEGGYVVLDESFNIGLKFEIAFEVRPRSSSGTLVHGHSVNGEYLNVHMKNGQVIVKVNNGIRDFSTSVTPKQSLCDGRWHRITVIRDSNVVQLDVDSEVNHVVGPLNPKPIDHREPVFVGGVPESLLTPRLAPSKPFTGCIRHFVIDGHPVSFSKAALVSGAVSINSCPAA
laminin subunit alpha-4 isoform 3 precursor (LAMA4-isoform 3); SEQ ID NO: 35	MALSSAWRSVLPLWLLWSAACSRAASGDDNAFPFDIEGSSAVGRQDPPETSEPRVALGRLPPAAEVQCPCHCHPAGAPAPPRAVPHSSFSLSPPLSSPQCLESFTWARSVRKLEIKSFPL
laminin subunit alpha-5 precursor (LAMA5); SEQ ID NO: 36	MAKRLCAGSALCVRGPRGPAPLLLVGLALLGAARAREEAGGGFSLHPPYFNLAEGARIAASATCGEEAPARGSPRPTEDLYCKLVGGPVAGGDPNQTIRGQYCDICTAANSNKAHPASNAIDGTERWWQSPPLSRGLEYNEVNVTLDLGQVFHVAYVLIKFANSPRPDLWVLERSMDFGRTYQPWQFFASSKRDCLERFGPQTLERITRDDAAICTTEYSRIVPLENGEIVVSLVNGRPGAMNFSYSPLLREFTKATNVRLRFLRTNTLLGHLMGKALRDPTVTRRYYYSIKDISIGGRCVCHGHADACDAKDPTDPFRLQCTCQHNTCGGTCDRCCPGFNQQPWKPATANSANECQSCNCYGHATDCYYDPEVDRRRASQSLDGTYQGGGVCIDCQHHTTGVNCERCLPGFYRSPNHPLDSPHVCRRCNCESDFTDGTCEDLTGRCYCRPNFSGERCDVCAEGFTGFPSCYPTPSSSNDTREQVLPAGQIVNCDCSAAGTQGNACRKDPRVGRCLCKPNFQGTHCELCAPGFYGPGCQPCQCSSPGVADDRCDPDTGQCRCRVGFEGATCDRCAPGYFHFPLCQLCGCSPAGTLPEGCDEAGRCLCQPEFAGPHCDRCRPGYHGFPNCQACTCDPRGALDQLCGAGGLCRCRPGYTGTACQECSPGFHGFPSCVPCHCSAEGSLHAACDPRSGQCSCRPRVTGLRCDTCVPGAYNFPYCEAGSCHPAGLAPVDPALPEAQVPCMCRAHVEGPSCDRCKPGFWGLSPSNPEGCTRCSCDLRGTLGGVAECQPGTGQCFCKPHVCGQACASCKDGEEGLDQADYFGCRSCRCDIGGALGQSCEPRTGVCRCRPNTQGPTCSEPARDHYLPDLHHLRLELEEAATPEGHAVRFGFNPLEFENFSWRGYAQMAPVQPRIVARLNLTSPDLFWLVFRYVNRGAMSVSGRVSVREEGRSATCANCTAQSQPVAFPPSTEPAFITVPQRGEGEPEVLNPGTWALRVEAEGVLLDYVVLLPSAYYEAALLQLRVTEACTYRPSAQQSGDNCLLYTHLPLDGFPSAAGLEALCRQDNSLPRPCPTEQLSPSHPPLITCTGSDVDVQLQVAVPQPGRYALVVEYANEDARQEVGVAVHTPQRAPQQGLLSLHPCLYSTLCRGTARDTQDHLAVFHLDSEASVRLTAEQARFFLHGVTLVPIEEESPEFVEPRVSCISSHGAFGPNSAACLPSRFPKPPQPIILRDCQVIPLPPGLPLTHAQDLTPAMSPAGPRPRPPTAVDPDAEPTLLREPQATVVFTTHVPTLGRYAELLHGYQPAEIPTEPVEVLINAGRVWQGHANASFCPHGYGCRTLVVCEGQALLDVTHSELTVTVRVPKGRWLWLDYVLVVPENVYSFGYLREEPLDKSYDFISHCAAQGYHISPSSSSLFCRNAAASLSLFYNNGARPCGCHEVGATGPTCEPFGGQCPCHAHVIGRDCSRCATGYWGFPNCRPCDCGARLCDELTGQCICPPRTIPPDCLLCQPQTFGCHPLVGCEECNCSGPGIQELTDPTCDTDSGQCKCRPNVTGRRCDTCSPGFHGYPRCRPCDCHEAGTAPGVCDPLTGQCYCKENVQGPKCDQCSLGTFSLDAANPKGCTRCFCFGATERCRSSSYTRQEFVDMEGWVLLSTDRQVVPHERQPGTEMLRADLRHVPEAVPEAFPELYWQAPPSYLGDRVSSYGGTLRYELHSETQRGDVFVPMESRPDVVLQGNQMSITFLEPAYPTPGHVHRGQLQLVEGNFRHTETRNTVSREELMMVLASLEQLQIRALFSQISSAVFLRRVALEV

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Human Laminin	Sequence
	ASPAGQGALASNVELCLCPASYRGDSCQECAPGFYRDVKGLFLGRCV PCQCHGHSDRCLPGSGVCVDCQHNTEGAHCERCQAGFVSSRDDPSAP CVSCPCPLSVPSNNFAEGCVLRGGRTQCLCKPGYAGASCERCAPGFFG NPLVLGSSCQPCDCSGNGDPNLLFSDCDPLTGACRGCLRHTTGPRCEIC APGFYGNALLPGNCTRCDCTPCGTEACDPHSGHCLCKAGVTGRRCDR CQEGHFGEDGCGGCRPCACGPAAEGSECHPQSGQCHCRPGTMGPQCR ECAPGYWGLPEQGCRRCQCPGGRCDPHTGRCNCPPGLSGERCDTCSQ QHQVPVPGGPVGHSIHCEVCDHCVVLLLDDLERAGALLPAIHEQLRGI NASSMAWARLHRLNASIADLQSQLRSPLGPRHETAQQLEVLEQQSTSL GQDARRLGGQAVGTRDQASQLLAGTEATLGHAKTLLAAIRAVDRTLS ELMSQTGHLGLANASAPSGEQLLRTLAEVERLLWEMRARDLGAPQAA AEAELAAAQRLLARVQEQLSSLWEENQALATQTRDRLAQHEAGLMD LREALNRAVDATREAQELNSRNQERLEEALQRKQELSRDNATLQATL HAARDTLASVFRLLHSLDQAKEELERLAASLDGARTPLLQRMQTFSPA GSKLRLVEAAEAHAQQLGQLALNLSSIILDVNQDRLTQRAIEASNAYS RILQAVQAAEDAAGQALQQADHTWATVVRQGLVDRAQQLLANSTAL EEAMLQEQQRLGLVWAALQGARTQLRDVRAKKDQLEAHIQAAQAM LAMDTDETSKKIAHAKAVAAEAQDTATRVQSQLQAMQENVERWQG QYEGLRGQDLGQAVLDAGHSVSTLEKTLPQLLAKLSILENRGVHNASL ALSASIGRVRELIAQARGAASKVKVPMKFNGRSGVQLRTPRDLADLA AYTALKFYLQGPEPEPGQGTEDRFVMYMGSRQATGDYMGVSLRDKK VHWVYQLGEAGPAVLSIDEDIGEQFAAVSLDRTLQFGHMSVTVERQM IQETKGDTVAPGAEGLLNLRPDDFVFYVGGYPSTFTPPPLLRFPGYRGC IEMDTLNEEVVSLYNEERTEQLDTAVDRPCARSKSTGDPWLTDGSYLD GTGEARISEDSQISTTKREEQELRLVSYSGVLEELKQQSQFLCLAVQEGS LVLLYDFGAGLKKAVPLQPPPPLTSASKAIQVFLLGGSRKRVLVRVER ATVYSVEQDNDLELADAYYLGGVPPDQLPPSLRRLFPTGGSVRGCVK GIKALGKYVDLKRLNTTGVSAGCTADLLVGRAMTFHGHGFLRLALSN VAPLTGNVYSGFGFHSAQDSALLYYRASPDGLCQVSLQQGRVSLQLL RTEVKTQAGFADGAPHYVAFYSNATGVWLYVDDQLQQMKPHRGPPP ELQPQPEGPPRLLLGGLPESGTIYNFSGCISNVFVQRLLGPQRVFDLQQ NLGSVNVSTGCAPALQAQTPGLGPRGLQATARKASRRSRQPARHPAC MLPPHLRTTRDSYQFGGSLSSHLEFVGILARHRNWPSLSMHVLPRSSR GLLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRAQSRQRSRPGR WHKVSVRWEKNRILLVTDGARAWSQEGPHRQHQGAEHPQPHTLFVG GLPASSHSSKLPVTVGFSGCVKRLRLHGRPLGAPTRMAGVTPCILGPLE AGLFFPGSGGVITLDLPGATLPDVGLELEVRPLAVTGLIFHLGQARTPP YLQLQVTEKQVLLRADDGAGEFSTSVTRPSVLCDGQWHRLAVMKSG NVLRLEVDAQSNHTVGPLLAAAAGAPAPLYLGGLPEPMAVQPWPPAY CGCMRRLAVNRSPVAMTRSVEVHGAVGASGCPAA
laminin subunit beta-1 precursor (LAMB1); SEQ ID NO: 37	MGLLQLLAFSFLALCRARVRAQEPEFSYGCAEGSCYPATGDLLIGRAQ KLSVTSTCGLHKPEPYCIVSHLQEDKKCFICNSQDPYHETLNPDSHLIE NVVTTFAPNRLKIWWQSENGVENVTIQLDLEAEFHFTHLIMTFKTFRP AAMLIERSSDFGKTWGVYRYFAYDCEASFPGISTGPMKKVDDIICDSR YSDIEPSTEGEVIFRALDPAFKIEDPYSPRIQNLLKITNLRIKFVKLHTLG DNLLDSRMEIREKYYYAVYDMVVRGNCFCYGHASECAPVDGFNEEV EGMVHGHCMCRHNTKGLNCELCMDFYHDLPWRPAEGRNSNACKKC NCNEHSISCHFDMAVYLATGNVSGGVCDDCQHNTMGRNCEQCKPFY YQHPERDIRDPNFCERCTCDPAGSQNEGICDSYTDFSTGLIAGQCRCKL NVEGEHCDVCKEGFYDLSSEDPFGCKSCACNPLGTIPGGNPCDSETGH CYCKRLVTGQHCDQCLPEHWGLSNDLDGCRPCDCDLGGALNNSCFA ESGQCSCRPHMIGRQCNEVEPGYYFATLDHYLYEAEEANLGPGVSIVE RQYIQDRIPSWTGAGFVRVPEGAYLEFFIDNIPYSMEYDILIRYEPQLPD HWEKAVITVQRPGRIPTSSRCGNTIPDDDNQVVSLSPGSRYVVLPRPVC FEKGTNYTVRLELPQYTSSDSDVESPYTLIDSLVLMPYCKSLDIFTVGG SGDGVVTNSAWETFQRYRCLENSRSVVKTPMTDVCRNIIFSISALLHQT GLACECDPQGSLSSVCDPNGGQCQCRPNVVGRTCNRCAPGTFGFGPS GCKPCECHLQGSVNAFCNPVTGQCHCFQGVYARQCDRCLPGHWGFPS CQPCQCNGHADDCDPVTGECLNCQDYTMGHNCERCLAGYYGDPIIGS GDHCRPCPCPDGPDSGRQFARSCYQDPVTLQLACVCDPGYIGSRCDDC ASGYFGNPSEVGGSCQPCQCHNNIDTTDPEACDKETGRCLKCLYHTEG EHCQFCRFGYYGDALQQDCRKCVCNYLGTVQEHCNGSDCQCDKATG QCLCLPNVIGQNCDRCAPNTWQLASGTGCDPCNCNAAHSFGPSCNEF TGQCQCMPGFGGRTCSECQELFWGDPDVECRACDCDPRGIETPQCDQ STGQCVCVEGVEGPRCDKCTRGYSGVFPDCTPCHQCFALWDVIIAELT NRTHRFLEKAKALKISGVIGPYRETVDSVERKVSEIKDILAQSPAAEPL KNIGNLFEEAEKLIKDVTEMMAQVEVKLSDTTSQSNSTAKELDSLQTE AESLDNTVKELAEQLEFIKNSDIRGALDSITKYFQMSLEAEERVNASTT EPNSTVEQSALMRDRVEDVMMERESQFKEKQEEQARLLDELAGKLQS LDLSAAAEMTCGTPPGASCSETECGGPNCRTDEGERKCGGPGCGGLV TVAHNAWQKAMDLDQDVLSALAEVEQLSKMVSEAKLRADEAKQSA EDILLKTNATKEKMDKSNEELRNLIKQIRNFLTQDSADLDSIEAVANEV

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Human Laminin	Sequence
	LKMEMPSTPQQLQNLTEDIRERVESLSQVEVILQHSAADIARAEMLLEE AKRASKSATDVKVTADMVKEALEEAEKAQVAAEKAIKQADEDIQGT QNLLTSHESETAASEETLFNASQRISELERNVEELKRKAAQNSGEAEYIE KVVYTVKQSAEDVKKTLDGELDEKYKKVENLIAKKTEESADARRKAE MLQNEAKTLLAQANSKLQLLKDLERKYEDNQRYLEDKAQELARLEG EVRSLLKDISQKVAVYSTCL
laminin subunit beta-2 precursor (LAMB2); SEQ ID NO: 38	MELTSRERGRGQPLPWELRLGLLLSVLAATLAQAPAPDVPGCSRGSCY PATGDLLVGRADRLTASSTCGLNGPQPYCIVSHLQDEKKCFLCDSRRP FSARDNPHSHRIQNVVTSFAPQRRAAWWQSENGIPAVTIQLDLEAEFH FTHLIMTFKTFRPAAMLVERSADFGRTWHVYRYFSYDCGADFPGVPL APPRHWDDVVCESRYSEIEPSTEGEVIYRVLDPAIPIPDPYSSRIQNLLKI TNLRVNLTRLHTLGDNLLDPRREIREKYYYALYELVVRGNCFCYGHA SECAPAPGAPAHAEGMVHGACICKHNTRGLNCEQCQDFYRDLPWRPA EDGHSHACRKCECHGHTHSCHFDMAVYLASGNVSGGVCDGCQHNTA GRHCELCRPFFYRDPTKDLRDPAVCRSCDCDPMGSQDGGRCDSHDDP ALGLVSGQCRCKEHVVGTRCQQCRDGFFGLSISDRLGCRRCQCNARG TVPGSTPCDPNSGSCYCKRLVTGRGCDRCLPGHWGLSHDLLGCRPCD CDVGGALDPQCDEGTGQCHCRQHMVGRRCEQVQPGYFRPFLDHLIW EAEDTRGQVLDVVERLVTPGETPSWTGSGFVRLQEGQTLEFLVASVPK AMDYDLLLRLEPQVPEQWAELELIVQRPGPVPAHSLCGHLVPKDDRIQ GTLQPHARYLIFPNPVCLEPGISYKLHLKLVRTGGSAQPETPYSGPGLLI DSLVLLPRVLVLEMFSGGDAAALERQATFERYQCHEEGLVPSKTSPSE ACAPLLISLSTLIYNGALPCQCNPQGSLSSECNPHGGQCLCKPGVVGRR CDLCAPGYYGFGPTGCQACQCSHEGALSSLCEKTSGQCLCRTGAFGLR CDRCQRGQWGFPSCRPCVCNGHADECNTHTGACLGCRDHTGGEHCE RCIAGFHGDPRLPYGGQCRPCPCPEGPGSQRHFATSCHQDEYSQQIVC HCRAGYTGLRCEACAPGHFGDPSRPGGRCQLCECSGNIDPMDPDACD PHTGQCLRCLHHTEGPHCAHCKPGFHGQAARQSCHRCTCNLLGTNPQ QCPSPDQCHCDPSSGQCPCLPNVQGPSCDRCAPNFWNLTSGHGCQPCA CHPSRARGPTCNEFTGQCHCRAGFGGRTCSECQELHWGDPGLQCHAC DCDSRGIDTPQCHRFTGHCSCRPGVSGVRCDQCARGFSGIFPACHPCH ACFGDWDRVVQDLAARTQRLEQRAQELQQTGVLGAFESSFWHMQEK LGIVQGIVGARNTSAASTAQLVEATEELRREIGEATEHLTQLEADLTDV QDENFNANHALSGLERDRLALNLTLRQLDQHLDLLKHSNFLGAYDSIR HAHSQSAEAERRANTSALAVPSPVSNSASARHRTEALMDAQKEDFNS KHMANQRALGKLSAHTHTLSLTDINELVCGAPGDAPCATSPCGGAGC RDEDGQPRCGGLSCNGAAATADLALGRARHTQAELQRALAEGGSILS RVAETRRQASEAQQRAQAALDKANASRGQVEQANQELQELIQSVKDF LNQEGADPDSIEMVATRVLELSIPASAEQIQHLAGAIAERVRSLADVDA ILARTVGDVRRAEQLLQDARRARSWAEDEKQKAETVQAALEEAQRA QGIAQGAIRGAVADTRDTEQTLYQVQERMAGAERALSSAGERARQLD ALLEALKLKRAGNSLAASTAEETAGSAQGRAQEAEQLLRGPLGDQYQ TVKALAERKAQGVLAAQARAEQLRDEARDLLQAAQDKLQRLQELEG TYEENERALESKAAQLDGLEARMRSVLQAINLQVQIYNTCQ
laminin subunit beta-3 precursor (LAMB3); SEQ ID NO: 39	MRPFFLLCFALPGLLHAQQACSRGACYPPVGDLLVGRTRFLRASSTCG LTKPETYCTQYGEWQMKCCKCDSRQPHNYYSHRVENVASSSGPMRW WQSQNDVNPVSLQLDLDRRFQLQEVMMEFQGPMPAGMLIERSSDFG KTWRVYQYLAADCTSTFPRVRQGRPQSWQDVRCQSLPQRPNARLNG GKVQLNLMDLVSGIPATQSQKIQEVGEITNLRVNFTRLAPVPQRGYHP PSAYYAVSQLRLQGSCFCHGHADRCAPKPGASAGPSTAVQVHDVCVC QHNTAGPNCERCAPFYNNRPWRPAEGQDAHECQRCDCNGHSETCHF DPAVFAASQGAYGGVCDNCRDHTEGKNCERCQLHYFRNRRPGASIQE TCISCECDPDGAVPGAPCDPVTGQCVCKEHVQGERCDLCKPGFTGLTY ANPQGCHRCDCNILGSRRDMPCDEESGRCLCLPNVVGPKCDQCAPYH WKLASGQGCEPCACDPHNSLSPQCNQFTGQCPCREGFGGLMCSAAAI RQCPDRTYGDVATGCRACDCDFRGTEGPGCDKASGRCLCRPGLTGPR CDQCQRGYCNRYPVCVACHPCFQTYDADLREQALRFGRLRNATASL WSGPGLEDRGLASRILDAKSKIEQIRAVLSSPAVTEQEVAQVASAILSL RRTLQGLQLDLPLEEETLSLPRDLESLDRSFNGLLTMYQRKREQFEKIS SADPSGAFRMLSTAYEQSAQAAQQVSDSSRLLDQLRDSRREAERLVR QAGGGGGTGSPKLVALRLEMSSLPDLTPTFNKLCGNSRQMACTPISCP GELCPQDNGTACGSRCRGVLPRAGGAFLMAGQVAEQLRGFNAQLQR TRQMIRAAEESASQIQSSAQRLETQVSASRSQMEEDVRRTRLLIQQVR DFLTDPDTDAATIQEVSEAVLALWLPTDSATVLQKMNEIQAIAARLPN VDLVLSQTKQDIARARRLQAEAEEARSRAHAVEGQVEDVVGNLRQGT VALQEAQDTMQGTSRSLRLIQDRVAEVQQVLRPAEKLVTSMTKQLGD FWTRMEELRHQARQQGAEAVQAQQLAEGASEQALSAQEGFERIKQK YAELKDRLGQSSMLGEQGARIQSVKTEAEELFGETMEMMDRMKDME LELLRGSQAIMLRSADLTGLEKRVEQIRDHINGRVLYYATCK

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Human Laminin	Sequence
laminin subunit beta-4 isoform 1 precursor (LAMB4-isoform 1); SEQ ID NO: 40	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWWQSENGLDHVSIRLDLEALFRFSHLILTFKTFRPAAMLVE RSTDYGHNWKVFKYFAKDCATSFPNITSGQAQGVGDIVCDSKYSDIEP STGGEVVLKVLDPSFEIENPYSPYIQDLVTLTNLRINFTKLHTLGDALLG RRQNDSLDKYYYALYEMIVRGSCFCNGHASECRPMQKMRGDVFSPPG MVHGQCVCQHNTDGPNCERCKDFFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTEGQHCDRCRPLFYRDP LKTISDPYACIPCECDPDGTISGGICVSHSDPALGSVAGQCLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCLS YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAPGYFFAPLNFYLYEAEEATTLQGLAPLGSETFGQ SPAVHVVLGEPVPGNPVTWTGPGFARVLPGAGLRFAVNNIPFPVDFTI AIHYETQSAADWTVQIVVNPPGGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGESHAHSHVLVDSLGLIPQINSLENF CSKQDLDEYQLHNCVEIASAMGPQVLPGACERLIISMSAKLHDGAVAC KCHPQGSVGSSCSRLGGQCQCKPLVVGRCCDRCSTGSYDLGHHGCHP CHCHPQGSKDTVCDQVTGQCPCHGEVSGRRCDRCLAGYFGFPSCHPC PCNRFAELCDPETGSCFNCGGFTTGRNCERCIDGYYGNPSSGQPCRPCL CPDDPSSNQYFAHSCYQNLWSSDVICNCLQGYTGTQCGECSTGFYGNP RISGAPCQPCACNNNIDVTDPESCSRVTGECLRCLHNTQGANCQLCKP GHYGSALNQTCRRCSCHASGVSPMECPPGGGACLCDPVTGACPCLPN VTGLACDRCADGYWNLVPGRGCQSCDCDPRTSQSSHCDQLTGQCPC KLGYGGKRCSECQENYYGDPPGRCIPCDCNRAGTQKPICDPDTGMCR CREGVSGQRCDRCARGHSQEFPTCLQCHLCFDQWDHTISSLSKAVQG LMRLAANMEDKRETLPVCEADFKDLRGNVSEIERILKHPVFPSGKFLK VKDYHDSVRRQIMQLNEQLKAVYEFQDLKDTIERAKNEADLLLEDLQ EEIDLQSSVLNASIADSSENIKKYYHISSSAEKKINETSSTINTSANTRND LLTILDTLTSKGNLSLERLKQIKIPDIQILNEKVCGDPGNVPCVPLPCGG ALCTGRKGHRKCRGPGCHGSLTLSTNALQKAQEAKSIIRNLDKQVRGL KNQIESISEQAEVSKNNALQLREKLGNIRNQSDSEEENINLFIKKVKNFL LEENVPPEDIEKVANGVLDIHLPIPSQNLTDELVKIQKHMQLCEDYRTD ENRLNEEADGAQKLLVKAKAAEKAANILLNLDKTLNQLQQAQITQGR ANSTITQLTANITKIKKNVLQAENQTREMKSELELAKQRSGLEDGLSLL QTKLQRHQDHAVNAKVQAESAQHQAGSLEKEFVELKKQYAILQRKTS TTGLTKETLGKVKQLKDAAEKLAGDTEAKIRRITDLERKIQDLNLSRQ AKADQLRILEDQVVAIKNEIVEQEKKYARCYS
laminin subunit beta-4 isoform 2 precursor (LAMB4-isoform 2); SEQ ID NO: 41	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWWQSENGLDHVSIRLDLEALFRFSHLILTFKTFRPAAMLVE RSTDYGHNWKVFKYFAKDCATSFPNITSGQAQGVGDIVCDSKYSDIEP STGGEVVLKVLDPSFEIENPYSPYIQDLVTLTNLRINFTKLHTLGDALLG RRQNDSLDKYYYALYEMIVRGSCFCNGHASECRPMQKMRGDVFSPPG MVHGQCVCQHNTDGPNCERCKDFFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTEGQHCDRCRPLFYRDP LKTISDPYACIPCECDPDGTISGGICVSHSDPALGSVAGQCLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCLS YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAPGYFFAPLNFYLYEAEEATTLQGLAPLGSETFGQ SPAVHVVLGEPVPGNPVTWTGPGFARVLPGAGLRFAVNNIPFPVDFTI AIHYETQSAADWTVQIVVNPPGGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGESHAHSHVLVDSLGLIPQINSLENF CSKQDLDEYQLHNCVEIASAMGPQVLPGACERLIISMSAKLHDGAVAC KCHPQGSVGSSCSRLGGQCQCKPLVVGRCCDRCSTGSYDLGHHGCHP CHCHPQGSKDTVCDQVTGQCPCHGEVSGRRCDRCLAGYFGFPSCHPC PCNRFAELCDPETGSCFNCGGFTTGRNCERCIDGYYGNPSSGQPCRPCL CPDDPSSNQYFAHSCYQNLWSSDVICNCLQGYTGTQCGECSTGFYGNP RISGAPCQPCACNNNIDVTDPESCSRVTGECLRCLHNTQGANCQLCKP GHYGSALNQTCRRCSCHASGVSPMECPPGGGACLCDPVTGACPCLPN VTGLACDRCADGYWNLVPGRGCQSCDCDPRTSQSSHCDQARYFKAY
laminin subunit beta-4 isoform 3 precursor (LAMB4-isoform 3); SEQ ID NO: 42	MQFQLTLFLHLGWLSYSKAQDDCNRGACHPTTGDLLVGRNTQLMAS STCGLSRAQKYCILSYLEGEQKCFICDSRFPYDPYDQPNSHTIENVIVSF EPDREKKWWQSENGLDHVSIRLDLEALFRFSHLILTFKTFRPAAMLVE RSTDYGHNWKVFKYFAKDCATSFPNITSGQAQGVGDIVCDSKYSDIEP STGGEVVLKVLDPSFEIENPYSPYIQDLVTLTNLRINFTKLHTLGDALLG RRQNDSLDKYYYALYEMIVRGSCFCNGHASECRPMQKMRGDVFSPPG MVHGQCVCQHNTDGPNCERCKDFFQDAPWRPAADLQDNACRSCSCN SHSSRCHFDMTTYLASGGLSGGVCEDCQHNTEGQHCDRCRPLFYRDP LKTISDPYACIPCECDPDGTISGGICVSHSDPALGSVAGQCLCKENVEG AKCDQCKPNHYGLSATDPLGCQPCDCNPLGSLPFLTCDVDTGQCLCLS

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Human Laminin	Sequence
	YVTGAHCEECTVGYWGLGNHLHGCSPCDCDIGGAYSNVCSPKNGQC ECRPHVTGRSCSEPAPGYFFAPLNFYLYEAEEATTLQGLAPLGSETFGQ SPAVHVVLGEPVPGNPVTWTGPGFARVLPGAGLRFAVNNIPFPVDFTI AIHYETQSAADWTVQIVVNPPGGSEHCIPKTLQSKPQSFALPAATRIML LPTPICLEPDVQYSIDVYFSQPLQGESHAHSHVLVDSAAVQWHNLGSL QPPPPECKQFSCFSFPSSWDYREIPPPHLANFCIFSRDGVSPHWPGWSQT PDLR
laminin subunit gamma-1 precursor (LAMC1); SEQ ID NO: 43	MRGSHRAAPALRPRGRLWPVLAVLAAAAAAGCAQAAMDECTDEGG RPQRCMPEFVNAAFNVTVVATNTCGTPPEEYCVQTGVTGVTKSCHLC DAGQPHLQHGAAFLTDYNNQADTTWWQSQTMLAGVQYPSSINLTLH LGKAFDITYVRLKFHTSRPESFAIYKRTREDGPWIPYQYYSGSCENTYS KANRGFIRTGGDEQQALCTDEFSDISPLTGGNVAFSTLEGRPSAYNFDN SPVLQEWVTATDIRVTLNRLNTFGDEVFNDPKVLKSYYYAISDFAVGG RCKCNGHASECMKNEFDKLVCNCKHNTYGVDCEKCLPFFNDRPWRR ATAESASECLPCDCNGRSQECYFDPELYRSTGHGGHCTNCQDNTDGA HCERCRENFFRLGNNEACSSCHCSPVGSLSTQCDSYGRCSCKPGVMGD KCDRCQPGFHSLTEAGCRPCSCDPSGSIDECNIETGRCVCKDNVEGFNC ERCKPGFFNLESSNPRGCTPCFCFGHSSVCTNAVGYSVYSISSTFQIDED GWRAEQRDGSEASLEWSSERQDIAVISDSYFPRYFIAPAKFLGKQVLSY GQNLSFSFRVDRRDTRLSAEDLVLEGAGLRVSVPLIAQGNSYPSETTV KYVFRLHEATDYPWRPALTPFEFQKLLNNLTSIKIRGTYSERSAGYLDD VTLASARPGPGVPATWVESCTCPVGYGGQFCEMCLSGYRRETPNLGP YSPCVLCACNGHSETCDPETGVCNCRDNTAGPHCEKCSDGYYGDSTA GTSSDCQPCPCPGGSSCAVVPKTKEVVCTNCPTGTTGKRCELCDDGYF GDPLGRNGPVRLCRLCQCSDNIDPNAVGNCNRLTGECLKCIYNTAGFY CDRCKDGFFGNPLAPNPADKCKACNCNLYGTMKQQSSCNPVTGQCE CLPHVTGQDCGACDPGFYNLQSGQGCERCDCHALGSTNGQCDIRTGQ CECQPGITGQHCERCEVNHFGFGPEGCKPCDCHPEGSLSLQCKDDGRC ECREGFVGNRCDQCEENYFYNRSWPGCQECPACYRLVKDKVADHRV KLQELESLIANLGTGDEMVTDQAFEDRLKEAEREVMDLLREAQDVKD VDQNLMDRLQRVNNTLSSQISRLQNIRNTIEETGNLAEQARAHVENTE RLIEIASRELEKAKVAAANVSVTQPESTGDPNNMTLLAEEARKLAERH KQEADDIVRVAKTANDTSTEAYNLLLRTLAGENQTAFEIEELNRKYEQ AKNISQDLEKQAARVHEEAKRAGDKAVEIYASVAQLSPLDSETLENEA NNIKMEAENLEQLIDQKLKDYEDLREDMRGKELEVKNLLEKGKTEQQ TADQLLARADAAKALAEEAAKKGRDTLQEANDILNNLKDFDRRVND NKTAAEEALRKIPAINQTITEANEKTREAQQALGSAAADATEAKNKAH EAERIASAVQKNATSTKAEAERTFAEVTDLDNEVNNMLKQLQEAEKE LKRKQDDADQDMMMAGMASQAAQEAEINARKAKNSVTSLLSIINDL LEQLGQLDTVDLNKLNEIEGTLNKAKDEMKVSDLDRKVSDLENEAKK QEAAIMDYNRDIEEIMKDIRNLEDIRKTLPSGCFNTPSIEKP
laminin subunit gamma-2 isoform a precursor (LAMC2-isoform a); SEQ ID NO: 44	MPALWLGCCLCFSLLLPAARATSRREVCDCNGKSRQCIFDRELHRQTG NGFRCLNCNDNTDGIHCEKCKNGFYRHRERDRCLPCNCNSKGSLSAR CDNSGRCSCKPGVTGARCDRCLPGFHMLTDAGCTQDQRLLDSKCDCD PAGIAGPCDAGRCVCKPAVTGERCDRCRSGYYNLDGGNPEGCTQCFC YGHSASCRSSAEYSVHKITSTFHQDVDGWKAVQRNGSPAKLQWSQRH QDVFSSAQRLDPVYFVAPAKFLGNQQVSYGQSLSFDYRVDRGGRHPS AHDVILEGAGLRITAPLMPLGKTLPCGLTKTYTFRLNEHPSNNWSPQLS YFEYRRLLRNLTALRIRATYGEYSTGYIDNVTLISARPVSGAPAPWVEQ CICPVGYKGQFCQDCASGYKRDSARLGPFGTCIPCNCQGGGACDPDTG DCYSGDENPDIECADCP1GFYNDPHDPRSCKPCPCHNGFSCSVMPETEE VVCNNCPPGVTGARCELCADGYFGDPFGEHGPVRPCQPCQCNNNVDP SASGNCDRLTGRCLKCIHNTAGIYCDQCKAGYFGDPLAPNPADKCRA CNCNPMGSEPVGCRSDGTCVCKPGFGGPNCEHGAFSCPACYNQVKIQ MDQFMQQLQRMEALISKAQGGDGVVPDTELEGRMQQAEQALQDILR DAQISEGASRSLGLQLAKVRSQENSYQSRLDDLKMTVERVRALGSQY QNRVRDTHRLITQMQLSLAESEASLGNTNIPASDHYVGPNGFKSLAQE ATRLAESHVESASNMEQLTRETEDYSKQALSLVRKALHEGVGSGSGSP DGAVVQGLVEKLEKTKSLAQQLTREATQAEIEADRSYQHSLRLLDSVS RLQGVSDQSFQVEEAKRIKQKADSLSSLVTRHMDEFKRTQKNLGNWK EEAQQLLQNGKSGREKSDQLLSRANLAKSRAQEALSMGNATFYEVESI LKNLREFDLQVDNRKAEAEEAMKRLSYISQKVSDASDKTQQAERALG SAAADAQRAKNGAGEALEISSEIEQEIGSLNLEANVTADGALAMEKGL ASLKSEMREVEGELERKELEFDTNMDAVQMVITEAQKVDTRAKNAG VTIQDTLNTLDGLLHLMDQPLSVDEEGLVLLEQKLSRAKTQINSQLRP MMSELEERARQQRGHLHLLETSIDGILADVKNLENIRDNLPPGCYNTQ ALEQQ

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Human Laminin	Sequence
laminin subunit gamma-2 isoform b precursor (LAMC2-isoform b); SEQ ID NO: 45	MPALWLGCCLCFSLLLPAARATSRREVCDCNGKSRQCIFDRELHRQTGNGFRCLNCNDNTDGIHCEKCKNGFYRHRERDRCLPCNCNSKGSLSARCDNSGRCSCKPGVTGARCDRCLPGFHMLTDAGCTQDQRLLDSKCDCDPAGIAGPCDAGRCVCKPAVTGERCDRCRSGYYNLDGGNPEGCTQCFCYGHSASCRSSAEYSVHKITSTFHQDVDGWKAVQRNGSPAKLQWSQRHQDVFSSAQRLDPVYFVAPAKFLGNQQVSYGQSLSFDYRVDRGGRHPSAHDVILEGAGLRITAPLMPLGKTLPCGLTKTYTFRLNEHPSNNWSPQLSYFEYRRLLRNLTALRIRATYGEYSTGYIDNVTLISARPVSGAPAPWVEQCICPVGYKGQFCQDCASGYKRDSARLGPFGTCIPCNCQGGGACDPDTGDCYSGDENPDIECADCP1GFYNDPHDPRSCKPCPCHNGFSCSVMPETEEVVCNNCPPGVTGARCELCADGYFGDPFGEHGPVRPCQPCQCNNNVDPSASGNCDRLTGRCLKCIHNTAGIYCDQCKAGYFGDPLAPNPADKCRACNCNPMGSEPVGCRSDGTCVCKPGFGGPNCEHGAFSCPACYNQVKIQMDQFMQQLQRMEALISKAQGGDGVVPDTELEGRMQQAEQALQDILRDAQISEGASRSLGLQLAKVRSQENSYQSRLDDLKMTVERVRALGSQYQNRVRDTHRLITQMQLSLAESEASLGNTNIPASDHYVGPNGFKSLAQEATRLAESHVESASNMEQLTRETEDYSKQALSLVRKALHEGVGSGSGSPDGAVVQGLVEKLEKTKSLAQQLTREATQAEIEADRSYQHSLRLLDSVSRLQGVSDQSFQVEEAKRIKQKADSLSSLVTRHMDEFKRTQKNLGNWKEEAQQLLQNGKSGREKSDQLLSRANLAKSRAQEALSMGNATFYEVESILKNLREFDLQVDNRKAEAEEAMKRLSYISQKVSDASDKTQQAERALGSAAADAQRAKNGAGEALEISSEIEQEIGSLNLEANVTADGALAMEKGLASLKSEMREVEGELERKELEFDTNMDAVQMVITEAQKVDTRAKNAGVTIQDTLNTLDGLLHLMGM
laminin subunit gamma-3 precursor (LAMC3); SEQ ID NO: 46	MAAAALLLGLALLAPRAAGAGMGACYDGAGRPQRCLPVFENAAFGRLAQASHTCGSPPEDFCPHVGAAGAGAHCQRCDAADPQRHEINASYLTDFHSQDESTWWQSPSMAFGVQYPTSVNITLRLGKAYEITYVRLKFHTSRPESFAIYKRSRADGPWEPYQFYSASCQKTYGRPEGQYLRPGEDERVAFCTSEFSDISPLSGGNVAFSTLEGRPSAYNFEESPGLQEWVTSTELLISLDRLNTFGDDIFKDPKVLQSYYYAVSDFSVGGRCKCNGHASECGPDVAGQLACRCQHNTTGTDCERCLPFFQDRPWARGTAEAAHECLPCNCSGRSEECTFDRELFRSTGHGGRCHHCRDHTAGPHCERCQENFYHWDPRMPCQPCDCQSAGSLHLQCDDTGTCACKPTVTGWKCDRCLPGFHSLSEGGCRPCTCNPAGSLDTCDPRSGRCPCKENVEGNLCDRCRPGTFNLQPHNPAGCSSCFCYGHSKVCASTAQFQVHHILSDFHQGAEGWWARSVGGSEHPPQWSPNGVLLSPEDEEELTAPEKFLGDQRFSYGQPLILTFRVPPGDSPLPVQLRLEGTGLALSLRHSSLSGPQDAGHPREVELRFHLQETSEDVAPPLPPFHFQRLLANLTSLRLRVSPGPSPAGPVFLTEVRLTSARPGLSPPASWVEICSCPTGYTGQFCESCAPGYKREMPQGGPYASCVPCTCNQHGTCDPNTGICVCSHHTEGPSCERCLPGFYGNPFAGQADDCQPCPCPGQSACTTIPESREVVCTHCPPGQRGRRCEVCDDGFFGDPLGLFGHPQPCHQCQCSGNVDPNAVGNCDPLSGHCLRCLHNTTGDHCEHCQEGFYGSALAPRPADKCMPCSCHPQGSVSEQMPCDPVTGQCSCLPHVTARDCSRCYPGFFDLQPGRGCRSCKCHPLGSQEDQCHPKTGQCTCRPGVTGQACDRCQLGFFGFSIKGCRACRCSPLGAASAQCHENGTCVCRPGFEGYKCDRCHDNFFLTADGTHCQQCPSCYALVKEEAAKLKARLTLTEGWLQGSDCGSPWGPLDILLGEAPRGDVYQGHEILLPGAREAFLEQMMSLEGAVKAAREQLQRLNKGARCAQAGSQKTCTQLADLEAVLESSEEEILHAAAILASLEIPQEGPSQPTKWSHLATEARALARSHRDTATKIAATAWRALLASNTSYALLWNLLEGRVALETQRDLEDRYQEVQAAQKALRTAVAEVLPEAESVLATVQQVGADTAPYLALLASPGALPQKSRAEDLGLKAKALEKTVASWQHMATEAARTLQTAAQATLRQTEPLTKLHQEARAALTQASSSVQAATVTVMGARTLLADLEGMKLQFPRPKDQAALQRKADSVSDRLLADTRKKTKQAERMLGNAAPLSSSAKKKGREAEVLAKDSAKLAKALLRERKQAHRRASRLTSQTQATLQQASQQVLASEARRQELEEAERVGAGLSEMEQQIRESRISLEKDIETLSELLARLGSLDTHQAPAQALNETQWALERLRLQLGSPGSLQRKLSLLEQESQQQELQIQGFESDLAEIRADKQNLEAILHSLPENCASWQ

[0080] Further exemplary peptides useful in the methods and compositions of the disclosure include:

SEQ ID NO:	Name (location) length	Peptide sequence
1	$\alpha3_{3043-3067}$ (LG4) 25 aa.	RLVFALGTDGKKLRIKSKEKCNDGK
9	$\alpha3_{3031\ 3043}$ (LG4) 13 aa.	KNSFMALYLSKGR
2	$\alpha3_{2932-2951}$ (Linker) 20 aa.	PPFLMLLKGSTRFNKTKTFR
3	$\alpha4_{1521-1543}$ (LG4) 23 aa.	TLFLAHGRLVYMFNVGHKKLKIR
4	$\alpha4_{1408-1434}$ (Linker) 27 aa.	PLFLLHKKGKNLSKPKASQNKKGGKSK
5	$\alpha5_{3539-3550}$ (LG5) 12 aa.	TLPDVGLELEVR
6	$\alpha5_{3417-3436}$ (LG4) 20 aa.	RQRSRPGRWHKVSVRWEKNR
10	$\alpha5_{3312-3325}$ (Linker) 14 aa.	ARKASRRSRQPARH
7	$\alpha5_{3300-3330}$ (Linker) 31 aa.	TPGLGPRGLQATARKASRRSRQPARHPACML
8	$\alpha2PI_{1-8}$-$\alpha3_{3043-3067}$ 33 aa.	NQEQVSPLRLVFALGTDGKKLRIKSKEKCNDGK
11	$\alpha2PI_{1-8}$-$\alpha5_{3312-3325}$ 22 aa.	NQEQVSPLARKASRRSRQPARH
12	$\alpha2PI_{1-8}$	NQEQVSPL
49	vWF A1	YIGLKDRKRPSELRRIASQVKYAC

[0081] 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)	ALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDSKPLYTPSSSFGVSSC
14	LAMA4_ Human, LG4 domain aa1469-aa1640 (UniprotKB database Q16363)	AYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDVIFIRERSSGRLVIDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCLSNLQLNGASITSASQTFSVTPC
15	LAMA5_ Human, LG4 domain aa3340-aa3513 (UniprotKB database O15230)	SYQFGGSLSSHLEFVGILARHRNWPSLSMHVLPRSSRGLLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRAQSRQRSRPGRWHKVSVRWEKNRILLVTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSHSSKLPVTVGFSGCVKRLRLHGRPLGAPTRMAGVTPC

[0082] In some embodiments, the compositions and methods include an engineered Laminin peptide comprising a factor XIIIa transglutaminase substrate domain from the α_2-plasmin inhibitor. Such exemplary peptides are described below:

SEQ ID NO.	Name	Sequence
16	Human $\alpha2PI_{1-8}$-LAMA3_ $LG4_{2986-3150}$	NQEQVSPLGGSGALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDSKPLYTPSSSFGVSSC
17	Human $\alpha2PI_{1-8}$-LAMA4_ $LG4_{1469-1640}$	NQEQVSPLGGSGAYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDVIFIRERSSGRLVIDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCLSNLQLNGASITSASQTFSVTPC
18	Human $\alpha2PI_{1-8}$-LAMA5_ $LG4_{3340-3513}$	NQEQVSPLGGSGSYQFGGSLSSHLEFVGILARHRNWPSLSMHVLPRSSRGLLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRAQSRQRSRPGRWHKVSVRWEKNRILLVTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSHSSKLPVTVGFSGCVKRLRLHGRPLGAPTRMAGVTPC

[0083] 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
47	vWF A3 domain	CSQPLDVILLLDGSSSFPASYFDEMKSFAKAFISKANIGPRLTQVSVLQYGSITTIDVPWNVVPEKAHLLSLVDVMQREGGPSQIGDALGFAVRYLTSEMHGARPGASKAVVILVTDVSVDSVDAAADAARSNRVTVFPIGIGDRYDAAQLRILAGPAGDSNVVKLQRIEDLPTMVTLGNSFLHKLCSGFVRICTG
48	Decorin	CGPFQQRGLFDFMLEDEASGIGPEVPDDRDFEPSLGPVCPFRCQCHLRVVQCSDLGLDKVPKDLPPDTTLLDLQNNKITEIKDGDFKNLKNLHALILVNNKISKVSPGAFTPLVKLERLYLSKNQLKELPEKMPKTLQELRAHENEITKVRKVTFNGLNQMIVIELGTNPLKSSGIENGAFQGMKKLSYIRIADTNITSIPQGLPPSLTELHLDGNKISRVDAASLKGLNNLAKLGLSFNSISAVDNGSLANTPHLRELHLDNNKLTRVPGGLAEHKYIQVVYLHNNNISVVGSSDFCPPGHNTKKASYSGVSLFSNPVQYWEIQPSTFRCVYVRSAIQLGNYK

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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

[0090] 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.

[0091] 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.

[0092] 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, tetramethylrhodamine, 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 by 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/strepavidin.

[0093] 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.

[0094] 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.

[0095] 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 polymerosomes or vesicles or covalently attached to the peptide ligand.

[0096] 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.

[0097] 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).

[0098] 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.

[0099] 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.

[0100] The molecular fusion may comprise a polymer. The polymer may be branched or linear.

[0101] 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

[0102] In certain embodiments, the current disclosure concerns recombinant polynucleotides encoding the proteins, polypeptides, and peptides of the disclosure.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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 considerably. 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.

[0108] 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).

[0109] The disclosure also contemplates the use of polynucleotides which are complementary to all the above described polynucleotides.

A. Vectors

[0110] 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.

[0111] 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

[0112] 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.

[0113] 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.

[0114] 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-DRα (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), α1-Antitrypain (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).

[0115] 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)x/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); MHW Class I Gene H-2κb—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).

[0116] 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)

[0117] 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.

[0118] 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

[0119] 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

[0120] 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.

[0121] 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

[0122] 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.

[0123] 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®.

[0124] 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

[0125] 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

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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 μg/kg or micrograms/kg/minute or mg/kg/min or micrograms/kg/hour or mg/kg/hour, or any range derivable therein of an agent of the disclosure (e.g. growth factor, cytokine, peptide, polypeptide, functional moiety, etc. . . .).

[0137] 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

[0138] 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-β1, TGF-β2, TGF-β3, NGF, NT-3, BDNF, PlGF-1, PlGF-2, PlGF-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-β1, TGF-β2, NT-3, BDNF, PlGF-1, PlGF-2, PlGF-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-β1, TGF-β2, NT-3, BDNF, PlGF-1, PlGF-2, PlGF-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

[0139] 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 alpha2 plasmin inhibitor (α_2PI_{1-8}, 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).

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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

[0147] 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).

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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 would healing and tissue regeneration would include in humans and agricultural, sports and pet animals.

VI. EXAMPLES

[0153] 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

[0154] 1. Results

[0155] a. Multiple GFs Bind to Multiple Isoforms of Laminin

[0156] 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. **1**A). Specifically, from the VEGF/PDGF family, VEGF-A165, PlGF-2, PDGF-AA, PDGF-BB, and PDGF-CC bound to all isoforms of laminin, in contrast to VEGF-A121, PlGF-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 βNGF 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-12γ bound to all laminin isoforms, whereas CXCL-11 and CXCL-12a bound weakly to laminin-332 but not to the other isoforms.

[0157] Next, the inventors measured the affinities between laminin-521, as an example, and VEGF-A165, PlGF-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. **1**B). K_D values were 5.8 nM for VEGF-A165, 12.9 nM for PlGF-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.

[0158] b. GFs Bind to the HBDs of Laminin

[0159] 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, PlGF-2 or FGF-2 in the presence of heparin added in excess (10 μM). As a result, the inventors observed that excess heparin inhibited GF binding to laminin (FIG. **2**A-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 α3, α4 and α5, within which HBDs of laminin were localized. It was found that VEGF-A165, PlGF-2, PDGF-BB, and FGF-2 bound to laminin LG domains $\alpha3_{2928-3150}$, $\alpha4_{826-1816}$ and $\alpha5_{3026-3482}$, in contrast to VEGF-A121 and PlGF-1 which did not show any binding (FIG. **3**A-C), as tested by ELISA. The binding affinities between $\alpha3_{2928-3150}$ 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. **3**D). These data again demonstrated the strong affinities of the laminin LG domain to the tested GFs.

[0160] 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. **4**A). 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 α3, α4 and α5 chains. Of 9 tested peptides, 6 bound to heparin (i.e. HBDs), namely $\alpha3_{2932-2951}$, $\alpha3_{3043-3067}$, $\alpha4_{1408-1434}$, $\alpha4_{1521-1543}$, $\alpha5_{3300-3330}$, and $\alpha5_{3417-3436}$ among which $\alpha3_{2932-2951}$, $\alpha4_{1408-1434}$, and $\alpha5_{3300-3330}$ are derived from the LG3-LG4 linker. Interestingly, $\alpha5_{3312-3325}$, which is a subdomain of $\alpha5_{3300-3330}$, did not bind to heparin.

[0161] Finally, the affinities of VEGF-A, PlGF, PDGF-BB, and FGF-2 to these peptides were examined (FIG. **4**B-F). The inventors observed that all heparin-binding peptides showed significant binding to some GFs. Indeed, $\alpha3_{3043-3067}$, $\alpha4_{1408-1434}$, and $\alpha5_{3417-3436}$ bound to VEGF-A165, PlGF-2, PDGF-BB, and FGF-2. $\alpha4_{1521-1543}$ showed similar results except for the binding to PDGF-BB, which was not statistically significant. $\alpha3_{2932-2951}$ and $\alpha5_{3300-3330}$ preferentially bound to VEGF-A165 and FGF-2, and VEGF-A165 and PlGF-2 respectively. As to the non-heparin-binding peptides, $\alpha5_{3312-3325}$ did not show particular binding to any tested GF. Interestingly, $\alpha5_{3539-3550}$, which did not show binding to heparin, significantly bound to all tested GFs, and $\alpha3_{3031-3043}$ bound to VEGF-A165. None of the tested laminin-derived peptides bound to VEGF-A121 nor to PlGF-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 $\alpha3_{3043-3067}$ peptide (FIG. **9**); scrambling the sequence of $\alpha3_{3043-3067}$ decreased the binding signals between $\alpha3_{3043-3067}$ and VEGF-A165, PlGF-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.

[0162] c. Laminin HBD Peptides Promote Adhesion of Multiple Types of Cells

[0163] 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. **5**A-D). $\alpha3_{3043-3067}$, $\alpha4_{1521-1543}$, $\alpha4_{1408-1434}$, $\alpha5_{3417-3436}$, and $\alpha5_{3300-3330}$ showed significant binding to all isoforms of recombinant syndecans, i.e. syndecan 1-4. $\alpha3_{2932-2951}$, $\alpha3_{3031-3043}$, and $\alpha5_{3312-3325}$ showed weak binding to the tested syndecans, while $\alpha5_{3539-3550}$ 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 $\alpha3_{2932-2951}$, $\alpha3_{3031-3043}$, $\alpha3_{3043-3067}$, $\alpha4_{1521-1543}$ and $\alpha5_{3417-3436}$-coated surfaces (FIG. **6**A). Fibroblast binding was observed even in the presence of EDTA, consistent with syndecan function (FIG. **6**B). Of these peptides, $\alpha3_{2932-2951}$, $\alpha3_{3043-3067}$, and $\alpha4_{1521-1543}$ also promoted HUVEC attachment (FIG. **6**C), even in the presence of EDTA in the case of $\alpha3_{3043-3067}$

(FIG. **6**D). 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. **4**A). VEGF-A165 increases the degree of migration of HUVEC cells in vitro (FIG. **10**). However, both in the presence and absence of VEGF-A165, $\alpha3_{3043-3067}$ did not increase the degree of cell migration.

[0164] d. Retention of VEGF-A165 and PDGF-BB in Fibrin Matrix is Increased by the Incorporation of Laminin HBD Peptides

[0165] 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 $\alpha3_{3043-3067}$ and $\alpha5_{3417-3436}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$, α_2PI_{1-8}-$\alpha5_{3417-3436}$ or no laminin-derived peptide were then monitored daily and quantified by ELISA (FIG. **7**A, 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ or α_2PI_{1-8}-$\alpha5_{3417-3436}$ allowed significant retention of VEGF-A165 and PDGF-BB into matrices, which were respectively released after 5 days, for VEGF-A165 (α_2PI_{1-8}-$\alpha3_{3043-3067}$: 25%, α_2PI_{1-8}-$\alpha5_{3417-3436}$: 31%) and for PDGF-BB (α_2PI_{1-8}-$\alpha3_{3043-3067}$: 45%, α_2PI_{1-8}-$\alpha5_{3417-3436}$: 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. **7**A, B). The inventors next evaluated the effect of α_2PI_{1-8}-$\alpha3_{3043-3067}$ on GF retention in diabetic wounds in the type 2 diabetic db/db mouse in vivo (FIG. **7**C). Incorporation of α_2PI_{1-8}-$\alpha3_{3043-3067}$ into fibrin matrices significantly enhanced the amount of VEGF-A165 remaining in the wounds 3 days after treatment, showing that incorporation of α_2PI_{1-8}-$\alpha3_{3043-3067}$ prolongs retention of GFs in vivo.

[0166] e. Laminin HBD-Functionalized Fibrin Matrices Potentiate GFs and Promote Wound Healing In Vivo

[0167] Although the etiology of non-healing wounds is multi-faceted 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 $\alpha3_{3043-3067}$, 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$, fibrin containing GFs, and fibrin functionalized with α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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. **8**A-C). In contrast, the co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with α_2PI_{1-8}-$\alpha3_{3043-3067}$ led to a significantly faster wound closure after 7 days, as well as a significant increase in granulation tissue formation (FIG. **8**A-C). GFs alone improved the amount of granulation tissue but not wound closure on day 10, suggesting that α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide speeds the wound healing process by these GFs. Representative wound morphology for all four treatments is presented in FIG. **8**D. Clear differences in granulation tissue thickness and extent of re-epithelialization can be visualized when GFs were delivered within the α_2PI_{1-8}-$\alpha3_{3043-3067}$ peptide-functionalized fibrin matrix compared to the other conditions.

[0168] 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. **8**E). Co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ (FIG. **8**C).

[0169] 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ promotes wound healing immunologically as well. Inclusion of α_2PI_{1-8}-$\alpha3_{3043-3067}$ improved the GF delivery capacity of fibrin in vivo, resulting in an accelerated wound healing.

[0170] 2. Discussion

[0171] 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 $\alpha3_{3031-3043}$ and $\alpha5_{3539-3550}$. 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.

[0172] 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. **4**A). On one side, the inventors discovered 3 novel heparin-, GF- and syndecan-binding peptides within the LG3-LG4 linker regions of $\alpha3$, $\alpha4$, and $\alpha5$ chains, namely $\alpha3_{2932-2951}$, $\alpha4_{1408-1434}$, and $\alpha5_{3300-3330}$, identifiable through their highly cationic sequences (FIG. **4**). Since $\alpha3$, $\alpha4$ and $\alpha5$ 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 $\alpha1$ chain, which is not proteolytically processed, and $\alpha2$ 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 $\alpha3$, $\alpha4$ and $\alpha5$ chains that displayed specific binding to GFs, in particular to VEGF-A165. Among them, $\alpha3_{3043-3067}$, $\alpha5_{3539-3550}$, and $\alpha5_{3417-3436}$ additionally bound to PDGF-BB, FGF-2 and PlGF-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.

[0173] 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 $\alpha3_{3043-3067}$, $\alpha4_{1521-1543}$ and $\alpha5_{3417-3446}$ 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 $\alpha3\beta1$ binds to $\alpha3_{2932-2943}$. 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 Ca^{2+}-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.

[0174] 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.

[0175] Here, the inventors showed that covalent incorporation of an engineered GF-binding domain derived from laminin, α_2PI_{1-8}-$\alpha3_{3043-3067}$, 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 a_2PI_{1-8}-$\alpha3_{3043-3067}$ 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 α_2PI_{1-8}-$\alpha3_{3043-3067}$ 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.

[0176] 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**).

[0177] 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 CXCL12γ, through their HBDs. By engineering a fibrin matrix displaying the $\alpha3_{3043-3067}$ 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.

[0178] 3. Tables

TABLE 1

The sequences of laminin-derived peptides.

Name (location) length	Peptide sequence
$\alpha 3_{2932-2951}$ (Linker) 20 aa.	PPFLMLLKGSTRFNKTKTFR (SEQ ID NO: 2)
$\alpha 3_{3031-3043}$ (LG4) 13 aa.	KNSFMALYLSKGR (SEQ ID NO: 9)
$\alpha 3_{3043-3067}$ (LG4) 25 aa.	RLVFALGTDGKKLRIKSKEKCNDGK (SEQ ID NO: 1)
$\alpha 4_{1408-1434}$ (Linker) 27 aa.	PLFLLHKKGKNLSKPKASQNKKGGKSK (SEQ ID NO: 4)
$\alpha 4_{1521-1543}$ (LG4) 23 aa.	TLFLAHGRLVYMFNVGHKKLKIR (SEQ ID NO: 3)
$\alpha 5_{3300-3330}$ (Linker) 31 aa.	TPGLGPRGLQATARKASRRSRQPARHPACML (SEQ ID NO: 7)
$\alpha 5_{3312-3325}$ (Linker) 14 aa.	ARKASRRSRQPARH (SEQ ID NO: 10)
$\alpha 5_{3417-3436}$ (LG4) 20 aa.	RQRSRPGRWHKVSVRWEKNR (SEQ ID NO: 6)
$\alpha 5_{3539-3550}$ (LG5) 12 aa.	TLPDVGLELEVR (SEQ ID NO: 5)
$\alpha 3_{3043-3067}$ Scr1 25 aa.	RLVKALKTDKFLGRIGSEKCNDKGK (SEQ ID NO: 74)
$\alpha 3_{3043-3067}$ Scr2 25 aa.	RKTDALELVFLKKGGIGSKKCNDKR (SEQ ID NO: 75)
$\alpha 3_{3043-3067}$ Scr3 25 aa.	CRKKKRKKKALLLGIGDFNSEVTDG (SEQ ID NO: 76)
$\alpha 3_{3043-3067}$ Scr4 25 aa.	KKRKLVALTDFLGICGSENDGRKKK (SEQ ID NO: 77)
$\alpha 3_{3043-3067}$ Scr5 25 aa.	LVRAKLTDKFLGKRIGSKECNKDKG (SEQ ID NO: 78)
$\alpha 3_{3043-3067}$ Scr6 25 aa.	ALLLGIGRDFNKKKRKKKSEVTDGC (SEQ ID NO: 79)
a2PI1-8-$\alpha 3_{3043-3067}$ 33 aa.	NQEQVSPLRLVFALGTDGKKLRIKSKEKCNDGK (SEQ ID NO: 8)
α2PI1-8-$\alpha 53_{312-3325}$ 22 aa.	NQEQVSPLARKASRRSRQPARH (SEQ ID NO: 11)

Table 2. Summary of laminin-derived peptide interactions.

Laminin-derived peptides	Interaction with			Cell adhesion	
	Heparin	**GFs**	**Syndecans**	**Fibroblasts**	**HUVECs**
$\alpha\ 3_{2932-2951}$	++	+	+	+	+
$\alpha\ 3_{3031-3043}$		+	+	+	
$\alpha\ 3_{3043-3067}$	++	++	++	++	++
$\alpha\ 4_{1408-1434}$	++	++	++		
$\alpha\ 4_{1521-1543}$	++	+	++	+	+
$\alpha\ 5_{3300-3330}$	++	+	++		
$\alpha\ 5_{3312-3325}$			+		
$\alpha\ 5_{3417-3436}$	++	++	++	+	
$\alpha\ 5_{3539-3550}$		+			

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

[0179] 4. Materials and Methods

[0180] a. Growth Factors and Chemokines

[0181] All growth factors (GFs) and chemokines were purchased in their mature forms, highly pure (>95% pure), carrier-free, and lyophilized[1]. Vascular endothelial growth factor (VEGF)-A121, VEGF-A165, placental growth factor (PlGF)-1, PlGF-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-12a were purchased from PeproTech. CXCL-12γ 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.

[0182] b. Detection of Laminin Binding to Recombinant GFs

[0183] 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 γ1 chain antibody (1:1000 dilution, Assay biotech) or rabbit anti-human laminin α3 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 μL TMB substrate (Sigma-Aldrich) was added. The reactions were stopped by adding 25 μL of 2 N H_2SO_4. Subsequently, the absorbance at 450 nm was measured with a reference of 570 nm.

[0184] c. Production and Purification of Recombinant Laminin $\alpha3_{2928\text{-}3150}$ Protein

[0185] Protein production and purification were performed as described previously[1]. 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 μg/mL plasmid DNA, 2 μg/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% CO_2. 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 NaH_2PO_4, 0.5 M NaCl, pH 7.4), protein was eluted with a gradient of 500 mM imidazole (in 20 mMNaH_2PO_4, 0.5 MNaCl, pH 7.4). The elusion 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.

[0186] d. Surface Plasmon Resonance (SPR)

[0187] SPR analysis was performed as described previously[2]. In brief, measurements were made with a Biacore 3000 SPR system (GE Healthcare). Laminin-521 or laminin $\alpha3_{2928\text{-}3150}$ 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 PlGF-2 was flowed at increasing concentrations in the running buffer at 20 μL/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).

[0188] e. Inhibition of Laminin-GF Binding by Heparin

[0189] ELISA plates (med-binding) were coated with 10 μg/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 μg/mL each of VEGF-A165, PlGF-2, or FGF-2 for 60 min at RT with 10 μM heparin. Next, the wells were incubated with biotinylated anti-VEGF, anti-PlGF, 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.

[0190] f. Detection of GF Binding to Recombinant Laminin LG Domain Protein and the Synthesized Laminin HBD Peptides

[0191] ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 μg/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 μg/mL of BSA served as non-binding protein control. After blocking with 2% BSA PBS-0.05% Tween 20 (PBS-T) solution, 1 μg/mL of the recombinant human proteins (VEGF-A121, VEGF-A165, PlGF-1, PlGF-2, PDGF-BB or FGF-2) or 10 μg/mL of biotinylated heparin (Sigma-Aldrich) were added. Bound GF was detected with biotinylated antibodies for human VEGF, PlGF, 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.

[0192] g. Detection of Recombinant Syndecan Binding to the Synthesized Laminin HBD Peptides

[0193] ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 μg/mL laminin peptide (sequences are described in Table 1, chemically synthesized by Genscript) in PBS for 2 hrs at 37° C. 1 μg/mL of BSA served as non-binding protein control. After blocking with 2% BSA PBS-T solution, 1 μg/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.

[0194] h. Cell Adhesion Assay

[0195] 96-well plates (non-tissue culture treated, Greiner Bio-one) were pre-coated with 1 μg/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 μg/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% CO_2. 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.

[0196] i. Migration Assay

[0197] A migration assay was performed as described previously[3]. 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 $\alpha 3_{3043\text{-}3067}$ peptide in medium (MCDB-131, 0.05% BSA) were added to the bottom side of the transwell (500 μL/well). Directly thereafter, HUVEC cells in medium containing 0.05% BSA (300 μL/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.

[0198] j. Release of GF from Fibrin Matrix

[0199] Fibrin matrices were generated with human fibrinogen (VWF and fibronectin depleted, Enzyme Research Laboratories) as described previously[1]. 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 (Sigma-Aldrich), 2 μM $\alpha_2PI_{1\text{-}8}$-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 $\alpha_2PI_{1\text{-}8}$ 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 μL 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.

[0200] k. Retention of VEGF-A165 at the Wound Site

[0201] Retention assays were performed as previously reported[1]. 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 μL total, fibrinogen (10 mg/mL), 2 U/mL human thrombin, 4 U/mL factor XIII, 5 mM calcium chloride, 2 μM $\alpha_2PI_{1\text{-}8}\text{-}\alpha 3_{3043\text{-}3067}$, 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 μL 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 10000×g 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%.

[0202] l. Mouse Skin Chronic Wound Healing Model

[0203] Skin wound healing assays were performed as previously reported[1]. 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 μL total, fibrinogen (10 mg/mL), 2 U/mL human thrombin, 4 U/mL factor XIII, 5 mM calcium chloride, 2 μM $\alpha_2PI_{1\text{-}8}\text{-}\alpha 3_{3043\text{-}3067}$, 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.

[0204] m. Histomorphometric Analysis of Wound Tissue Sections

[0205] Histomorphometric analyses were performed as previously reported[1]. 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 μm 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.

[0206] n. Flow Cytometric Analysis of the Wounds

[0207] 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 mm^2) 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 μL 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.).

[0208] o. Statistical Analysis

[0209] 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

[0210] 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.

[0211] 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.

[0212] 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 α3, α4 or α5-chain isoforms of laminin can be incorporated into fibrin-containing biomaterials through enzymatic crosslinking by the factor XIIIa during fibrin polymerization.

[0213] 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.

[0214] 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 α3, α4 or α5-chains; so that the end construct will be α_2PI_{1-8}-GGSG (SEQ ID NO: 81)-LG4 (see sequences below).

[0215] 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. IgGκ signal sequence), downstream of a strong ubiquitous promotor (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 6× 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.

[0216] 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.

[0217] 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.

[0218] Interpretation: This molecular engineering of LG4 domains of α3, α4 and α5-chains of human laminin illustrates 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 domains able to be sequestered into natural or synthetic biomaterials could be similarly envisioned.

1. Native Human Sequences of Laminin α-Chain Isoforms

[0219]

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

(SEQ ID NO: 13)
ALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTKNSFM

ALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDGEKGRLVVD

GLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDS

KPLYTPSSSFGVSSC

NCBI-CCDS database (CCDS11880.1):

(SEQ ID NO: 19)
GCCCTCCAGTTTGGGGACATTCCCACCAGCCACTTGCTATTCAAGCTTCC

TCAGGAGCTGCTGAAACCCAGGTCACAGTTTGCTGTGGACATGCAGACAA

CATCCTCCAGAGGACTGGTGTTTCACACGGGCACTAAGAACTCCTTTATG

GCTCTTTATCTTTCAAAAGGACGTCTGGTCTTTGCACTGGGGACAGATGG

GAAAAAATTGAGGATCAAAAGCAAGGAGAAATGCAATGATGGGAAATGGC

ACACGGTGGTGTTTGGCCATGATGGGGAAAAGGGGCGCTTGGTTGTGGAT

GGACTGAGGGCCCGGGAGGGAAGTTTGCCTGGAAACTCCACCATCAGCAT

CAGAGCGCCAGTTTACCTGGGATCACCTCCATCAGGGAAACCAAAGAGCC

TCCCCACAAACAGCTTTGTGGGATGCCTGAAGAACTTTCAGCTGGATTCA

AAACCCTTGTATACCCCTTCTTCAAGCTTCGGGGTGTCTTCCTGC.

LAMA4_Human, LG4 domain aa1469-aa1640 (UniprotKB database Q16363):

(SEQ ID NO: 14)
AYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEEND

FMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDVIFIRERSSGRLV

IDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNVQINSIYSFSGCL

SNLQLNGASITSASQTFSVTPC.

NCBI-CCDS database (CCDS34514.1):

(SEQ ID NO: 20)
GCCTATCAATATGGAGGAACAGCCAACAGCCGCCAAGAGTTTGAACACTT

AAAAGGAGATTTTGGTGCCAAATCTCAGTTTTCCATTCGTCTGAGAACTC

GTTCCTCCCATGGCATGATCTTCTATGTCTCAGATCAAGAAGAGAATGAC

TTCATGACTCTATTTTTGGCCCATGGCCGCTTGGTTTACATGTTTAATGT

-continued

TGGTCACAAAAAACTGAAGATTAGAAGCCAGGAGAAATACAATGATGGCC

TGTGGCATGATGTGATATTTATTCGAGAAAGGAGCAGTGGCCGACTGGTA

ATTGATGGTCTCCGAGTCCTAGAAGAAAGTCTTCCTCCTACTGAAGCTAC

CTGGAAAATCAAGGGTCCCATTTATTTGGGAGGTGTGGCTCCTGGAAAGG

CTGTGAAAAATGTTCAGATTAACTCCATCTACAGTTTTAGTGGCTGTCTC

AGCAATCTCCAGCTCAATGGGGCCTCCATCACCTCTGCTTCTCAGACATT

CAGTGTGACCCCTTGC

LAMA5_Human, LG4 domain aa3340-aa3513 (UniprotKB database 015230):

(SEQ ID NO: 15)
SYQFGGSLSSHLEFVGILARHRNWPSLSMHVLPRSSRGLLLFTARLRPGS

PSLALFLSNGHFVAQMEGLGTRLRAQSRQRSRPGRWHKVSVRWEKNRILL

VTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSHSSKLPVTVGFSG

CVKRLRLHGRPLGAPTRMAGVTPC

NCBI-CCDS database (CCDS33502.1):

(SEQ ID NO: 21)
TCCTACCAGTTTGGGGGTTCCCTGTCCAGTCACCTGGAGTTTGTGGGCAT

CCTGGCCCGACATAGGAACTGGCCCAGTCTCTCCATGCACGTCCTCCCGC

GAAGCTCCCGAGGCCTCCTCCTCTTCACTGCCCGTCTGAGGCCCGGCAGC

CCCTCCCTGGCGCTCTTCCTGAGCAATGGCCACTTCGTTGCACAGATGGA

AGGCCTCGGGACTCGGCTCCGCGCCCAGAGCCGCCAGCGCTCCCGGCCTG

GCCGCTGGCACAAGGTCTCCGTGCGCTGGGAGAAGAACCGGATCCTGCTG

GTGACGGACGGGGCCCGGGCCTGGAGCCAGGAGGGGCCGCACCGGCAGCA

CCAGGGGGCAGAGCACCCCCAGCCCCACACCCTCTTTGTGGGCGGCCTCC

CGGCCAGCAGCCACAGCTCCAAACTTCCGGTGACCGTCGGGTTCAGCGGC

TGTGTGAAGAGACTGAGGCTGCACGGGAGGCCCCTGGGGGCCCCCACACG

GATGGCAGGGGTCACACCCTGC

2. Engineered Human Sequences of Laminin α-Chain Isoforms

[0220] 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 α2-plasmin inhibitor domain (NQEQVSPL—SEQ ID NO:12) could have been alternatively added to the C-terminus of LG4 domains (sequences not shown).

Human $\alpha 2PI_{1-8}$-$LAMA3\_LG4_{2986-3150}$:

(SEQ ID NO: 16)
NQEQVSPLGGSGALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRG

LVFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVF

GHDGEKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNS

FVGCLKNFQLDSKPLYTPSSSFGVSSC.

-continued

Possible DNA sequence of human
α2PI$_{1-8}$-LAMA3_LG4$_{2986-3150}$:

(SEQ ID NO: 22)

AACCAGGAGCAGGTGTCCCCACTTGGTGGATCCGGCGCCCTCCAGTTTGG

GGACATTCCCACCAGCCACTTGCTATTCAAGCTTCCTCAGGAGCTGCTGA

AACCCAGGTCACAGTTTGCTGTGGACATGCAGACAACATCCTCCAGAGGA

CTGGTGTTTCACACGGGCACTAAGAACTCCTTTATGGCTCTTTATCTTTC

AAAAGGACGTCTGGTCTTTGCACTGGGGACAGATGGGAAAAAATTGAGGA

TCAAAAGCAAGGAGAAATGCAATGATGGGAAATGGCACACGGTGGTGTTT

GGCCATGATGGGGAAAAGGGGCGCTTGGTTGTGGATGGACTGAGGGCCCG

GGAGGGAAGTTTGCCTGGAAACTCCACCATCAGCATCAGAGCGCCAGTTT

ACCTGGGATCACCTCCATCAGGGAAACCAAAGAGCCTCCCCACAAACAGC

TTTGTGGGATGCCTGAAGAACTTTCAGCTGGATTCAAAACCCTTGTATAC

CCCTTCTTCAAGCTTCGGGGTGTCTTCCTGC.

Human α2PI$_{1-8}$-LAMA4_LG4$_{1469-1640}$:

(SEQ ID NO: 17)

NQEQVSPLGGSGAYQYGGTANSRQEFEHLKGDFGAKSQFSIRLRTRSSHG

MIFYVSDQEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYNDGLWHDV

IFIRERSSGRLVIDGLRVLEESLPPTEATWKIKGPIYLGGVAPGKAVKNV

QINSIYSFSGCLSNLQLNGASITSASQTFSVTPC.

Possible DNA sequence of human
α2PI$_{1-8}$-LAMA4_LG4$_{1469-1640}$:

(SEQ ID NO: 23)

AACCAGGAGCAGGTGTCCCCACTTGGTGGATCCGGCGCCTATCAATATGG

AGGAACAGCCAACAGCCGCCAAGAGTTTGAACACTTAAAAGGAGATTTTG

GTGCCAAATCTCAGTTTTCCATTCGTCTGAGAACTCGTTCCTCCCATGGC

ATGATCTTCTATGTCTCAGATCAAGAAGAGAATGACTTCATGACTCTATT

TTTGGCCCATGGCCGCTTGGTTTACATGTTTAATGTTGGTCACAAAAAAC

TGAAGATTAGAAGCCAGGAGAAATACAATGATGGCCTGTGGCATGATGTG

ATATTTATTCGAGAAAGGAGCAGTGGCCGACTGGTAATTGATGGTCTCCG

AGTCCTAGAAGAAAGTCTTCCTCCTACTGAAGCTACCTGGAAAATCAAGG

GTCCCATTTATTTGGGAGGTGTGGCTCCTGGAAAGGCTGTGAAAAATGTT

CAGATTAACTCCATCTACAGTTTTAGTGGCTGTCTCAGCAATCTCCAGCT

CAATGGGGCCTCCATCACCTCTGCTTCTCAGACATTCAGTGTGACCCCTT

GC

Human α2PI$_{1-8}$-LAMA5_LG4$_{3340-3513}$:

(SEQ ID NO: 18)

NQEQVSPLGGSGSYQFGGSLSSHLEFVGILARHRNWPSLSMHVLPRSSRG

LLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRAQSRQRSRPGRWHK

VSVRWEKNRILLVTDGARAWSQEGPHRQHQGAEHPQPHTLFVGGLPASSH

SSKLPVTVGFSGCVKRLRLHGRPLGAPTRMAGVTPC.

-continued

Possible DNA sequence of human
α2PI$_{1-8}$-LAMA5_LG4$_{3340-3513}$:

(SEQ ID NO: 24)

AACCAGGAGCAGGTGTCCCCACTTGGTGGATCCGGCTCCTACCAGTTTGG

GGGTTCCCTGTCCAGTCACCTGGAGTTTGTGGGCATCCTGGCCCGACATA

GGAACTGGCCCAGTCTCTCCATGCACGTCCTCCCGCGAAGCTCCCGAGGC

CTCCTCCTCTTCACTGCCCGTCTGAGGCCCGGCAGCCCCTCCCTGGCGCT

CTTCCTGAGCAATGGCCACTTCGTTGCACAGATGGAAGGCCTCGGGACTC

GGCTCCGCGCCCAGAGCCGCCAGCGCTCCCGGCCTGGCCGCTGGCACAAG

GTCTCCGTGCGCTGGGAGAAGAACCGGATCCTGCTGGTGACGGACGGGGC

CCGGGCCTGGAGCCAGGAGGGGCCGCACCGGCAGCACCAGGGGGCAGAGC

ACCCCCAGCCCCACACCCTCTTTGTGGGCGGCCTCCCGGCCAGCAGCCAC

AGCTCCAAACTTCCGGTGACCGTCGGGTTCAGCGGCTGTGTGAAGAGACT

GAGGCTGCACGGGAGGCCCCTGGGGGCCCCCACACGGATGGCAGGGGTCA

CACCCTGC.

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

[0221] 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.

[0222] 1. Protein Designs

[0223] 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).

[0224] 2. Materials and Methods

[0225] a. DNA Sequences Preparation

[0226] 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.

[0227] b. Protein Production of FabCol, FabCol-LamLG4, FabCol-p(FgHBD)

[0228] 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.

[0229] c. Chemical Conjugation of FgHBD to FabCol

[0230] 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, agter 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.

[0231] d. SDS-PAGE Analyses

[0232] 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).

[0233] e. Binding Assay to Bovine Type I Collagen

[0234] ELISA plates (NUNC MaxiSorp, ThermoFisher Scientific) were coated overnight with 10 μg/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).

[0235] f. Binding Assay to rhBMP-2

[0236] 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.

[0237] g. Binding Assay to Engineered Super-Affinity Growth Factors

[0238] 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 Peprotech (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.

[0239] h. Release from Collagen Matrix

[0240] Collagen hydrogels of 150 μL 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× 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.

[0241] i. Immunohistochemistry Assessment of rhBMP-2 Retention into Collagen Sponge

[0242] 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 μL; 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).

[0243] 3. Results:

[0244] a. Conjugation of a Collagen-Binding Domain FabCol to a Growth Factor-Binding Domain FgHBD

[0245] 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. **13**A). 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. **13**B). 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. **13**C). In addition, FabCol-FgHBD conjugates strongly bound to rhBMP-2, whereas FabCol only did not (FIG. **13**D).

[0246] b. FabCol-FgHBD Conjugates Increased Retention of rhBMP-2 into Collagen Biomaterials

[0247] When incorporated into collagen hydrogels, FabCol-FgHBD strikingly increased the retention of rhBMP-2 (FIG. **13**E); 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. **13**F). Under the tested experimental conditions, rhBMP-2 showed some retention into collagen sponge, yet the presence of FabCol-FgHBD conjugates substantially increased this retention.

[0248] 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

[0249] Two recombinant fusion proteins were made to bridge growth factors, particularly rhBMP-2, to collagen biomaterials (FIG. **14**A). 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. **14**B). Importantly, strong affinity of FabCol-p(FgHBD) and FabCol-LamLG4 to bovine type I collagen was observed by ELISA, with Kis around 1.7 nM and 2.3 nM respectively (FIG. **14**C). Similarly, both variants strongly bound to rhBMP-2, with FabCol-LamLG4 being superior to FabCol-p(FgHBD) (FIG. **14**D). Finally, release tests showed that rhBMP-2 sequestration into type I collagen is substantially increased in presence of FabCol-LamLG4 (FIG. **14**E).

[0250] d. Combining FabCol-LamLG4 Bridge Protein Technology with the Engineering of Super-Affinity ECM-Binding Growth Factors to Further Enhance Growth Factors Delivery

[0251] 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, PlGF-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. **14**F that the binding of FabCol-LamLG4 to PlGF-2-engineered growth factors was significantly higher than the one to non-engineered wild-type growth factors. This results would suggests 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 PlGF-2-derived ECM-binding domain, and so that these two technologies could rationally be used in combination.

[0252] 4. Sequences:

FabCol light chain with the human Fab constant region:

(SEQ ID NO: 62)

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY

GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG

QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK

VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ

GLSSPVTKSFNRGEC

-continued

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

GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG

QGTKVEIK

FabCol heavy chain with the human Fab constant region:
(SEQ ID NO: 64)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEQVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTL

AAFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

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

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTL

AAFDYWGQGTLVTV

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

In some embodiments, the FgHBD comprises:
(SEQ ID NO: 67)
SLRPAPPPISGGGYRARPAKAAATQKKVERKAPDA

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

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTL

AAFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

VNHKPSNTKVDKRVEPKSCGSGGGSGG***SLNKPPFLMLLKGSTRFNKT***

KTFRINQLLQDTPVASPRSVKVWQDACSPLPKTQANH

GALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGL

VFHTGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEK

CNDGKWHTVVFGHDGEKGRLVVDGLRAREGSLPG

NSTISIRAPVYLGSPPSGKPKSLPTNSFVGCLKNFQLDSKPL

YTPSSSFGVSSCTG.

LamLG4 :
(SEQ ID NO: 68)
SLNKPPFLMLLKGSTRFNKTKTFRINQLLQDTPVASPRSVKVWQDACSPL

PKTQANHGALQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFH

TGTKNSFMALYLSKGRLVFALGTDGKKLRIKSKEKCNDGKWHTVVFGHDG

EKGRLVVDGLRAREGSLPGNSTISIRAPVYLGSPPSGKPKSLPTNSFVGC

LKNFQLDSKPLYTPSSSFGVSSCTG.

-continued

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)
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY

GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAIGFPQTFG

QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK

VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ

GLSSPVTKSFNRGECGAGGGSGG***GHRPLDK***

KREEAPSLRPAPPPISGGGYRARPAKAAATQKKVERKA

PDAGGGSGGGSGGGHRPLDKKREEAPSLRPAPPPISGGG

YRARPAKAAATQKKVERKAPDAGGGSGGGSGGGHRPL

DKKREEAPSLRPAPPPISGGGYRARPAKAAATQKK

VERKAPDAGGGT.

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

GSGGGSGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAKAAATQKKVE

RKAPDAGGGSGGGSGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAKA

AATQKKVERKAPDAGGGT
or

(SEQ ID NO: 70)
GHRPLDKKREEAPSLRPAPPPISGGGYRARPAKAAATQKKVERKAPDAGG

GSGGGSGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAKAAATQKKVE

RKAPDAGGGSGGGSGGGHRPLDKKREEAPSLRPAPPPISGGGYRARPAKA

AATQKKVERKAPDAGGTG

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)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEQVSA

ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTL

AAFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

VNHKPSNTKVDKRVEPKSCGSGGGSGG***GHRPLDKKREEAPSLRPAPPPI***

SGGGYRARPAKAAATQKKVERKAPDAGGGSGGGSG

GGHRPLDKKREEAPSLRPAPPPISGGGYRARPAKAA

ATQKKVERKAPDAGGGSGGGSGGGHRPLDKKREEAPSLR

PAPPPISGGGYRARPAKAAATQKKVERKAPDAGGTG.

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

[0253] 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.

[0254] 1. Materials and Methods

[0255] a. Wound-Healing of vWF-Deficient Mice

[0256] 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.

[0257] b. Histomorphometric Analysis of Wound Tissue Sections

[0258] 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 μm 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.

[0259] c. Flow Cytometric Analysis of the Wounds

[0260] The wounded skins regions were removed, cut into small pieces (<0.5 mm^2) 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 μL 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).

[0261] d. Quantification of VEGF-A in the Wounds

[0262] 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 μL 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×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).

[0263] e. Mouse Diabetic Skin Wound Healing Model

[0264] 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 μM α_2PI_{1-8}-vWF peptide, 100 ng of VEGF-A165, and 50 ng of PDGF-BB] were polymerized on the wounds; the N-terminal α2 plasmin inhibitor peptide (α_2PI_{1-8}) 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.

[0265] f. Statistical Analysis

[0266] 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). For single comparisons, a two-tailed Student's t-test was used. The symbols * and ** indicatep values less than 0.05 and 0.01, respectively; N.S., not significant.

[0267] 2. Results

[0268] a. vWF Deficiency Results in Delayed Wound Healing by Decreased Angiogenesis

[0269] 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. **15**A-B). vWF deficiency decreased the proliferation of $CD31^+$ endothelial cells and smooth muscle cells (SMCs), in the wounds, suggesting impaired angiogenesis (FIG. **8**C-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. **15**E). These results suggest that vWF contributes to skin tissue repair through angiogenesis and GF involvement.

[0270] b. vWF Binds to Multiple GFs

[0271] The inventors then tested the hypothesis that vWF promiscuously binds to GFs. A panel of GFs from the PDGF/VEGF, FGF, TGFβ/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. **16**A-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-β1 and BMP-2, but not to TGF-β3 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-12α did not, whereas its isoform CXCL-12γ 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.

[0272] The binding affinity of vWF to VEGF-A165 and PDGF-BB was determined by SPR (FIG. **16**C-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.

[0273] c. vWF Binds to VEGF-A in Human Serum

[0274] 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. **17**A-B). These data suggest that VEGF-A-vWF complexes are present in the circulation.

[0275] d. The HBD of vWF A1 Domain Binds to Multiple GFs

[0276] 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 μM) 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. **18**A); thus the inventors evaluated GF binding to the recombinant A1 domain. VEGF-A165, PlGF-2, PDGF-BB, FGF-2 and CXCL-12γ showed strong binding to recombinant A1 domain, as measured by ELISA (FIG. **18**B). 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-12γ 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. **18**C). These data show that the vWF A1 peptide binds to GFs.

[0277] e. vWF Binds to Heparin-Binding VEGF-A Via the HBD within the A1 Domain

[0278] The inventors examined the association between multiple recombinant isoforms of VEGF-A and vWF domains (FIG. **23**A). VEGF-A165 was found to bind plasma-derived purified vWF as well as immature, propeptide-containing recombinant vWF (FIG. **23**B). Similarly, VEGF-A145, which also contains VEGF's HBD, bound to vWF (FIG. **23**C), whilst VEGF-A121, which lacks a HBD, did not (FIG. **23**D). 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. **23**B-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. **23**B-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. **23**B-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.

[0279] f. Type 2B vWD R1341 Mutation Impairs vWF Binding to GF In Vitro and in Human Serum

[0280] 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 GPIbα 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. **23**B-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. **19**A). 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. **19**B). 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. **19**C).

[0281] 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_2PI_{1-8}-vWF HBD, were polymerized to form a fibrin matrix using thrombin and factor XIII. GF release from the matrix was determined by ELISA (FIG. **20**A-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 α_2PI_{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-12γ 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.

[0282] g. $\alpha2PI_{1-8}$-vWF HBD Peptide Functionalized Fibrin Matrix Promotes Chronic Wound Healing In Vivo.

[0283] 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 α_2PI_{1-8} sequence to fibrin with the α_2PI_{1-8}-vWF HBD to functionalize the matrix. Four groups of treatment were established: fibrin only, fibrin functionalized with α_2PI_{1-8}-vWF HBD, fibrin containing the GFs, and fibrin functionalized with a_2PI_{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. **20**C). In contrast, the combined delivery of VEGF-A165 and PDGF-BB by fibrin functionalized with α_2PI_{1-8}-vWF HBD led to significantly faster wound closure due to re-epithelialization. The development of granulation tissue was maintained (FIG. **20**D). The inventors next examined endothelial cells in the wounds (FIG. **20**E). Co-delivery of VEGF-A165 and PDGF-BB in fibrin functionalized with α_2PI_{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 α_2PI_{1-8}-vWF HBD functionalized fibrin significantly increased frequency of $Ki67^+$, a proliferation marker, within SMCs compared to fibrin only and α_2PI_{1-8}-vWF HBD functionalized fibrin only treatment groups on day 5 (FIG. **20**F). These data show that treatment with α_2PI_{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.

[0284] h. vWF HBD does not Affect Endothelial or Fibroblast Proliferation In Vitro.

[0285] 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. **25**A); 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. **25**B). 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. **25**C). Similarly, vWF HBD did not affect endothelial proliferation in vitro (FIG. **25**D). 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.

[0286] i. Growth Factors and Chemokines

[0287] 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-β1, TGF-β3, BMP-2, BMP-7, NGF, NT-3, IGF-I, IGF-II, EGF, CXCL-11, and CXCL-12α were purchased from PeproTech. CXCL-12γ was purchased from R & D Systems. Except for PDGF-DD, TGF-β1, TGF-β3, 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.

[0288] j. Detection of vWF Binding to Recombinant GFs

[0289] 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 μg/mL of plasma-derived vWF (EMD Millipore) was added. Bound vWF was detected with 1 μg/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.

[0290] k. Surface Plasmon Resonance (SPR)

[0291] 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 μL/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 BIAevalution 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.

[0292] l. Inhibition of vWF-GF Binding by Heparin

[0293] ELISA plates (med-binding) were coated with 10 μg/mL vWF. Then, wells were blocked with 2% BSA-containing PBS-T and further incubated with 1 μg/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.

[0294] m. Detection of vWF Binding to VEGF-A by Western Blotting

[0295] One mL of human serum was immunoprecipitated with 10 μg of monoclonal rabbit anti-human vWF antibody (SinoBiological) or control rabbit IgG (EMD Millipore) and 50 μL 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 μg/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).

[0296] n. Detection of vWF Binding to GFs in Human Serum by ELISA

[0297] 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 μg/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.

[0298] o. Expression of Recombinant vWF

[0299] 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 heparinSepharose affinity chromatography as previously described3,4. 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 HeparinSepharose 6 fast flow column (Amersham Pharmacia, UK). The purity of vWF was assessed by SDS-PAGE gel electrophoresis and concentration determined by vWF-ELISA.

[0300] p. Detection of Recombinant GF Binding to the vWF Recombinant Protein and A1 HBD Peptide.

[0301] ELISA tests were performed as described above. In brief, ELISA plates were coated with 1 μg/mL of FL-vWF (WT or R1341Q), 1 μg/mL of vWF A1 recombinant protein (U-Protein Express) or 1 μg/mL of vWF A1 HBD peptide (sequence YIGLKDRKRPSELRRIASQVKYA, (SEQ ID NO:50) chemically synthesized by Genscript) at 37° C. overnight. After blocking with 2% BSA solution containing PBS-T, 1 μg/mL of the recombinant human proteins VEGF-A121, VEGF-A165, PlGF-1, PlGF-2, PDGF-BB, FGF-2, CXCL-12α and CXCL-12γ were added. 1 μg/mL of BSA served as non-binding protein control. Bound GF or chemokine was detected with biotinylated antibodies for human VEGF-A, PlGF, 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.

[0302] q. Detection of vWF Binding to Recombinant VEGF-A Isoforms

[0303] 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 μg/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 μg/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.

[0304] r. Release of GF from Fibrin Matrix

[0305] Fibrin matrices were generated with human fibrinogen as described previously1,5. 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 μM □2PI1-8-vWF HBD peptide (NQEQVSPLYIGLKDRKRPSELRRIASQVKYA (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 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 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. After 5 d, the cumulative release of GF was quantified by ELISA (DuoSet; R&D Systems), using the 100% released control as a reference.

[0306] s. Release of GFs from Fibrin-Mimetic Matrix

[0307] Fibrin-mimetic matrices were formed from reactive PEG precursors as previously described6. Matrices (50 μL) were generated in 50 mM Tris buffer (pH 7.6) to obtain 1.75% (wt/vol) PEG, 10 μM vWF HBD-Cys (YIGLKDRKRPSELRRIASQVKYAC (SEQ ID NO:49), chemically synthesized by Genscript), 10 U/mL factor XIIIa, 50 mM CaCl2, 1 μg/mL FGF-2 and 1 μg/mL CXCL-12γ. 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.

[0308] t. Cell Adhesion Assay

[0309] 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).

[0310] u. Cell Proliferation Assay with vWF HBD

[0311] 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	YIGLKDRKRPSELRRIASQVKYAC
52	Scrambled HBD	LYCEIARGYSLKRKVPDQIRSRKA
53	Arg substituted HBD	YIGLKDSKSPSELSSIASQVKYAC
54	Naïve	YIGLKDRKRPSELRRIASQVKYA
55	R1341L	YIGLKDRKRPSELLRIASQVKYA
56	R1341P	YIGLKDRKRPSELPRIASQVKYA
57	R1341Q	YIGLKDRKRPSELQRIASQVKYA
58	R1341W	YIGLKDRKRPSELWRIASQVKYA
59	R13415	YIGLKDRKRPSELSRIASQVKYA

[0312] 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 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," respectively.

REFERENCES

[0313] 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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Asp Gly Lys Lys Leu Arg Ile Lys Ser Lys Glu Lys Cys Asn Asp Gly
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Lys


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Arg Gln Pro Ala Arg His
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            20                  25                  30

Thr Thr Ser Ser Arg Gly Leu Val Phe His Thr Gly Thr Lys Asn Ser
        35                  40                  45

Phe Met Ala Leu Tyr Leu Ser Lys Gly Arg Leu Val Phe Ala Leu Gly
    50                  55                  60

Thr Asp Gly Lys Lys Leu Arg Ile Lys Ser Lys Glu Lys Cys Asn Asp
65                  70                  75                  80

Gly Lys Trp His Thr Val Val Phe Gly His Asp Gly Glu Lys Gly Arg
                85                  90                  95

Leu Val Val Asp Gly Leu Arg Ala Arg Glu Gly Ser Leu Pro Gly Asn
            100                 105                 110

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

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

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Leu Lys Pro Arg Ser Gln Phe Ala Val Asp Met Gln Thr Thr Ser Ser
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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
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Ser Leu Pro Thr Asn Ser Phe Val Gly Cys Leu Lys Asn Phe Gln Leu
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Cys


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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
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Trp His Asp Val Ile Phe Ile Arg Glu Arg Ser Ser Gly Arg Leu Val
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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
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Lys Ala Val Lys Asn Val Gln Ile Asn Ser Ile Tyr Ser Phe Ser Gly
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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
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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
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Leu Pro Ala Ser Ser His Ser Ser Lys Leu Pro Val Thr Val Gly Phe
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tttggtgcca aatctcagtt ttccattcgt ctgagaactc gttcctccca tggcatgatc 120

ttctatgtct cagatcaaga agagaatgac ttcatgactc tatttttggc ccatggccgc 180

ttggtttaca tgtttaatgt tggtcacaaa aaactgaaga ttagaagcca ggagaaatac 240

aatgatggcc tgtggcatga tgtgatattt attcgagaaa ggagcagtgg ccgactggta 300

attgatggtc tccgagtcct agaagaaagt cttcctccta ctgaagctac ctggaaaatc 360

aagggtccca tttatttggg aggtgtggct cctggaaagg ctgtgaaaaa tgttcagatt 420

aactccatct acagttttag tggctgtctc agcaatctcc agctcaatgg ggcctccatc 480

acctctgctt ctcagacatt cagtgtgacc ccttgc 516

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

<400> SEQUENCE: 21

tcctaccagt ttgggggttc cctgtccagt cacctggagt ttgtgggcat cctggcccga 60

cataggaact ggcccagtct ctccatgcac gtcctcccgc gaagctcccg aggcctcctc 120

ctcttcactg cccgtctgag gcccggcagc ccctccctgg cgctcttcct gagcaatggc 180

cacttcgttg cacagatgga aggcctcggg actcggctcc gcgcccagag ccgccagcgc 240

tcccggcctg gccgctggca caaggtctcc gtgcgctggg agaagaaccg gatcctgctg 300

gtgacggacg gggcccgggc ctggagccag gaggggccgc accggcagca ccagggggca 360

gagcaccccc agccccacac cctctttgtg ggcggcctcc cggccagcag ccacagctcc 420

aaacttccgg tgaccgtcgg gttcagcggc tgtgtgaaga gactgaggct gcacgggagg 480

cccctggggg cccccacacg gatggcaggg gtcacaccct gc 522

<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 aacccaggtc acagtttgct 120

gtggacatgc agacaacatc ctccagagga ctggtgtttc acacgggcac taagaactcc 180

tttatggctc tttatctttc aaaaggacgt ctggtctttg cactggggac agatgggaaa 240

aaattgagga tcaaaagcaa ggagaaatgc aatgatggga aatggcacac ggtggtgttt 300

ggccatgatg gggaaaaggg gcgcttggtt gtggatggac tgagggcccg ggagggaagt 360

ttgcctggaa actccaccat cagcatcaga gcgccagttt acctgggatc acctccatca 420

gggaaaccaa agagcctccc cacaaacagc tttgtgggat gcctgaagaa ctttcagctg 480

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gattcaaaac ccttgtatac cccttcttca agcttcgggg tgtcttcctg c             531


<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 tccggcgcct atcaatatgg aggaacagcc     60

aacagccgcc aagagtttga acacttaaaa ggagattttg gtgccaaatc tcagttttcc    120

attcgtctga gaactcgttc ctcccatggc atgatcttct atgtctcaga tcaagaagag    180

aatgacttca tgactctatt tttggcccat ggccgcttgg tttacatgtt taatgttggt    240

cacaaaaaac tgaagattag aagccaggag aaatacaatg atggcctgtg gcatgatgtg    300

atatttattc gagaaaggag cagtggccga ctggtaattg atggtctccg agtcctagaa    360

gaaagtcttc ctcctactga agctacctgg aaaatcaagg gtcccattta tttgggaggt    420

gtggctcctg gaaaggctgt gaaaaatgtt cagattaact ccatctacag ttttagtggc    480

tgtctcagca atctccagct caatggggcc tccatcacct ctgcttctca gacattcagt    540

gtgacccctt gc                                                        552


<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 ctcctcctct tcactgcccg tctgaggccc    180

ggcagcccct ccctggcgct cttcctgagc aatggccact tcgttgcaca gatggaaggc    240

ctcgggactc ggctccgcgc ccagagccgc cagcgctccc ggcctggccg ctggcacaag    300

gtctccgtgc gctgggagaa gaaccggatc ctgctggtga cggacggggc ccgggcctgg    360

agccaggagg ggccgcaccg gcagcaccag ggggcagagc acccccagcc ccacaccctc    420

tttgtgggcg gcctcccggc 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

<400> SEQUENCE: 25

Met Arg Gly Gly Val Leu Leu Val Leu Leu Leu Cys Val Ala Ala Gln
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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

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
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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
                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
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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

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
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    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

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
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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
    1925                 1930                 1935

Ser Asn  Gly Lys Ala Ala Val  Gln Arg Ser Ser Arg  Phe Leu Lys
    1940                 1945                 1950

Glu Gly  Asn Asn Leu Ser Arg  Lys Leu Pro Gly Ile  Ala Leu Glu
    1955                 1960                 1965
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Leu Ser  Glu Leu Arg Asn Lys  Thr Asn Arg Phe Gln  Glu Asn Ala
    1970                 1975                 1980

Val Glu  Ile Thr Arg Gln Thr  Asn Glu Ser Leu Leu  Ile Leu Arg
    1985                 1990                 1995

Ala Ile  Pro Lys Gly Ile Arg  Asp Lys Gly Ala Lys  Thr Lys Glu
    2000                 2005                 2010

Leu Ala  Thr Ser Ala Ser Gln  Ser Ala Val Ser Thr  Leu Arg Asp
    2015                 2020                 2025

Val Ala  Gly Leu Ser Gln Glu  Leu Leu Asn Thr Ser  Ala Ser Leu
    2030                 2035                 2040

Ser Arg  Val Asn Thr Thr Leu  Arg Glu Thr His Gln  Leu Leu Gln
    2045                 2050                 2055

Asp Ser  Thr Met Ala Thr Leu  Leu Ala Gly Arg Lys  Val Lys Asp
    2060                 2065                 2070

Val Glu  Ile Gln Ala Asn Leu  Leu Phe Asp Arg Leu  Lys Pro Leu
    2075                 2080                 2085

Lys Met  Leu Glu Glu Asn Leu  Ser Arg Asn Leu Ser  Glu Ile Lys
    2090                 2095                 2100

Leu Leu  Ile Ser Gln Ala Arg  Lys Gln Ala Ala Ser  Ile Lys Val
    2105                 2110                 2115

Ala Val  Ser Ala Asp Arg Asp  Cys Ile Arg Ala Tyr  Gln Pro Gln
    2120                 2125                 2130

Ile Ser  Ser Thr Asn Tyr Asn  Thr Leu Thr Leu Asn  Val Lys Thr
    2135                 2140                 2145

Gln Glu  Pro Asp Asn Leu Leu  Phe Tyr Leu Gly Ser  Ser Thr Ala
    2150                 2155                 2160

Ser Asp  Phe Leu Ala Val Glu  Met Arg Arg Gly Arg  Val Ala Phe
    2165                 2170                 2175

Leu Trp  Asp Leu Gly Ser Gly  Ser Thr Arg Leu Glu  Phe Pro Asp
    2180                 2185                 2190

Phe Pro  Ile Asp Asp Asn Arg  Trp His Ser Ile His  Val Ala Arg
    2195                 2200                 2205

Phe Gly  Asn Ile Gly Ser Leu  Ser Val Lys Glu Met  Ser Ser Asn
    2210                 2215                 2220

Gln Lys  Ser Pro Thr Lys Thr  Ser Lys Ser Pro Gly  Thr Ala Asn
    2225                 2230                 2235

Val Leu  Asp Val Asn Asn Ser  Thr Leu Met Phe Val  Gly Gly Leu
    2240                 2245                 2250

Gly Gly  Gln Ile Lys Lys Ser  Pro Ala Val Lys Val  Thr His Phe
    2255                 2260                 2265

Lys Gly  Cys Leu Gly Glu Ala  Phe Leu Asn Gly Lys  Ser Ile Gly
    2270                 2275                 2280

Leu Trp  Asn Tyr Ile Glu Arg  Glu Gly Lys Cys Arg  Gly Cys Phe
    2285                 2290                 2295

Gly Ser  Ser Gln Asn Glu Asp  Pro Ser Phe His Phe  Asp Gly Ser
    2300                 2305                 2310

Gly Tyr  Ser Val Val Glu Lys  Ser Leu Pro Ala Thr  Val Thr Gln
    2315                 2320                 2325

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
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    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

Thr Gln  Asn Ser His Phe Ile  Leu Pro Phe Asn Gln  Ser Ala Val
    2720                2725                2730
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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

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<400> SEQUENCE: 26

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

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
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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

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                 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
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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
            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
    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
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    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
    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
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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

Leu Asn  Glu Thr Leu Gly Thr  Arg Asp Glu Ala Phe  Glu Arg Asn
    1700                 1705                 1710

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
    1940                 1945                 1950
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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
    1970                 1975                 1980

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
    2030                 2035                 2040

Ala Asn  Asp Thr Ala Lys Asp  Val Leu Ala Gln Ile  Thr Glu Leu
    2045                 2050                 2055

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
    2090                 2095                 2100

Gln Glu  Ala Asp Arg Leu Ile  Asp Lys Leu Lys Pro  Ile Lys Glu
    2105                 2110                 2115

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

Phe Leu  Ala Ile Glu Met Arg  Lys Gly Lys Val Ser  Phe Leu Trp
    2195                 2200                 2205

Asp Val  Gly Ser Gly Val Gly  Arg Val Glu Tyr Pro  Asp Leu Thr
    2210                 2215                 2220

Ile Asp  Asp Ser Tyr Trp Tyr  Arg Ile Val Ala Ser  Arg Thr Gly
    2225                 2230                 2235

Arg Asn  Gly Thr Ile Ser Val  Arg Ala Leu Asp Gly  Pro Lys Ala
    2240                 2245                 2250

Ser Ile  Val Pro Ser Thr His  His Ser Thr Ser Pro  Pro Gly Tyr
    2255                 2260                 2265

Thr Ile  Leu Asp Val Asp Ala  Asn Ala Met Leu Phe  Val Gly Gly
    2270                 2275                 2280

Leu Thr  Gly Lys Leu Lys Lys  Ala Asp Ala Val Arg  Val Ile Thr
    2285                 2290                 2295

Phe Thr  Gly Cys Met Gly Glu  Thr Tyr Phe Asp Asn  Lys Pro Ile
    2300                 2305                 2310

Gly Leu  Trp Asn Phe Arg Glu  Lys Glu Gly Asp Cys  Lys Gly Cys
    2315                 2320                 2325

Thr Val  Ser Pro Gln Val Glu  Asp Ser Glu Gly Thr  Ile Gln Phe
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    2330                2335                2340

Asp Gly  Glu Gly Tyr Ala Leu  Val Ser Arg Pro Ile  Arg Trp Tyr
    2345                2350                2355

Pro Asn  Ile Ser Thr Val Met  Phe Lys Phe Arg Thr  Phe Ser Ser
    2360                2365                2370

Ser Ala  Leu Leu Met Tyr Leu  Ala Thr Arg Asp Leu  Arg Asp Phe
    2375                2380                2385

Met Ser  Val Glu Leu Thr Asp  Gly His Ile Lys Val  Ser Tyr Asp
    2390                2395                2400

Leu Gly  Ser Gly Met Ala Ser  Val Val Ser Asn Gln  Asn His Asn
    2405                2410                2415

Asp Gly  Lys Trp Lys Ser Phe  Thr Leu Ser Arg Ile  Gln Lys Gln
    2420                2425                2430

Ala Asn  Ile Ser Ile Val Asp  Ile Asp Thr Asn Gln  Glu Glu Asn
    2435                2440                2445

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
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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

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
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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

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

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
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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

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                 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
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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
            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
    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
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    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
    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
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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

Leu Asn  Glu Thr Leu Gly Thr  Arg Asp Glu Ala Phe  Glu Arg Asn
    1700                 1705                 1710

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
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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
    1940                1945                1950

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
    1970                1975                1980

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
    2030                2035                2040

Ala Asn  Asp Thr Ala Lys Asp  Val Leu Ala Gln Ile  Thr Glu Leu
    2045                2050                2055

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
    2090                2095                2100

Gln Glu  Ala Asp Arg Leu Ile  Asp Lys Leu Lys Pro  Ile Lys Glu
    2105                2110                2115

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

Phe Leu  Ala Ile Glu Met Arg  Lys Gly Lys Val Ser  Phe Leu Trp
    2195                2200                2205

Asp Val  Gly Ser Gly Val Gly  Arg Val Glu Tyr Pro  Asp Leu Thr
    2210                2215                2220

Ile Asp  Asp Ser Tyr Trp Tyr  Arg Ile Val Ala Ser  Arg Thr Gly
    2225                2230                2235

Arg Asn  Gly Thr Ile Ser Val  Arg Ala Leu Asp Gly  Pro Lys Ala
    2240                2245                2250

Ser Ile  Val Pro Ser Thr His  His Ser Thr Ser Pro  Pro Gly Tyr
    2255                2260                2265

Thr Ile  Leu Asp Val Asp Ala  Asn Ala Met Leu Phe  Val Gly Gly
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    2270                2275                2280

Leu Thr  Gly Lys Leu Lys Lys  Ala Asp Ala Val Arg  Val Ile Thr
    2285                2290                2295

Phe Thr  Gly Cys Met Gly Glu  Thr Tyr Phe Asp Asn  Lys Pro Ile
    2300                2305                2310

Gly Leu  Trp Asn Phe Arg Glu  Lys Glu Gly Asp Cys  Lys Gly Cys
    2315                2320                2325

Thr Val  Ser Pro Gln Val Glu  Asp Ser Glu Gly Thr  Ile Gln Phe
    2330                2335                2340

Asp Gly  Glu Gly Tyr Ala Leu  Val Ser Arg Pro Ile  Arg Trp Tyr
    2345                2350                2355

Pro Asn  Ile Ser Thr Val Met  Phe Lys Phe Arg Thr  Phe Ser Ser
    2360                2365                2370

Ser Ala  Leu Leu Met Tyr Leu  Ala Thr Arg Asp Leu  Arg Asp Phe
    2375                2380                2385

Met Ser  Val Glu Leu Thr Asp  Gly His Ile Lys Val  Ser Tyr Asp
    2390                2395                2400

Leu Gly  Ser Gly Met Ala Ser  Val Val Ser Asn Gln  Asn His Asn
    2405                2410                2415

Asp Gly  Lys Trp Lys Ser Phe  Thr Leu Ser Arg Ile  Gln Lys Gln
    2420                2425                2430

Ala Asn  Ile Ser Ile Val Asp  Ile Asp Thr Asn Gln  Glu Glu Asn
    2435                2440                2445

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 Arg  Pro Glu Val Asn Leu  Lys Lys Tyr Ser Gly  Cys Leu Lys
    2480                2485                2490

Asp Ile  Glu Ile Ser Arg Thr  Pro Tyr Asn Ile Leu  Ser Ser Pro
    2495                2500                2505

Asp Tyr  Val Gly Val Thr Lys  Gly Cys Ser Leu Glu  Asn Val Tyr
    2510                2515                2520

Thr Val  Ser Phe Pro Lys Pro  Gly Phe Val Glu Leu  Ser Pro Val
    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

Asn Leu  Thr Val Glu Gln Pro  Ile Glu Val Lys Lys  Leu Phe Val
    2645                2650                2655
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Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile
    2660                2665                2670

Pro Pro Phe Glu Gly Cys Ile Trp Asn Leu Val Ile Asn Ser Val
    2675                2680                2685

Pro Met Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile
    2690                2695                2700

Gly Arg Cys Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala
    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

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

Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu
    2900                2905                2910

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
    2930                2935                2940

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

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
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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
    3080                 3085                 3090

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

Gly Val  Gln Pro Val Ser Cys  Pro Ala Asn
    3110                 3115


<210> SEQ ID NO 28
<211> LENGTH: 3333
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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
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

Asn Ile Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu Gly His Leu
            260                 265                 270
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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
            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                 400

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
            420                 425                 430

Ala Asp Gly Cys Glu Gln Gly Ser Gly Arg Cys His Cys Lys Pro Asn
        435                 440                 445

Phe His Gly Asp Asn Cys Glu Lys Cys Ala Ile Gly Tyr Tyr Asn Phe
    450                 455                 460

Pro Phe Cys Leu Arg Ile Pro Ile Phe Pro Val Ser Thr Pro Ser Ser
465                 470                 475                 480

Glu Asp Pro Val Ala Gly Asp Ile Lys Gly Cys Asp Cys Asn Leu Glu
                485                 490                 495

Gly Val Leu Pro Glu Ile Cys Asp Ala His Gly Arg Cys Leu Cys Arg
            500                 505                 510

Pro Gly Val Glu Gly Pro Arg Cys Asp Thr Cys Arg Ser Gly Phe Tyr
        515                 520                 525

Ser Phe Pro Ile Cys Gln Ala Cys Trp Cys Ser Ala Leu Gly Ser Tyr
    530                 535                 540

Gln Met Pro Cys Ser Ser Val Thr Gly Gln Cys Glu Cys Arg Pro Gly
545                 550                 555                 560

Val Thr Gly Gln Arg Cys Asp Arg Cys Leu Ser Gly Ala Tyr Asp Phe
                565                 570                 575

Pro His Cys Gln Gly Ser Ser Ser Ala Cys Asp Pro Ala Gly Thr Ile
            580                 585                 590

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
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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
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    1070                 1075                 1080

Leu Ser  Gly Arg Pro Phe Pro  His Leu Pro Gln Gln  Ser Ser Pro
    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
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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

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
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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
    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
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    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

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
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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

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
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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
    3320                 3325                 3330


<210> SEQ ID NO 29
<211> LENGTH: 1724
<212> TYPE: PRT
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

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

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
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785                 790                 795                 800

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

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
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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

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

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
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
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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
            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                 400

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
            420                 425                 430

Ala Asp Gly Cys Glu Gln Gly Ser Gly Arg Cys His Cys Lys Pro Asn
        435                 440                 445

Phe His Gly Asp Asn Cys Glu Lys Cys Ala Ile Gly Tyr Tyr Asn Phe
    450                 455                 460

Pro Phe Cys Leu Arg Ile Pro Ile Phe Pro Val Ser Thr Pro Ser Ser
465                 470                 475                 480

Glu Asp Pro Val Ala Gly Asp Ile Lys Gly Cys Asp Cys Asn Leu Glu
                485                 490                 495

Gly Val Leu Pro Glu Ile Cys Asp Ala His Gly Arg Cys Leu Cys Arg
            500                 505                 510

Pro Gly Val Glu Gly Pro Arg Cys Asp Thr Cys Arg Ser Gly Phe Tyr
        515                 520                 525

Ser Phe Pro Ile Cys Gln Ala Cys Trp Cys Ser Ala Leu Gly Ser Tyr
    530                 535                 540

Gln Met Pro Cys Ser Ser Val Thr Gly Gln Cys Glu Cys Arg Pro Gly
545                 550                 555                 560

Val Thr Gly Gln Arg Cys Asp Arg Cys Leu Ser Gly Ala Tyr Asp Phe
                565                 570                 575

Pro His Cys Gln Gly Ser Ser Ser Ala Cys Asp Pro Ala Gly Thr Ile
            580                 585                 590
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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                 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
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        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
    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
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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  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
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    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
    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
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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

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
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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

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
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    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

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
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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

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
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        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
            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
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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

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
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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
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
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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
            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                 400

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                 480

Gly Phe Ile Ala Cys Lys Trp Lys
                485


<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
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                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
    370                 375                 380

Val Glu Gln Ala His Asp Met Arg Asp Lys Ile Gln Glu Ile Asn Asn
385                 390                 395                 400

Lys Met Leu Tyr Tyr Gly Glu Glu His Glu Leu Ser Pro Lys Glu Ile
                405                 410                 415

Ser Glu Lys Leu Val Leu Ala Gln Lys Met Leu Glu Glu Ile Arg Ser
            420                 425                 430

Arg Gln Pro Phe Phe Thr Gln Arg Glu Leu Val Asp Glu Glu Ala Asp
        435                 440                 445

Glu Ala Tyr Glu Leu Leu Ser Gln Ala Glu Ser Trp Gln Arg Leu His
    450                 455                 460

Asn Glu Thr Arg Thr Leu Phe Pro Val Val Leu Glu Gln Leu Asp Asp
465                 470                 475                 480

Tyr Asn Ala Lys Leu Ser Asp Leu Gln Glu Ala Leu Asp Gln Ala Leu
                485                 490                 495
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Asn Tyr Val Arg Asp Ala Glu Asp Met Asn Arg Ala Thr Ala Ala Arg
            500                 505                 510

Gln Arg Asp His Glu Lys Gln Gln Glu Arg Val Arg Glu Gln Met Glu
        515                 520                 525

Val Val Asn Met Ser Leu Ser Thr Ser Ala Asp Ser Leu Thr Thr Pro
    530                 535                 540

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

Ile Tyr Ala Glu Ile Asp Gly Ala Lys Ser Glu Leu Gln Val Lys Leu
                565                 570                 575

Ser Asn Leu Ser Asn Leu Ser His Asp Leu Val Gln Glu Ala Ile Asp
            580                 585                 590

His Ala Gln Asp Leu Gln Gln Glu Ala Asn Glu Leu Ser Arg Lys Leu
        595                 600                 605

His Ser Ser Asp Met Asn Gly Leu Val Gln Lys Ala Leu Asp Ala Ser
    610                 615                 620

Asn Val Tyr Glu Asn Ile Val Asn Tyr Val Ser Glu Ala Asn Glu Thr
625                 630                 635                 640

Ala Glu Phe Ala Leu Asn Thr Thr Asp Arg Ile Tyr Asp Ala Val Ser
                645                 650                 655

Gly Ile Asp Thr Gln Ile Ile Tyr His Lys Asp Glu Ser Glu Asn Leu
            660                 665                 670

Leu Asn Gln Ala Arg Glu Leu Gln Ala Lys Ala Glu Ser Ser Ser Asp
        675                 680                 685

Glu Ala Val Ala Asp Thr Ser Arg Arg Val Gly Gly Ala Leu Ala Arg
    690                 695                 700

Lys Ser Ala Leu Lys Thr Arg Leu Ser Asp Ala Val Lys Gln Leu Gln
705                 710                 715                 720

Ala Ala Glu Arg Gly Asp Ala Gln Gln Arg Leu Gly Gln Ser Arg Leu
                725                 730                 735

Ile Thr Glu Glu Ala Asn Arg Thr Thr Met Glu Val Gln Gln Ala Thr
            740                 745                 750

Ala Pro Met Ala Asn Asn Leu Thr Asn Trp Ser Gln Asn Leu Gln His
        755                 760                 765

Phe Asp Ser Ser Ala Tyr Asn Thr Ala Val Asn Ser Ala Arg Asp Ala
    770                 775                 780

Val Arg Asn Leu Thr Glu Val Val Pro Gln Leu Leu Asp Gln Leu Arg
785                 790                 795                 800

Thr Val Glu Gln Lys Arg Pro Ala Ser Asn Val Ser Ala Ser Ile Gln
                805                 810                 815

Arg Ile Arg Glu Leu Ile Ala Gln Thr Arg Ser Val Ala Ser Lys Ile
            820                 825                 830

Gln Val Ser Met Met Phe Asp Gly Gln Ser Ala Val Glu Val His Ser
        835                 840                 845

Arg Thr Ser Met Asp Asp Leu Lys Ala Phe Thr Ser Leu Ser Leu Tyr
    850                 855                 860

Met Lys Pro Pro Val Lys Arg Pro Glu Leu Thr Glu Thr Ala Asp Gln
865                 870                 875                 880

Phe Ile Leu Tyr Leu Gly Ser Lys Asn Ala Lys Lys Glu Tyr Met Gly
                885                 890                 895
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Leu Ala Ile Lys Asn Asp Asn Leu Val Tyr Val Tyr Asn Leu Gly Thr
            900                 905                 910

Lys Asp Val Glu Ile Pro Leu Asp Ser Lys Pro Val Ser Ser Trp Pro
        915                 920                 925

Ala Tyr Phe Ser Ile Val Lys Ile Glu Arg Val Gly Lys His Gly Lys
    930                 935                 940

Val Phe Leu Thr Val Pro Ser Leu Ser Ser Thr Ala Glu Glu Lys Phe
945                 950                 955                 960

Ile Lys Lys Gly Glu Phe Ser Gly Asp Asp Ser Leu Leu Asp Leu Asp
                965                 970                 975

Pro Glu Asp Thr Val Phe Tyr Val Gly Gly Val Pro Ser Asn Phe Lys
            980                 985                 990

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

Ala Thr  Leu Asn Asn Asp Val  Ile Ser Leu Tyr Asn  Phe Lys His
    1010                 1015                 1020

Ile Tyr  Asn Met Asp Pro Ser  Thr Ser Val Pro Cys  Ala Arg Asp
    1025                 1030                 1035

Lys Leu  Ala Phe Thr Gln Ser  Arg Ala Ala Ser Tyr  Phe Phe Asp
    1040                 1045                 1050

Gly Ser  Gly Tyr Ala Val Val  Arg Asp Ile Thr Arg  Arg Gly Lys
    1055                 1060                 1065

Phe Gly  Gln Val Thr Arg Phe  Asp Ile Glu Val Arg  Thr Pro Ala
    1070                 1075                 1080

Asp Asn  Gly Leu Ile Leu Leu  Met Val Asn Gly Ser  Met Phe Phe
    1085                 1090                 1095

Arg Leu  Glu Met Arg Asn Gly  Tyr Leu His Val Phe  Tyr Asp Phe
    1100                 1105                 1110

Gly Phe  Ser Gly Gly Pro Val  His Leu Glu Asp Thr  Leu Lys Lys
    1115                 1120                 1125

Ala Gln  Ile Asn Asp Ala Lys  Tyr His Glu Ile Ser  Ile Ile Tyr
    1130                 1135                 1140

His Asn  Asp Lys Lys Met Ile  Leu Val Val Asp Arg  Arg His Val
    1145                 1150                 1155

Lys Ser  Met Asp Asn Glu Lys  Met Lys Ile Pro Phe  Thr Asp Ile
    1160                 1165                 1170

Tyr Ile  Gly Gly Ala Pro Pro  Glu Ile Leu Gln Ser  Arg Ala Leu
    1175                 1180                 1185

Arg Ala  His Leu Pro Leu Asp  Ile Asn Phe Arg Gly  Cys Met Lys
    1190                 1195                 1200

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
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    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
    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
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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

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
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            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
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
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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                 640

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                 720

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                 800

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                 880

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                 960

Gly Asp Asp Ser Leu Leu Asp Leu Asp Pro Glu Asp Thr Val Phe Tyr
                965                 970                 975

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

Phe Thr  Arg Val Asp Arg Asp  Val Glu Val Glu Asp  Phe Gln Arg
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    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
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Arg Glu  Pro Val Phe Val Gly  Gly Val Pro Glu Ser  Leu Leu Thr
    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                  80

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                  80

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
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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
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                 240

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                 320

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 Gly Val Cys Ile Asp Cys Gln His His Thr
385                 390                 395                 400

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                 480

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
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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                 560

Arg Cys Arg Val Gly Phe Glu Gly Ala Thr Cys Asp Arg Cys Ala Pro
                565                 570                 575

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 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
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    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

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
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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
    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
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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

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
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    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

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
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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
    2570                 2575                 2580

Gly Leu  Val Trp Ala Ala Leu  Gln Gly Ala Arg Thr  Gln Leu Arg
    2585                 2590                 2595

Asp Val  Arg Ala Lys Lys Asp  Gln Leu Glu Ala His  Ile Gln Ala
    2600                 2605                 2610

Ala Gln  Ala Met Leu Ala Met  Asp Thr Asp Glu Thr  Ser Lys Lys
    2615                 2620                 2625

Ile Ala  His Ala Lys Ala Val  Ala Ala Glu Ala Gln  Asp Thr Ala
    2630                 2635                 2640

Thr Arg  Val Gln Ser Gln Leu  Gln Ala Met Gln Glu  Asn Val Glu
    2645                 2650                 2655

Arg Trp  Gln Gly Gln Tyr Glu  Gly Leu Arg Gly Gln  Asp Leu Gly
    2660                 2665                 2670

Gln Ala  Val Leu Asp Ala Gly  His Ser Val Ser Thr  Leu Glu Lys
    2675                 2680                 2685

Thr Leu  Pro Gln Leu Leu Ala  Lys Leu Ser Ile Leu  Glu Asn Arg
    2690                 2695                 2700

Gly Val  His Asn Ala Ser Leu  Ala Leu Ser Ala Ser  Ile Gly Arg
    2705                 2710                 2715

Val Arg  Glu Leu Ile Ala Gln  Ala Arg Gly Ala Ala  Ser Lys Val
    2720                 2725                 2730

Lys Val  Pro Met Lys Phe Asn  Gly Arg Ser Gly Val  Gln Leu Arg
    2735                 2740                 2745

Thr Pro  Arg Asp Leu Ala Asp  Leu Ala Ala Tyr Thr  Ala Leu Lys
    2750                 2755                 2760

Phe Tyr  Leu Gln Gly Pro Glu  Pro Glu Pro Gly Gln  Gly Thr Glu
    2765                 2770                 2775

Asp Arg  Phe Val Met Tyr Met  Gly Ser Arg Gln Ala  Thr Gly Asp
    2780                 2785                 2790

Tyr Met  Gly Val Ser Leu Arg  Asp Lys Lys Val His  Trp Val Tyr
    2795                 2800                 2805

Gln Leu  Gly Glu Ala Gly Pro  Ala Val Leu Ser Ile  Asp Glu Asp
    2810                 2815                 2820

Ile Gly  Glu Gln Phe Ala Ala  Val Ser Leu Asp Arg  Thr Leu Gln
    2825                 2830                 2835
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Phe Gly  His Met Ser Val Thr  Val Glu Arg Gln Met  Ile Gln Glu
    2840                 2845                 2850

Thr Lys  Gly Asp Thr Val Ala  Pro Gly Ala Glu Gly  Leu Leu Asn
    2855                 2860                 2865

Leu Arg  Pro Asp Asp Phe Val  Phe Tyr Val Gly Gly  Tyr Pro Ser
    2870                 2875                 2880

Thr Phe  Thr Pro Pro Pro Leu  Leu Arg Phe Pro Gly  Tyr Arg Gly
    2885                 2890                 2895

Cys Ile  Glu Met Asp Thr Leu  Asn Glu Glu Val Val  Ser Leu Tyr
    2900                 2905                 2910

Asn Phe  Glu Arg Thr Phe Gln  Leu Asp Thr Ala Val  Asp Arg Pro
    2915                 2920                 2925

Cys Ala  Arg Ser Lys Ser Thr  Gly Asp Pro Trp Leu  Thr Asp Gly
    2930                 2935                 2940

Ser Tyr  Leu Asp Gly Thr Gly  Phe Ala Arg Ile Ser  Phe Asp Ser
    2945                 2950                 2955

Gln Ile  Ser Thr Thr Lys Arg  Phe Glu Gln Glu Leu  Arg Leu Val
    2960                 2965                 2970

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
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    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

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
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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
1               5                   10                  15

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
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                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

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
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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
    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
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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

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
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    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

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


<210> SEQ ID NO 38
<211> LENGTH: 1798
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 38

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

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                 320

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
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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

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
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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
    1070                 1075                 1080

Trp Asn  Leu Thr Ser Gly His  Gly Cys Gln Pro Cys  Ala Cys His
    1085                 1090                 1095

Pro Ser  Arg Ala Arg Gly Pro  Thr Cys Asn Glu Phe  Thr Gly Gln
    1100                 1105                 1110

Cys His  Cys Arg Ala Gly Phe  Gly Gly Arg Thr Cys  Ser Glu Cys
    1115                 1120                 1125

Gln Glu  Leu His Trp Gly Asp  Pro Gly Leu Gln Cys  His Ala Cys
    1130                 1135                 1140

Asp Cys  Asp Ser Arg Gly Ile  Asp Thr Pro Gln Cys  His Arg Phe
    1145                 1150                 1155

Thr Gly  His Cys Ser Cys Arg  Pro Gly Val Ser Gly  Val Arg Cys
    1160                 1165                 1170

Asp Gln  Cys Ala Arg Gly Phe  Ser Gly Ile Phe Pro  Ala Cys His
    1175                 1180                 1185
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Pro Cys  His Ala Cys Phe Gly  Asp Trp Asp Arg Val  Val Gln Asp
    1190                 1195                 1200

Leu Ala  Ala Arg Thr Gln Arg  Leu Glu Gln Arg Ala  Gln Glu Leu
    1205                 1210                 1215

Gln Gln  Thr Gly Val Leu Gly  Ala Phe Glu Ser Ser  Phe Trp His
    1220                 1225                 1230

Met Gln  Glu Lys Leu Gly Ile  Val Gln Gly Ile Val  Gly Ala Arg
    1235                 1240                 1245

Asn Thr  Ser Ala Ala Ser Thr  Ala Gln Leu Val Glu  Ala Thr Glu
    1250                 1255                 1260

Glu Leu  Arg Arg Glu Ile Gly  Glu Ala Thr Glu His  Leu Thr Gln
    1265                 1270                 1275

Leu Glu  Ala Asp Leu Thr Asp  Val Gln Asp Glu Asn  Phe Asn Ala
    1280                 1285                 1290

Asn His  Ala Leu Ser Gly Leu  Glu Arg Asp Arg Leu  Ala Leu Asn
    1295                 1300                 1305

Leu Thr  Leu Arg Gln Leu Asp  Gln His Leu Asp Leu  Leu Lys His
    1310                 1315                 1320

Ser Asn  Phe Leu Gly Ala Tyr  Asp Ser Ile Arg His  Ala His Ser
    1325                 1330                 1335

Gln Ser  Ala Glu Ala Glu Arg  Arg Ala Asn Thr Ser  Ala Leu Ala
    1340                 1345                 1350

Val Pro  Ser Pro Val Ser Asn  Ser Ala Ser Ala Arg  His Arg Thr
    1355                 1360                 1365

Glu Ala  Leu Met Asp Ala Gln  Lys Glu Asp Phe Asn  Ser Lys His
    1370                 1375                 1380

Met Ala  Asn Gln Arg Ala Leu  Gly Lys Leu Ser Ala  His Thr His
    1385                 1390                 1395

Thr Leu  Ser Leu Thr Asp Ile  Asn Glu Leu Val Cys  Gly Ala Pro
    1400                 1405                 1410

Gly Asp  Ala Pro Cys Ala Thr  Ser Pro Cys Gly Gly  Ala Gly Cys
    1415                 1420                 1425

Arg Asp  Glu Asp Gly Gln Pro  Arg Cys Gly Gly Leu  Ser Cys Asn
    1430                 1435                 1440

Gly Ala  Ala Ala Thr Ala Asp  Leu Ala Leu Gly Arg  Ala Arg His
    1445                 1450                 1455

Thr Gln  Ala Glu Leu Gln Arg  Ala Leu Ala Glu Gly  Gly Ser Ile
    1460                 1465                 1470

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
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    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
            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
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-continued

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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

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
```

-continued

```
        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 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

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
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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

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
```

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            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

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
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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
            900                 905                 910
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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 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
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    1295                1300                1305

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
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Gly Leu  Thr Lys Glu Thr Leu  Gly Lys Val Lys Gln  Leu Lys Asp
    1685                 1690                 1695

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
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            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

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
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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
            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
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Trp Asn  Leu Val Pro Gly Arg  Gly Cys Gln Ser Cys  Asp Cys Asp
     1070                1075                     1080

Pro Arg  Thr Ser Gln Ser Ser  His Cys Asp Gln Ala  Arg Tyr Phe
     1085                1090                     1095

Lys Ala  Tyr
     1100


<210> SEQ ID NO 42
<211> LENGTH: 772
<212> TYPE: PRT
<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
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```
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

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
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```
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

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 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
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```
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

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
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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
        835                 840                 845

Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys
    850                 855                 860

Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys
865                 870                 875                 880

Cys Lys Ala Cys Asn Cys Asn Leu Tyr Gly Thr Met Lys Gln Gln Ser
                885                 890                 895

Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr
            900                 905                 910

Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser
        915                 920                 925

Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn
    930                 935                 940

Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile
945                 950                 955                 960

Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly
                965                 970                 975

Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser
            980                 985                 990

Leu Gln Cys Lys Asp Asp Gly Arg  Cys Glu Cys Arg Glu  Gly Phe Val
        995                 1000                 1005

Gly Asn  Arg Cys Asp Gln Cys  Glu Glu Asn Tyr Phe  Tyr Asn Arg
    1010                 1015                 1020

Ser Trp  Pro Gly Cys Gln Glu  Cys Pro Ala Cys Tyr  Arg Leu Val
    1025                 1030                 1035

Lys Asp  Lys Val Ala Asp His  Arg Val Lys Leu Gln  Glu Leu Glu
    1040                 1045                 1050

Ser Leu  Ile Ala Asn Leu Gly  Thr Gly Asp Glu Met  Val Thr Asp
    1055                 1060                 1065

Gln Ala  Phe Glu Asp Arg Leu  Lys Glu Ala Glu Arg  Glu Val Met
    1070                 1075                 1080

Asp Leu  Leu Arg Glu Ala Gln  Asp Val Lys Asp Val  Asp Gln Asn
    1085                 1090                 1095

Leu Met  Asp Arg Leu Gln Arg  Val Asn Asn Thr Leu  Ser Ser Gln
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    1100                 1105                 1110

Ile Ser  Arg Leu Gln Asn Ile  Arg Asn Thr Ile Glu  Glu Thr Gly
    1115                 1120                 1125

Asn Leu  Ala Glu Gln Ala Arg  Ala His Val Glu Asn  Thr Glu Arg
    1130                 1135                 1140

Leu Ile  Glu Ile Ala Ser Arg  Glu Leu Glu Lys Ala  Lys Val Ala
    1145                 1150                 1155

Ala Ala  Asn Val Ser Val Thr  Gln Pro Glu Ser Thr  Gly Asp Pro
    1160                 1165                 1170

Asn Asn  Met Thr Leu Leu Ala  Glu Glu Ala Arg Lys  Leu Ala Glu
    1175                 1180                 1185

Arg His  Lys Gln Glu Ala Asp  Asp Ile Val Arg Val  Ala Lys Thr
    1190                 1195                 1200

Ala Asn  Asp Thr Ser Thr Glu  Ala Tyr Asn Leu Leu  Leu Arg Thr
    1205                 1210                 1215

Leu Ala  Gly Glu Asn Gln Thr  Ala Phe Glu Ile Glu  Glu Leu Asn
    1220                 1225                 1230

Arg Lys  Tyr Glu Gln Ala Lys  Asn Ile Ser Gln Asp  Leu Glu Lys
    1235                 1240                 1245

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
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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
<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
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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
                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
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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
            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
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    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

<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
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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
                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
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            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
            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
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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 Gly  Met
    1100                 1105                 1110


<210> SEQ ID NO 46
<211> LENGTH: 1575
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

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

Ala Ala Gly Ala Gly Met Gly Ala Cys Tyr Asp Gly Ala Gly Arg Pro
            20                  25                  30

Gln Arg Cys Leu Pro Val Phe Glu Asn Ala Ala Phe Gly Arg Leu Ala
        35                  40                  45

Gln Ala Ser His Thr Cys Gly Ser Pro Pro Glu Asp Phe Cys Pro His
    50                  55                  60

Val Gly Ala Ala Gly Ala Gly Ala His Cys Gln Arg Cys Asp Ala Ala
65                  70                  75                  80

Asp Pro Gln Arg His His Asn Ala Ser Tyr Leu Thr Asp Phe His Ser
                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
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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

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
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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

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
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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
    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
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    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

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
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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

Ser Ile Ser Ala Val Asp Asn Gly Ser Leu Ala Asn Thr Pro His Leu
                245                 250                 255

Arg Glu Leu His Leu Asp Asn Asn Lys Leu Thr Arg Val Pro Gly Gly
            260                 265                 270

Leu Ala Glu His Lys Tyr Ile Gln Val Val Tyr Leu His Asn Asn Asn
        275                 280                 285

Ile Ser Val Val Gly Ser Ser Asp Phe Cys Pro Pro Gly His Asn Thr
    290                 295                 300
```

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Lys Lys Ala Ser Tyr Ser Gly Val Ser Leu Phe Ser Asn Pro Val Gln
305                 310                 315                 320

Tyr Trp Glu Ile Gln Pro Ser Thr Phe Arg Cys Val Tyr Val Arg Ser
                325                 330                 335

Ala Ile Gln Leu Gly Asn Tyr Lys
            340


<210> SEQ ID NO 49
<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: 49

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 Cys
            20


<210> SEQ ID NO 50
<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: 50

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 51
<211> LENGTH: 31
<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: 51

Asn Gln Glu Gln Val Ser Pro Leu Tyr Ile Gly Leu Lys Asp Arg Lys
1               5                   10                  15

Arg Pro Ser Glu Leu Arg Arg Ile Ala Ser Gln Val Lys Tyr Ala
            20                  25                  30


<210> SEQ ID NO 52
<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: 52

Leu Tyr Cys Glu Ile Ala Arg Gly Tyr Ser Leu Lys Arg Lys Val Pro
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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

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
```

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<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 Gly Ser Gly Gly
1               5                   10                  15

Gly Ser Gly Gly Gly Ser Gly Gly
```

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            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

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


<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

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
```

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```
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
    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
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```
Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val Glu Arg Lys Ala
            20                  25                  30

Pro Asp Ala
        35


<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
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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
                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 Thr Gly
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                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"

<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
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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

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
```

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```
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

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
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```
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
            260                 265                 270

Pro Asp Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly His Arg
        275                 280                 285

Pro Leu Asp Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro
    290                 295                 300

Pro Pro Ile Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala
305                 310                 315                 320

Ala Thr Gln Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Gly
                325                 330                 335

Ser Gly Gly Gly Ser Gly Gly Gly His Arg Pro Leu Asp Lys Lys Arg
            340                 345                 350

Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro Pro Ile Ser Gly Gly
        355                 360                 365

Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala Thr Gln Lys Lys Val
    370                 375                 380

Glu Arg Lys Ala Pro Asp Ala Gly Gly Thr Gly
385                 390                 395


<210> SEQ ID NO 74
<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: 74

Arg Leu Val Lys Ala Leu Lys Thr Asp Lys Phe Leu Gly Arg Ile Gly
1               5                   10                  15

Ser Glu Lys Cys Asn Asp Lys Gly Lys
            20                  25


<210> SEQ ID NO 75
<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: 75
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Arg Lys Thr Asp Ala Leu Glu Leu Val Phe Leu Lys Lys Gly Gly Ile
1               5                   10                  15

Gly Ser Lys Lys Cys Asn Asp Lys Arg
            20                  25


<210> SEQ ID NO 76
<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: 76

Cys Arg Lys Lys Lys Arg Lys Lys Lys Ala Leu Leu Leu Gly Ile Gly
1               5                   10                  15

Asp Phe Asn Ser Glu Val Thr Asp Gly
            20                  25


<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
```

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```
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"

<400> SEQUENCE: 81

Gly Gly Ser Gly
1
```

1. A peptide comprising a growth factor binding domain having 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.

2. The peptide of claim **1**, wherein the peptide is attached to a transglutaminase-reactive peptide.

3. (canceled)

4. The peptide of claim **2**, wherein the transglutaminase-reactive peptide is from the α2-plasmin inhibitor.

5-11. (canceled)

12. The peptide of claim **1**, wherein 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.

13. The peptide of claim **12**, wherein the peptides are separated by one or more linkers.

14-15. (canceled)

16. The peptide of claim **1**, wherein the peptide is attached to a collagen binding peptide.

17-24. (canceled)

25. The peptide of claim **1**, wherein 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.

26-32. (canceled)

33. The peptide of claim **1**, wherein the peptide comprises a methionine immediately adjacent to the first amino acid of one of SEQ ID NOS:1-7 or 13-15.

34. The peptide of claim **1**, wherein the peptide is attached to a cell adhesion moiety.

35-36. (canceled)

37. The peptide of claim **1**, wherein the peptide is attached to a tag or a functional moiety.

38-42. (canceled)

43. The peptide of claim **1**, wherein 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.

44-46. (canceled)

47. A molecular complex comprising the peptide of claim **1**.

48-53. (canceled)

54. A composition comprising the peptide of claim **1**.

55-56. (canceled)

57. A biomaterial scaffold comprising the peptide of claim **1**.

58-66. (canceled)

67. An implant comprising the peptide of claim **1**.

68. (canceled)

69. A method for regenerating tissue in a subject, the method comprising administering the biomaterial of claim **57**.

70. A method for facilitating wound or tissue healing in a subject, the method comprising administering the biomaterial of claim **57** to the subject.

71-81. (canceled)

82. A method for treating von Willebrand Disease, angiodysplasia, and/or mucosal/cutaneous bleeding in a subject, the method comprising administering the biomaterial scaffold of claim **57** to the subject.

83-87. (canceled)

88. A biomaterial scaffold comprising the peptide of SEQ ID NO:49, wherein the peptide is covalently linked to fibrin, and wherein the biomaterial scaffold further comprises exogenously added VEGF and PDGF.

89. A method for facilitating wound or tissue healing in a subject, the method comprising administering the biomaterial scaffold of claim **88** to the subject.

* * * * *