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CORRECTED PUBLICATION

(54) **STABILIZED INSULIN-LIKE GROWTH FACTOR POLYPEPTIDES**

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(15) Correction of US 2014/0235538 A1 Aug. 21, 2014
See (62) and (60) Related U.S. Application Data.

(65) US 2014/0235538 A1 Aug. 21, 2014

Related U.S. Application Data

(62) Division of application No. 13/664,055, filed on Oct. 30, 2012, now Pat. No. 8,722,621, which is a division of application No. 12/304,068, filed on Dec. 9, 2008, now Pat. No. 8,343,918, filed as application No. PCT/US07/70468 on Jun. 6, 2007.

(60) Provisional application No. 60/812,349, filed on Jun. 9, 2006, provisional application No. 60/862,244, filed on Oct. 20, 2006, provisional application No. 60/897,187, filed on Jan. 24, 2007.

Publication Classification

(51) **Int. Cl.**
C07K 14/475 (2006.01)

(52) **U.S. Cl.**
CPC ***C07K 14/475*** (2013.01)

(57) **ABSTRACT**

The invention relates to stabilized polypeptides having an IGF-1 or IGF-2 sequence and an E-peptide sequence, where the natural physiological cleavage of the E-peptide from the IGF is prevented.

Fig. 1A

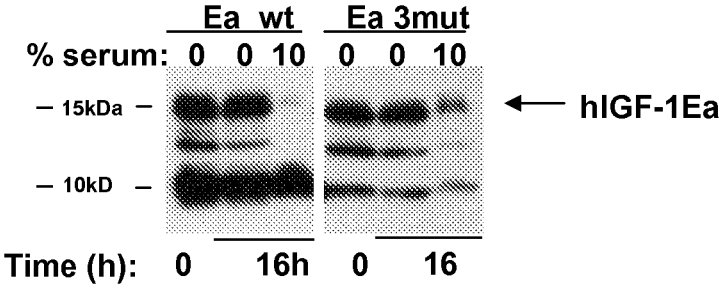


Fig. 1B

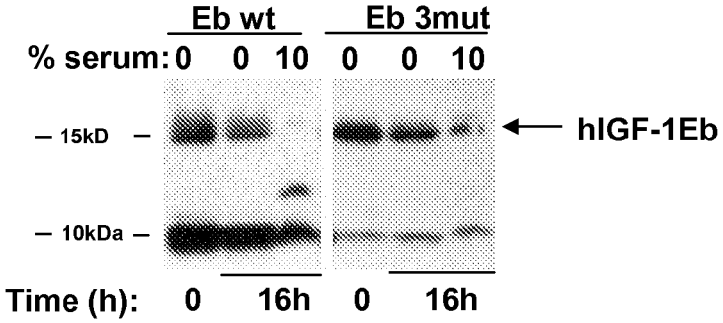


Fig. 1C

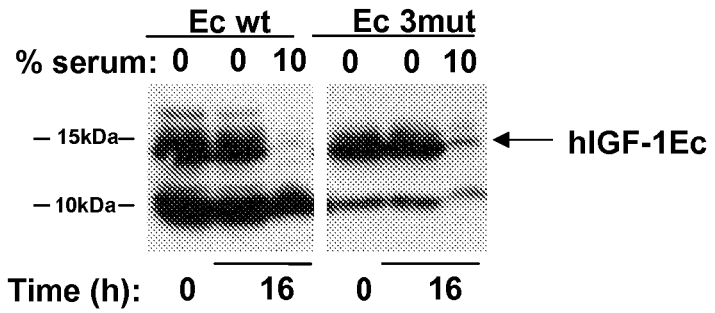


Fig. 2A

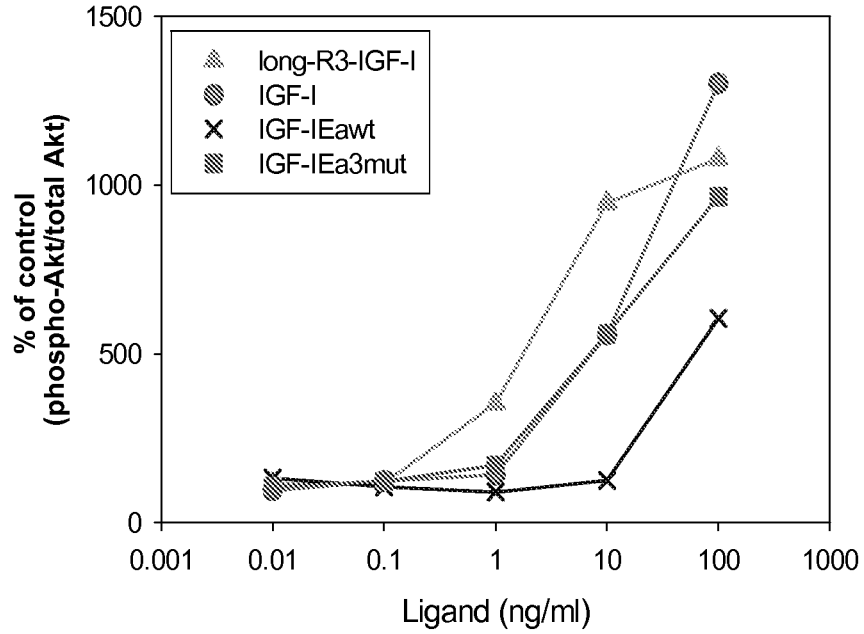

1500
1000
500
0
% of control
(phospho-Akt/total Akt)
long-R3-IGF-I
IGF-I
IGF-IEawt
IGF-IEa3mut
0.001
0.01
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 2B

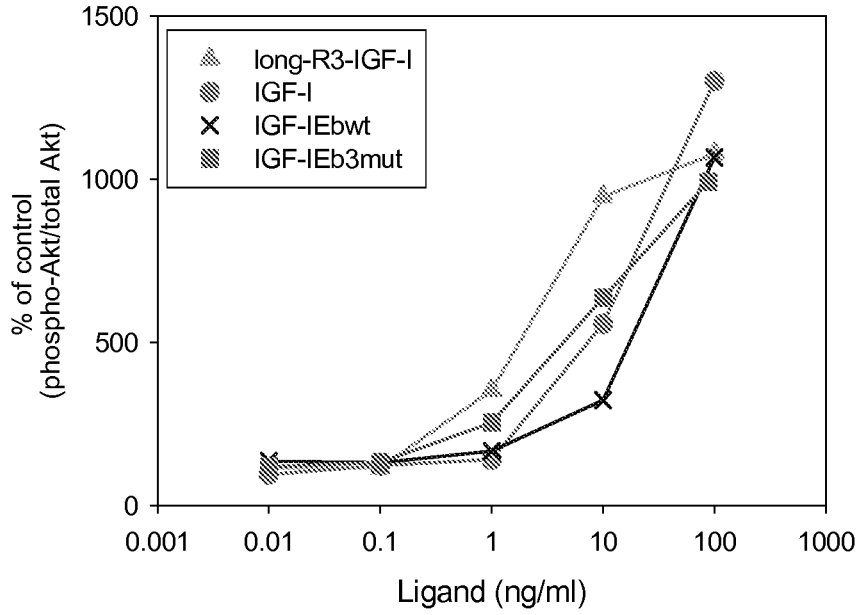
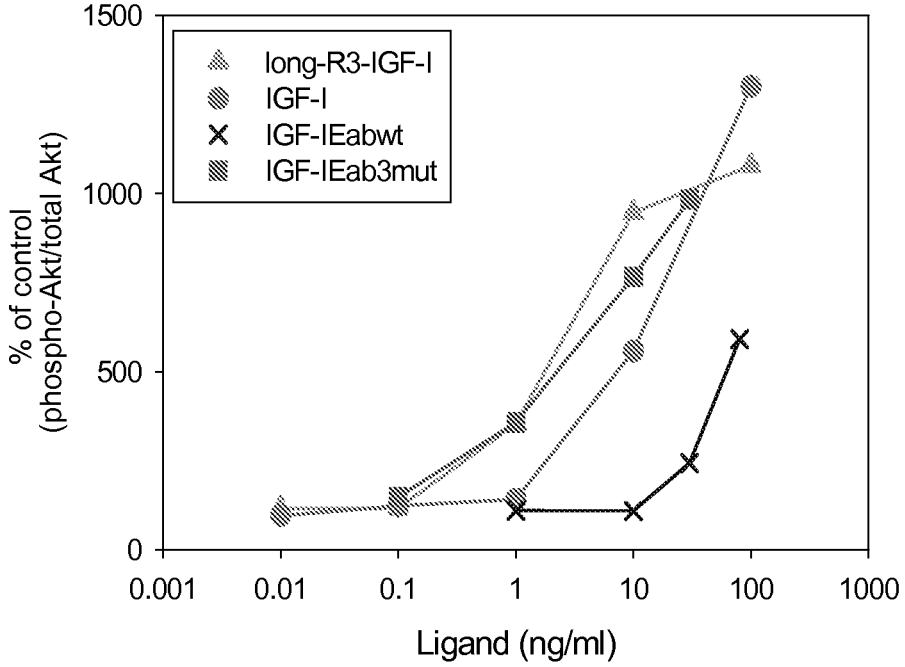

1500
1000
500
0
% of control
(phospho-Akt/total Akt)
long-R3-IGF-I
IGF-I
IGF-IEbwt
IGF-IEb3mut
0.001
0.01
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 2C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1000
500
0
% of control
(phospho-Akt/total Akt)
long-R3-IGF-I
IGF-I
IGF-IEabwt
IGF-IEab3mut
0.001
0.01
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 2D

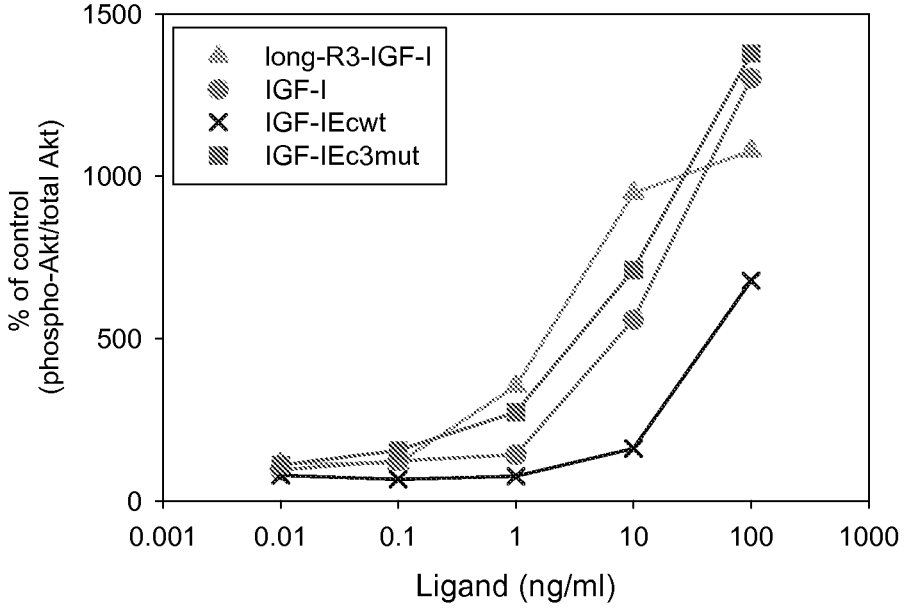
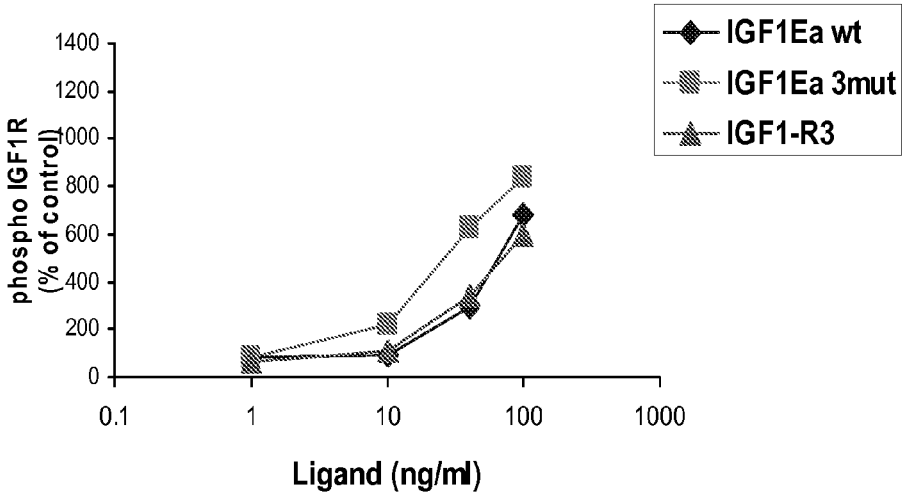

1500
1000
500
0
% of control
(phospho-Akt/total Akt)
long-R3-IGF-I
IGF-I
IGF-IEcwt
IGF-IEc3mut
0.001
0.01
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 3A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IGF1Ea 3mut
IGF1-R3
phospho IGF1R
(% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 3B

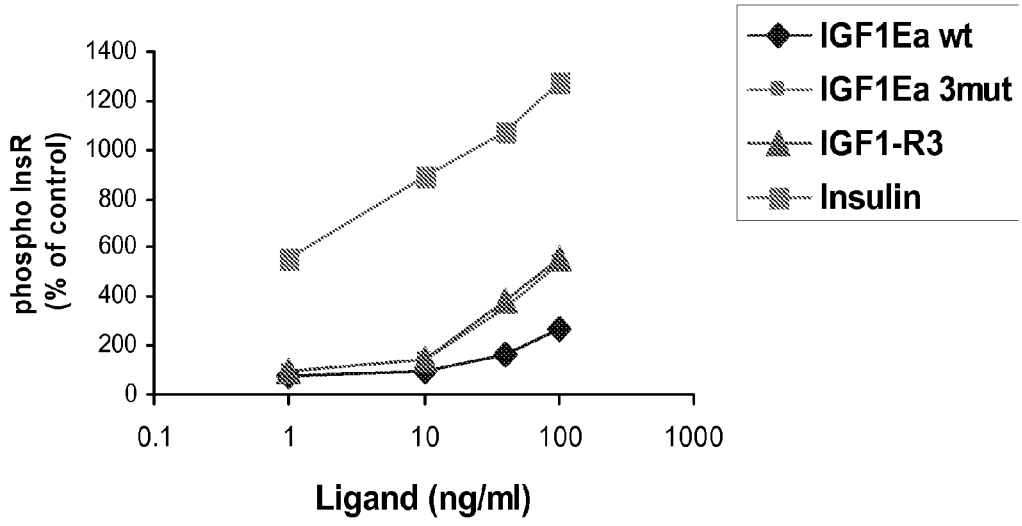

IGF1Ea wt
IGF1Ea 3mut
IGF1-R3
Insulin
phospho InsR
(% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 3C

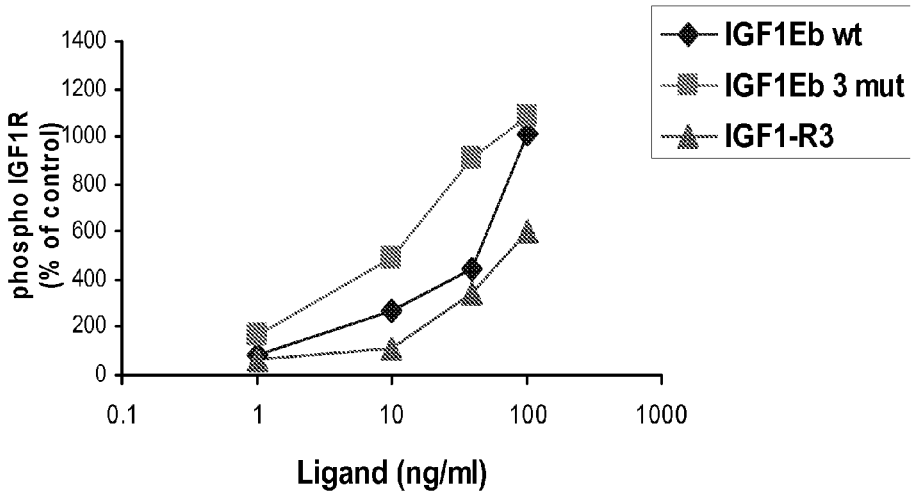

IGF1Eb wt
IGF1Eb 3 mut
IGF1-R3
phospho IGF1R (% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 3D

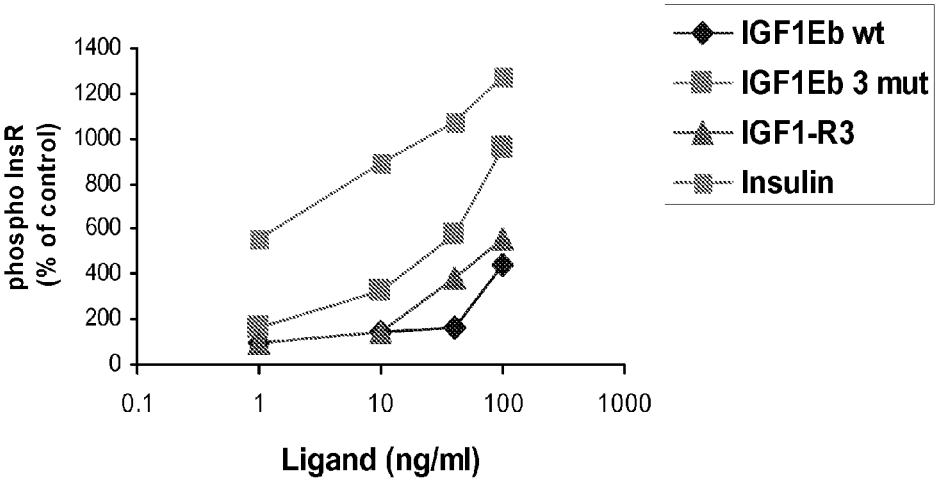
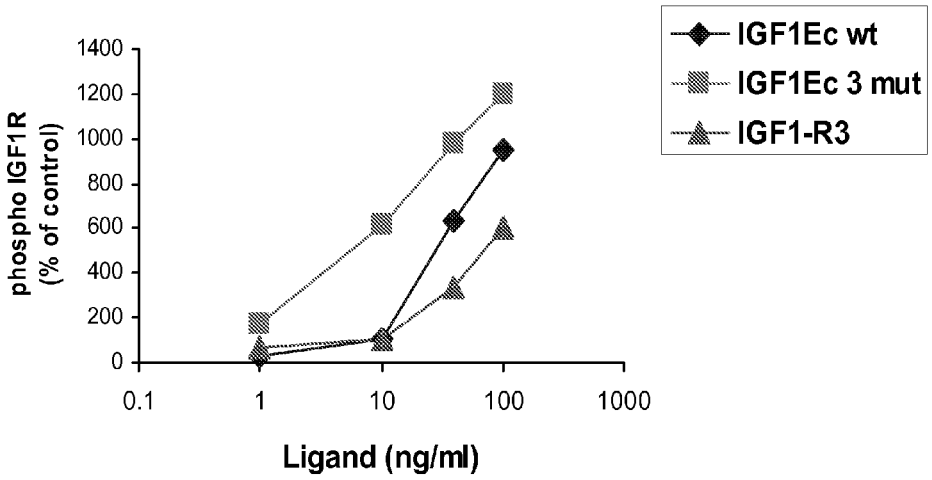

IGF1Eb wt
IGF1Eb 3 mut
IGF1-R3
Insulin
phospho InsR (% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 4A


IGF1Ec wt
IGF1Ec 3 mut
IGF1-R3
phospho IGF1R (% of control)
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1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 4B

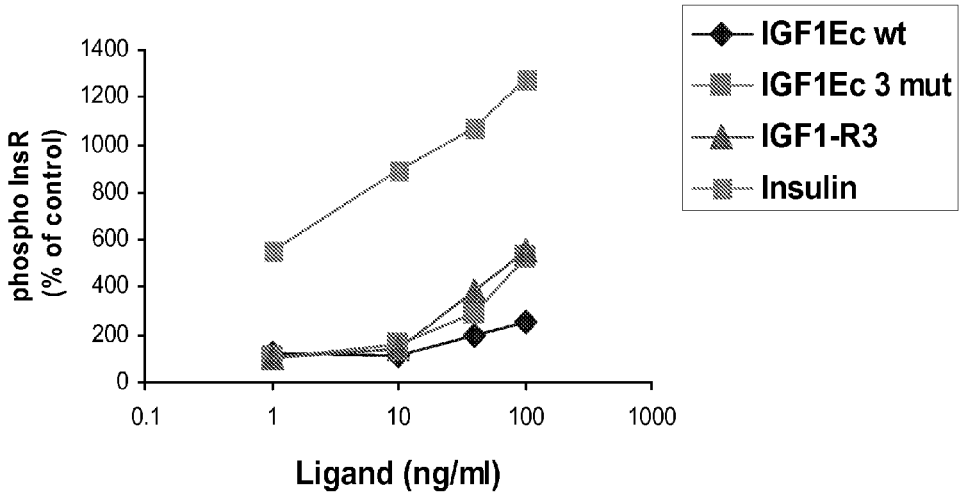

IGF1Ec wt
IGF1Ec 3 mut
IGF1-R3
Insulin
phospho InsR (% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 4C

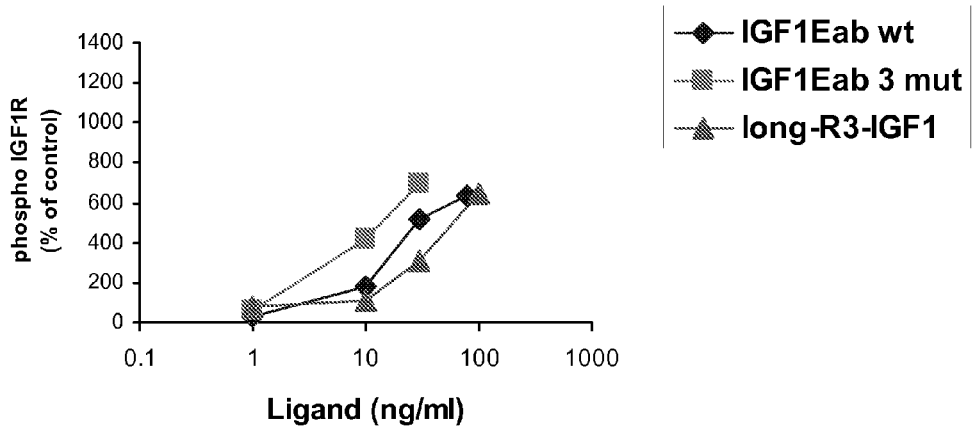

IGF1Eab wt
IGF1Eab 3 mut
long-R3-IGF1
phospho IGF1R (% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
Ligand (ng/ml)

Fig. 4D

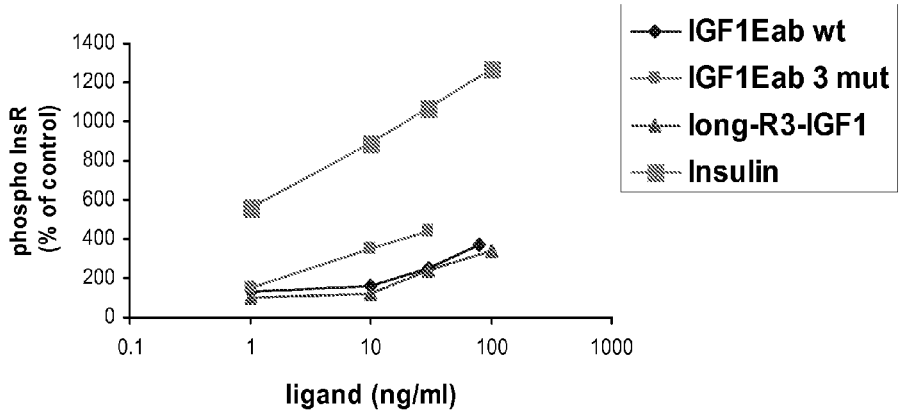

IGF1Eab wt
IGF1Eab 3 mut
long-R3-IGF1
Insulin
phospho InsR (% of control)
1400
1200
1000
800
600
400
200
0
0.1
1
10
100
1000
ligand (ng/ml)

Fig. 5

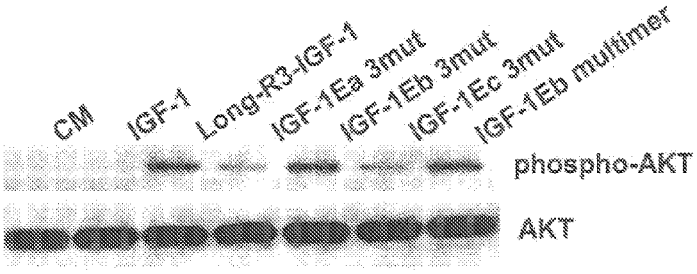


Fig. 6A

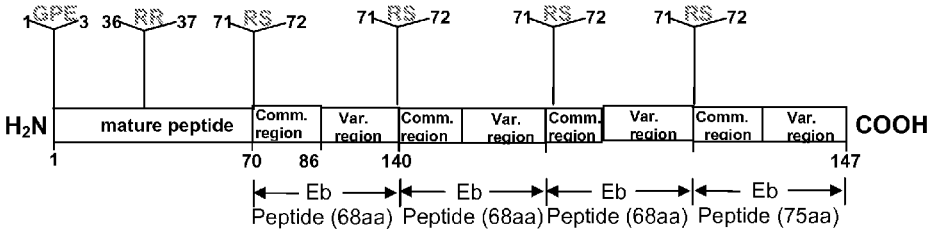


Fig. 6B

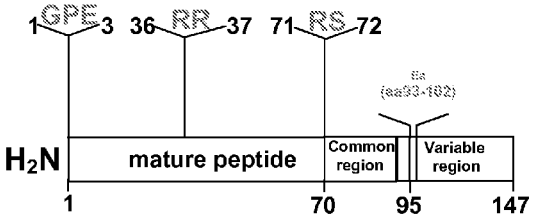
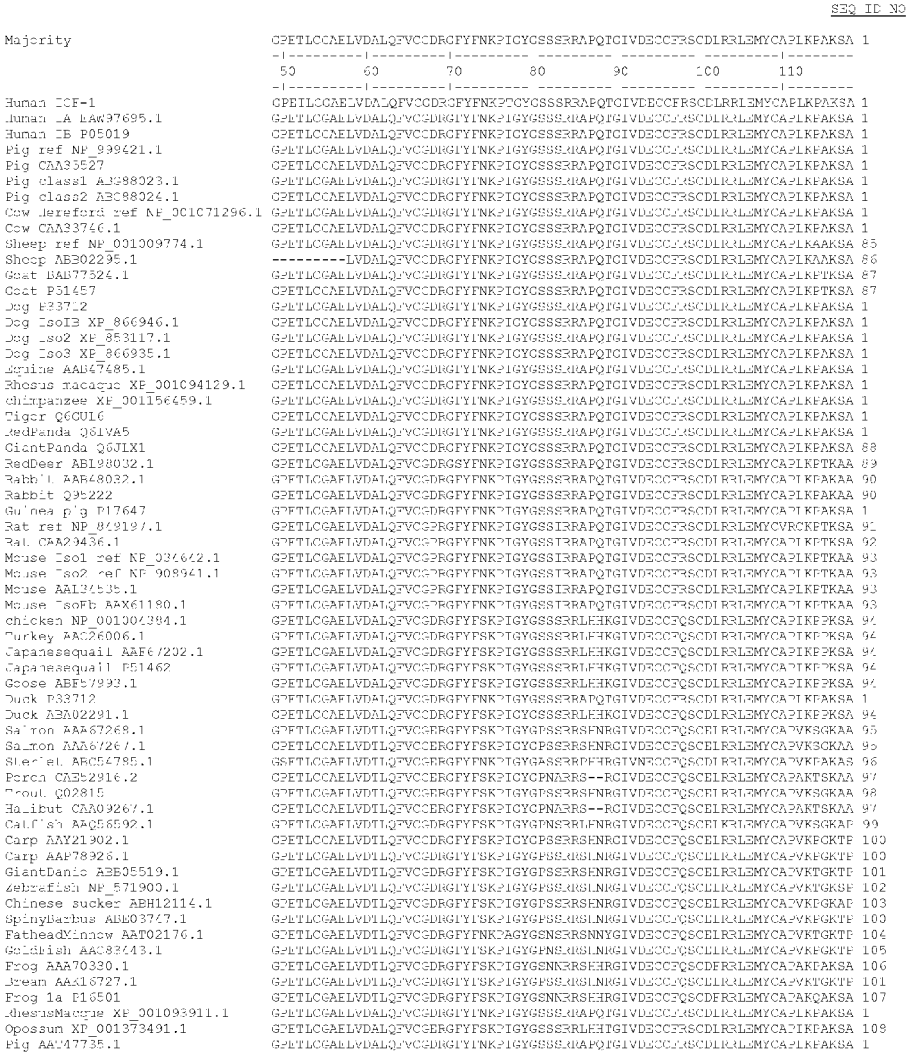


Fig. 7A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Majority
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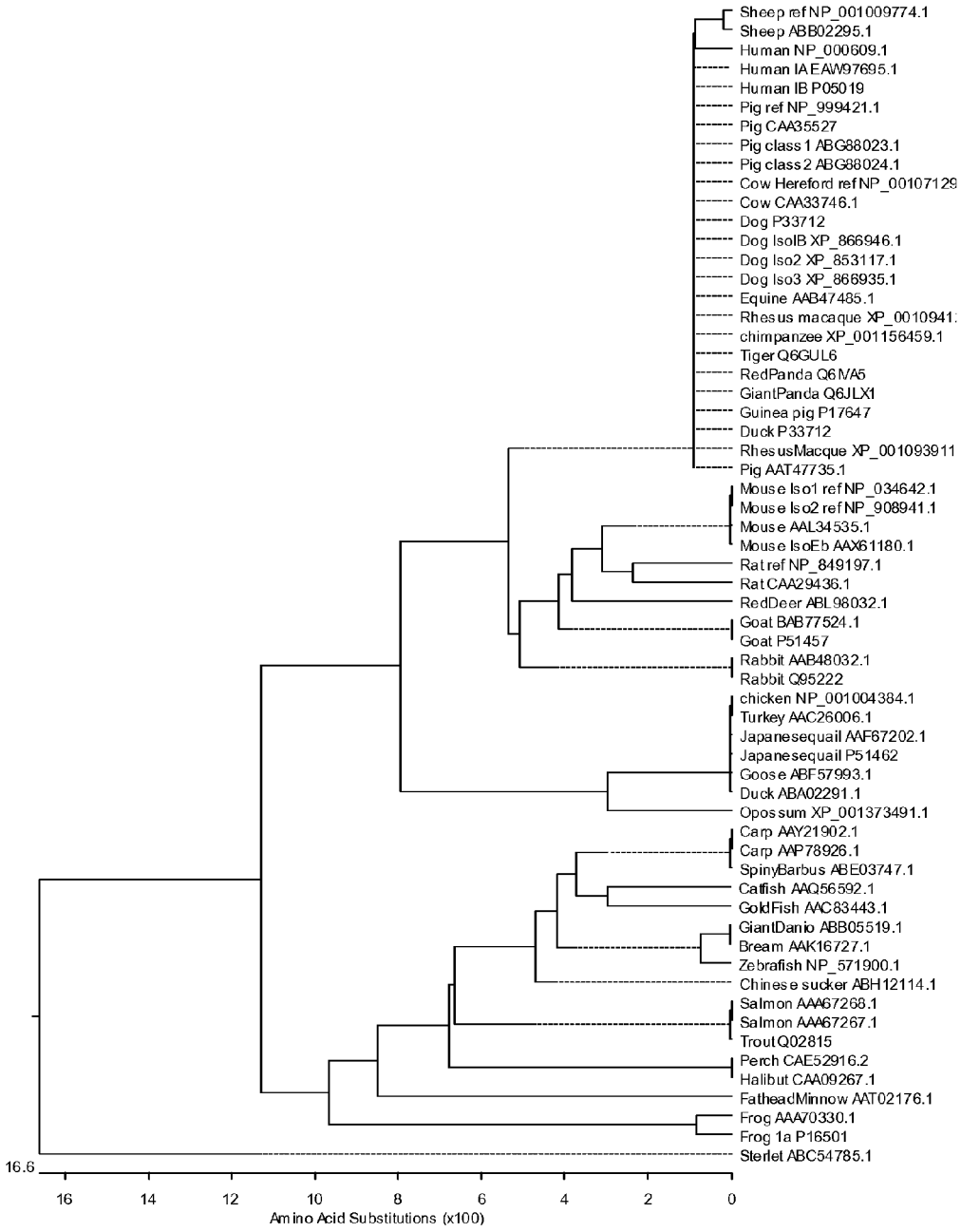
Human LA AAW37695.1
Human IB P05019
Pig ref NP_999421.1
Pig CAA35527
Pig class1 ABC88023.1
Pig class2 ABC88024.1
Cow Hereford ref NP_001071296.1
Cow CAA33746.1
Sheep ref NP_001009774.1
Sheep ABB02295.1
Goat BAB77324.1
Goat P51457
Dog P33712
Dog IsoIB XP_866946.1
Dog Iso2 XP_853117.1
Dog Iso3 XP_866935.1
Equine AAB47485.1
Rhesus macaque XP_001094129.1
chimpanzee XP_001156459.1
Tiger Q6CUL6
RedPanda Q81VA5
GiantPanda Q6JLX1
RedDeer ABI98002.1
Rabbit AAB48032.1
Rabbit Q95222
Guinea pig P17647
Rat ref NP_062917.1
Rat CAA29436.1
Mouse Iso1 ref NP_034642.1
Mouse Iso2 ref NP_908941.1
Mouse AAL34535.1
Mouse IsoFb AAX61180.1
chicken NP_001004384.1
Turkey AAG26006.1
Japanesequail AAF67202.1
Japanesequail P51462
Goose ABF57992.1
Duck P33712
Duck ABA02291.1
Salmon AAA67268.1
Salmon AAA67267.1
Sleeffel ABC54785.1
Perch CAB52916.2
Trout Q02815
Halibut CAA09267.1
Catfish AAQ58592.1
Carp AAY21902.1
Carp AAP78926.1
GiantDanio ABE05519.1
Zebrafish NP_571900.1
Chinese sucker ABH12114.1
SpinyBarbus ABE03747.1
FatheadMinnow AAT02176.1
Goldfish AAC83243.1
Frog AAA70330.1
Xream AAA16727.1
Frog 1a P16501
RhesusMacaque XP_001093911.1
Opossum XP_001373491.1
Pig AAM47735.1

Fig. 7B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Human NP_000609.1
Human IAEAW97695.1
Human IB P05019
Pig ref NP_999421.1
Pig CAA35527
Pig class 1 ABG88023.1
Pig class 2 ABG88024.1
Cow Hereford ref NP_00107129
Cow CAA33746.1
Dog P33712
Dog IsoIB XP_866946.1
Dog Iso2 XP_853117.1
Dog Iso3 XP_866935.1
Equine AAB47485.1
Rhesus macaque XP_0010941
chimpanzee XP_001156459.1
Tiger Q6GUL6
RedPanda Q6MA5
GiantPanda Q6JLX1
Guinea pig P17647
Duck P33712
RhesusMacque XP_001093911
Pig AAT47735.1
Mouse Iso1 ref NP_034642.1
Mouse Iso2 ref NP_908941.1
Mouse AAL34535.1
Mouse IsoEb AAX61180.1
Rat ref NP_849197.1
Rat CAA29436.1
RedDeer ABL98032.1
Goat BAB77524.1
Goat P51457
Rabbit AAB48032.1
Rabbit Q95222
chicken NP_001004384.1
Turkey AAC26006.1
Japanesequail AAF67202.1
Japanesequail P51462
Goose ABF57993.1
Duck ABA02291.1
Opossum XP_001373491.1
Carp AAY21902.1
Carp AAP78926.1
SpinyBarbus ABE03747.1
Catfish AAQ56592.1
GoldFish AAC83443.1
GiantDanio ABB05519.1
Bream AAK16727.1
Zebrafish NP_571900.1
Chinese sucker ABH12114.1
Salmon AAA67268.1
Salmon AAA67267.1
Trout Q02815
Perch CAE52916.2
Halibut CAA09267.1
FatheadMinnow AAT02176.1
Frog AAA70330.1
Frog 1a P16501
Sterlet ABC54785.1
16.6
16
14
12
10
8
6
4
2
0
Amino Acid Substitutions (x100)

Fig. 8A

```
                                                                SEQ ID NO

Majority                          RSVRAQRHTDMPKAQKEVHLKNTSRGSTGNKNYRM 184
                                  ---------+---------+---------+-----
                                           10        20        30
                                  ---------+---------+---------+-----
Human Ea                          RSVRAQRHTDMPKTQKEVHLKNASRGSAGNKNYRM 2
Pig ref NP_999421.1               RSVRAQRHTDMPKAQKEVHLKNTSRGSSGNKNYRM 109
Pig CAA35527                      RSVRAQRHTDMPKAQKEVHLKNTSRGSSGNKNYRM 109
Pig class1 ABG88023.1             RSVRAQRHTDMPKARKEVHLKNTSRGSSGNKNYRM 110
Pig class2 ABG88024.1             RSVRAQRHTDMPKARKEVHLKNTSRGSSGNKNYRM 110
Cow Hereford ref NP_001071296.1   RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Cow CAA33746.1                    RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Sheep ref NP_001009774.1          RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Sheep ABB02295.1                  RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Goat BAB77524.1                   RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Goat P51457                       RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Dog P33712                        RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKTY   112
Dog Iso2 XP_853117.1              RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKNYRM 113
Dog Iso3 XP_866935.1              RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKNYRM 113
Equine AAB47485.1                 RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Rhesus macaque XP_001094129.1     RSVRAQRHTDMPKTQKEVHLKNASRGSAGNKNYRM 2
Tiger Q6GUL6                      RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKNYRM 113
RedPanda Q6IVA5                   RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKNYRM 113
GiantPanda Q6JLX1                 RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKNYRM 113
RedDeer ABL98032.1                RSVRAQRHTDMPKAQKEVHLKNTSRGSAGNKNYRM 111
Rabbit AAB48032.1                 RSVRAQRHTDMPKTQKEVHLKNTSRGSAGNKNYRM 114
Guinea pig P17647                 RSVRAQRHTDMPKTQKEVHLKNASRGSAGNKNYRM 2
Rat ref NP_849197.1               RSIRAQRHTDMPKTQKEVHLKNTSRGSAGNKTYRM 115
Rat CAA29436.1                    RSIRAQRHTDMPKTQKEVHLKNTSRGSAGNKTYRM 115
Mouse AAL34535.1                  RSIRAQRHTDMPKTQKEVHLKNTSRGSAGNKTYRM 115
chicken NP_001004384.1            RSVRAQRHTDMPKAQKEVHLKNTSRGNTGNRNYRM 116
Turkey AAC26006.1                 RSVRAQRHTDMPKAQKELHLKNTSRGNTGNRNYRM 117
Japanesequail AAF67202.1          RSVRAQRHTDMPKAQKEVHLKNTSRGNTGNRNYRM 116
Japanesequail P51462              RSVRAQRHTDMPKAQKEVHLKNTSRGNTGNRNYRM 116
Goose ABF57993.1                  RSVRAQRHTDMPKAQKEVHLKNTSRGNTEN      118
Duck P33712                       RSVRAQRHTDMPKAQKEVHLKNASRGSAGNKTY   112
Salmon AAA67268.1                 RSVRAQRHTDMPRTPKEVHQKNSSRGNTGGRNYRM 119
Salmon AAA67267.1                 RSVRAQRHTDMPRTPKEVHQKNSSRGNTGGRNYRM 119
Sterlet ABC54785.1                RSVRAQRHTDMPKAQKEVHSKNSSRGNTGNRNYRI 120
Perch CAE52916.2                  RSVRAQRHTDMPRAPKEVHQKNSSRGNTGGRNYRM 121
Trout Q02815                      RSVRAQRHTDMPRTPKEVHQKNSSRGNTGGRNYRM 119
Halibut CAA09267.1                RSVRAQRHTDMPRAPKEVHQKNSSRGTTGGRNYRM 122
Catfish AAQ56592.1                RSVREQRHTDTPKTPKEVHQKNSSRGNTGGRNYRM 123
Carp AAY21902.1                   RSIRAQRHTDSPKTAKEVHQKNSSRGNTGGRNYRM 124
Carp AAP78926.1                   RSVRAQRHTDSPRTAKEVHQKNSSRGNTGGRNYRI 125
GiantDanio ABB05519.1             RSLRAQRHTDIPRTAKEVHQKNSSRGNTGGRNYRM 126
Zebrafish NP_571900.1             RSLRAQRHTDIPRTPKEVHQKNSSRGNTGGRNYRM 127
Chinese sucker ABH12114.1         RSLRAQRHTDIPRTPKDVHQKNSSRGNTGGRNYRM 128
SpinyBarbus ABE03747.1            RSLRAQRHTDSPRTAKEVHQKNSSRGNTGGRNYRI 129
FatheadMinnow AAT02176.1          RSLRAQRHTDITRTAKEVHQKNSSRGITGGRNYRM 130
GoldFish AAC83443.1               RSLRAQRHTDGTRTAKEVHQKNSSRGNTGGRNYRM 131
Frog AAA70330.1                   RSVRAQRHTDMPKAQKEVHPKNTSRGNTGSRGFRM 132
Bream AAK16727.1                  RSLRAQRHTDITRTAKEVHQKNSSRGNTGGRNYRI 133
Frog 1a P16501                    RSVRTQRHTDMPKAQKEVHPKNTSRGNTGSRGFRM 134
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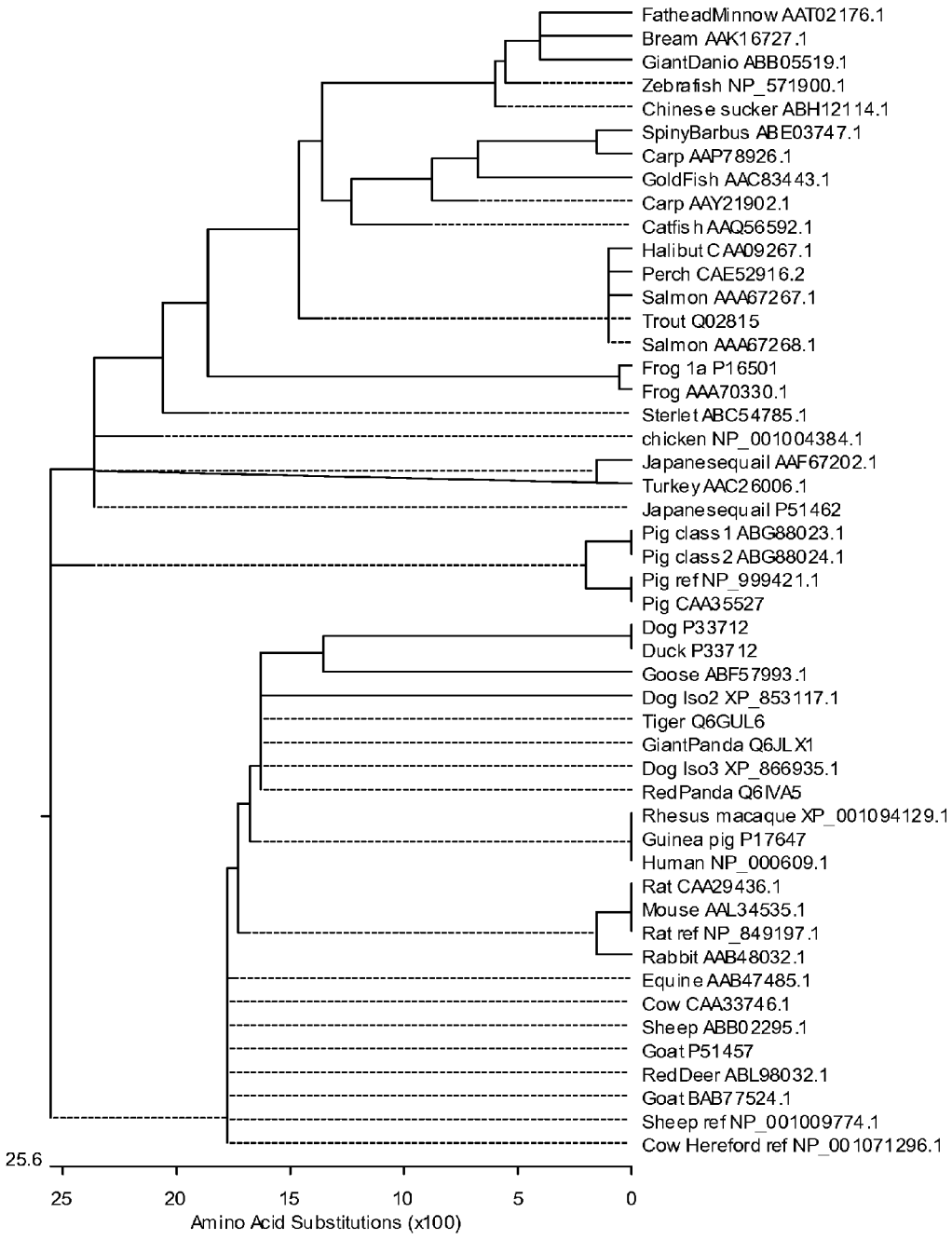
Fig. 8B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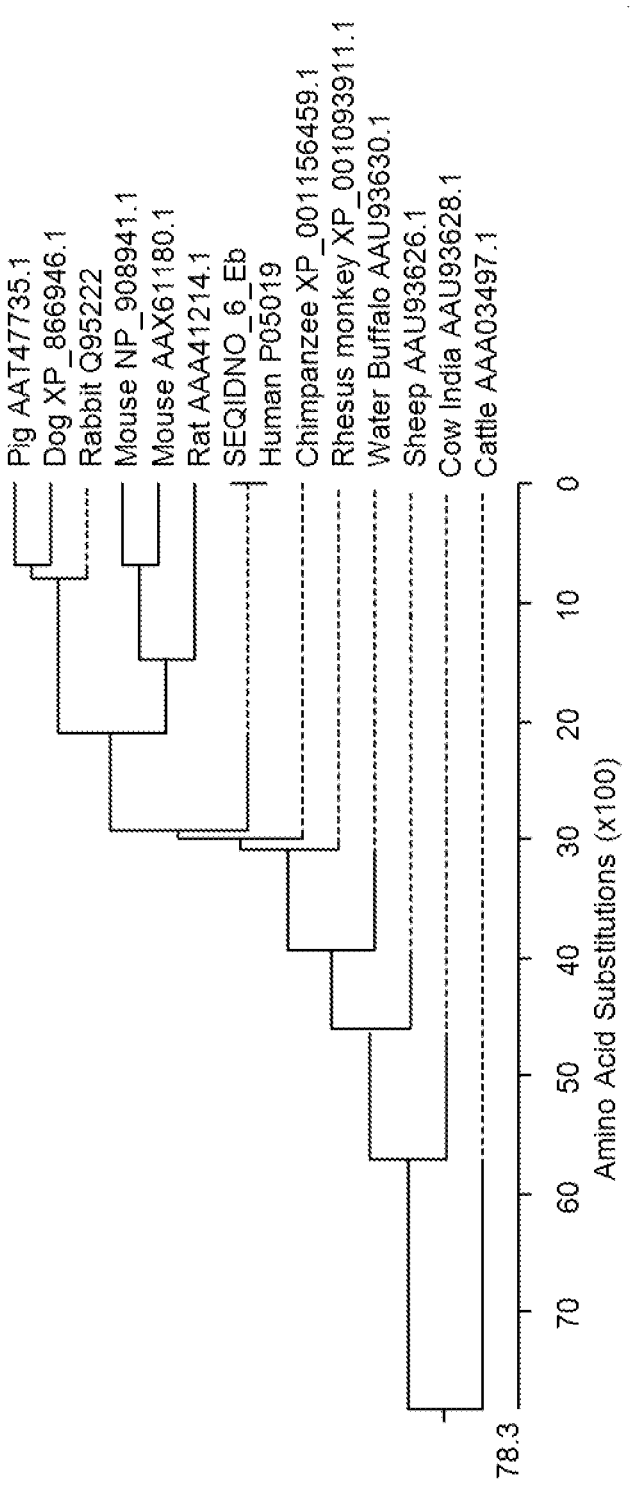
Zebrafish NP_571900.1
Chinese sucker ABH12114.1
SpinyBarbus ABE03747.1
Carp AAP78926.1
GoldFish AAC83443.1
Carp AAY21902.1
Catfish AAQ56592.1
Halibut CAA09267.1
Perch CAE52916.2
Salmon AAA67267.1
Trout Q02815
Salmon AAA67268.1
Frog 1a P16501
Frog AAA70330.1
Sterlet ABC54785.1
chicken NP_001004384.1
Japanesequail AAF67202.1
Turkey AAC26006.1
Japanesequail P51462
Pig class1 ABG88023.1
Pig class2 ABG88024.1
Pig ref NP_999421.1
Pig CAA35527
Dog P33712
Duck P33712
Goose ABF57993.1
Dog Iso2 XP_853117.1
Tiger Q6GUL6
GiantPanda Q6JLX1
Dog Iso3 XP_866935.1
RedPanda Q6IVA5
Rhesus macaque XP_001094129.1
Guinea pig P17647
Human NP_000609.1
Rat CAA29436.1
Mouse AAL34535.1
Rat ref NP_849197.1
Rabbit AAB48032.1
Equine AAB47485.1
Cow CAA33746.1
Sheep ABB02295.1
Goat P51457
RedDeer ABL98032.1
Goat BAB77524.1
Sheep ref NP_001009774.1
Cow Hereford ref NP_001071296.1
25.6
25
20
15
10
5
0
Amino Acid Substitutions (x100)

Fig. 9A

SEQ ID NO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Rabbit Q95222
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Rat AAA41214.1
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Human P05019
Chimpanzee XP_001156459.1
Rhesus monkey XP_001093911.1
Water Buffalo AAU93630.1
Sheep AAU93626.1
Cow India AAU93628.1
Cattle AAA03497.1
78.3
70
60
50
40
30
20
10
0
Amino Acid Substitutions (x100)

Fig. 9B

Fig. 10A

```
                                                                    SEQ ID NO
Majority                    RSVRAQRHTDMPKTQKYQPPSTNKKTKSQRRRKGSTFEEH-  148
                            ---------+---------+---------+- --------+
                                     10        20        30         40
                            ---------+---------+---------+- --------+
human Ec                    RSVRAQRHTDMPKTQKYQPPSTNKNTKSQRR-KGSTFEERK  4
Human EAW97695.1            RSVRAQRHTDMPKTQKYQPPSTNKNTKSQRR-KGSTFEER   149
Human AAA96152.1            RSVRAQRHTDMPKTQKYQPPSTNKNTKSQRR-KGSTFEER   149
Pig AAT47735.1              RSVRAQRHTDMPKAQKYQPPSTNKKTKSQRRRKGSTFEEH   150
Dog Ib XP_866946.1          RSVRAQRHTDMPKAQKYHPPSTTKRMKSQRRRKGSTFEEC   151
Rabbit Q95222               RSVRAQRHTDMPKTQKYQPPSTNKKMKSQRRRKGSTFEEH   152
Rhesus monkey XP_001094016.1 RSVRAQRHTDMPKTQKYQPPSTNKNTKSQRRRKGSTFEER  153
Mouse Ib AAX61180.1         RSIRAQRHTDMPKTQKSPSLSTNKKTKLQRRRKGSTFEEH   154
Mouse Iso1 NP_034642.1      RSIRAQRHTDMPKTQKSPSLSTNKKTKLQRRRKGSTFEEH   154
Rat Ib A40912               RSIRAQRHTDMPKTQKSQPLSTHKKRKLQRRRKGSTLEEH   155
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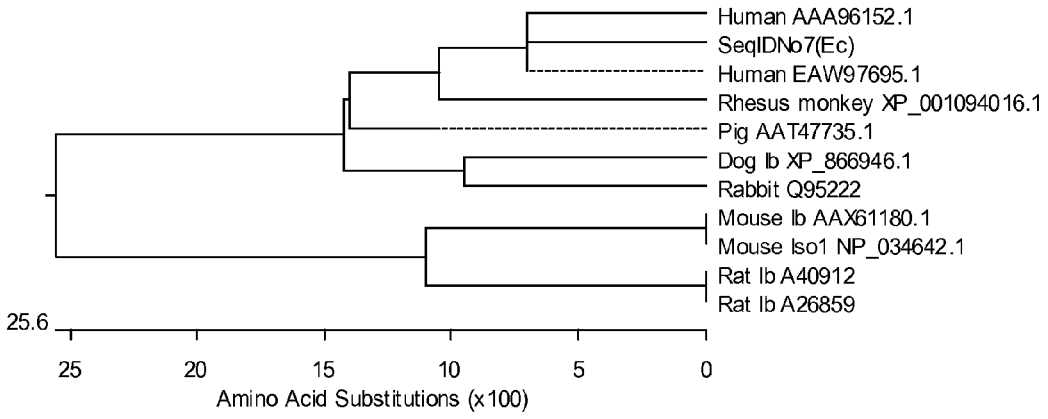
Fig. 10B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SeqIDNo7(Ec)
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Rhesus monkey XP_001094016.1
Pig AAT47735.1
Dog Ib XP_866946.1
Rabbit Q95222
Mouse Ib AAX61180.1
Mouse Iso1 NP_034642.1
Rat Ib A40912
Rat Ib A26859
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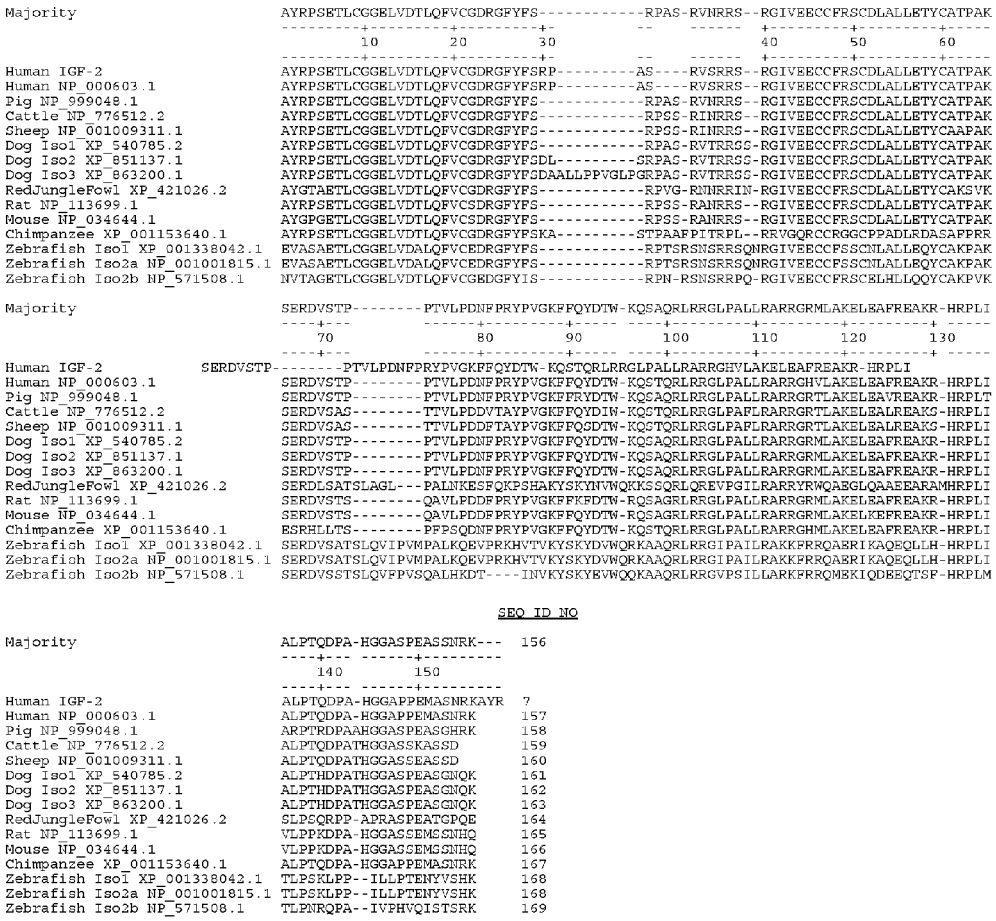
25
20
15
10
5
0
Amino Acid Substitutions (x100)

Fig. 11A


Majority
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Human NP_000603.1
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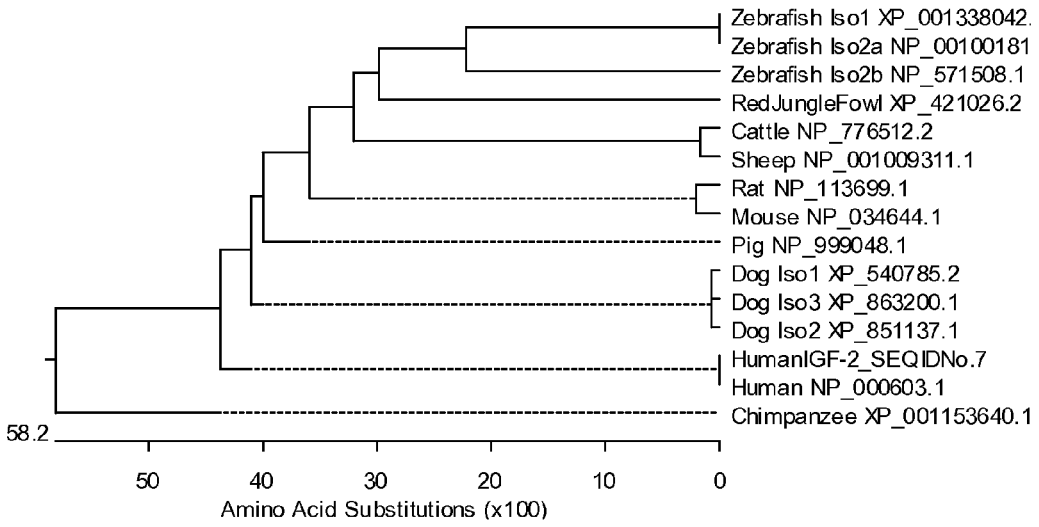
Cattle NP_776512.2
Sheep NP_001009311.1
Dog Isol XP_540785.2
Dog Iso2 XP_851137.1
Dog Iso3 XP_863200.1
RedJungleFowl XP_421026.2
Rat NP_113699.1
Mouse NP_034644.1
Chimpanzee XP_001153640.1
Zebrafish Isol XP_001338042.1
Zebrafish Iso2a NP_001001815.1
Zebrafish Iso2b NP_571508.1
SEQ ID NO

Fig. 11B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RedJungleFowl XP_421026.2
Cattle NP_776512.2
Sheep NP_001009311.1
Rat NP_113699.1
Mouse NP_034644.1
Pig NP_999048.1
Dog Iso1 XP_540785.2
Dog Iso3 XP_863200.1
Dog Iso2 XP_851137.1
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Human NP_000603.1
Chimpanzee XP_001153640.1
58.2
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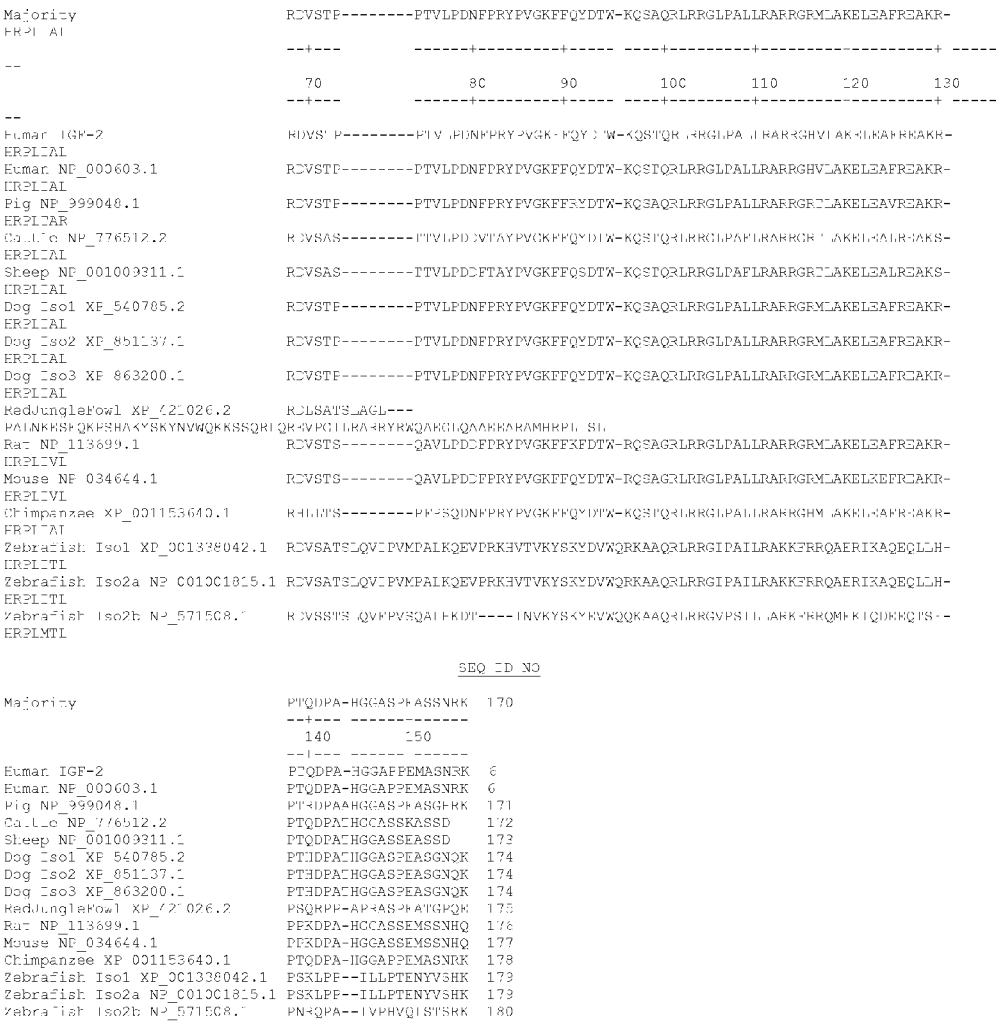
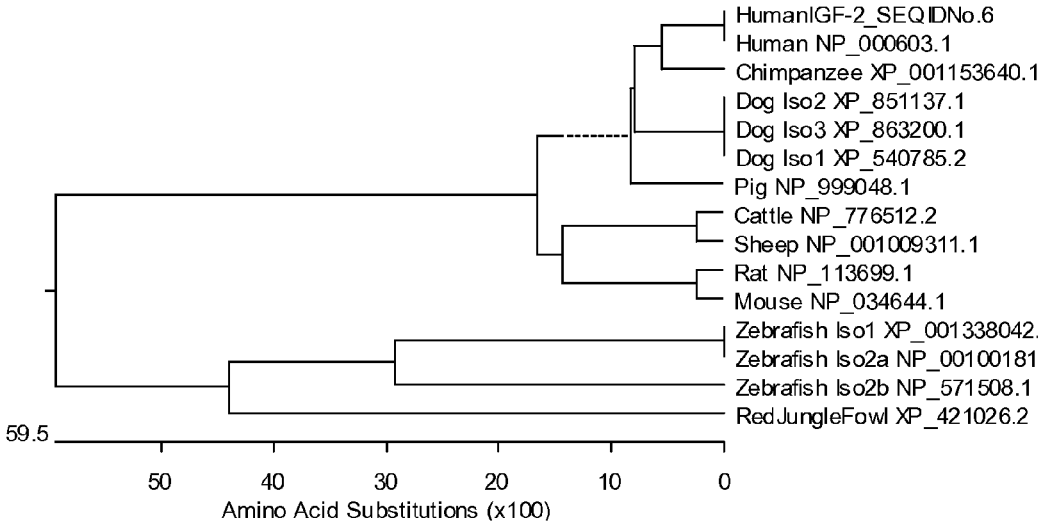
40
30
20
10
0
Amino Acid Substitutions (x100)

Fig. 12A



SEQ ID NO

Fig. 12B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Chimpanzee XP_001153640.1
Dog Iso2 XP_851137.1
Dog Iso3 XP_863200.1
Dog Iso1 XP_540785.2
Pig NP_999048.1
Cattle NP_776512.2
Sheep NP_001009311.1
Rat NP_113699.1
Mouse NP_034644.1
Zebrafish Iso1 XP_001338042.
Zebrafish Iso2a NP_00100181
Zebrafish Iso2b NP_571508.1
RedJungleFowl XP_421026.2
59.5
50
40
30
20
10
0
Amino Acid Substitutions (x100)

STABILIZED INSULIN-LIKE GROWTH FACTOR POLYPEPTIDES

[0001] This application is a divisional of U.S. patent application Ser. No. 13/664,055, filed Oct. 30, 2012; which is a divisional of U.S. Pat. No. 8,343,918, issued Jan. 1, 2013; which is a 371 of PCT/US2007/070468; filed Jun. 6, 2007, which claims priority to U.S. Provisional Application No. 60/897,187, filed Jan. 24, 2007; U.S. Provisional Application No. 60/862,244, filed Oct. 20, 2006; and U.S. Provisional Application No. 60/812,349, filed Jun. 9, 2006.

BACKGROUND OF THE INVENTION

[0002] Insulin-like growth factors (IGFs) are part of a complex system that cells use to communicate with their physiologic environment. This complex system (often referred to as the insulin-like growth factor axis) consists of two cell-surface receptors (IGF-1 R and IGF-2R), two ligands (IGF-1 and IGF-2), a family of six high-affinity IGF-binding proteins (IGFBP 1-6), and associated IGFBP degrading enzymes (proteases). This system is important not only for the regulation of normal physiology but also for a number of pathological states (Glass, Nat Cell Biol 5:87-90, 2003).

[0003] The IGF axis has been shown to play roles in the promotion of cell proliferation and the inhibition of cell death (apoptosis). IGF-1 is mainly secreted by the liver as a result of stimulation by human growth hormone (hGH). Almost every cell in the human body is affected by IGF-1, especially cells in muscles, cartilage, bones, liver, kidney, nerves, skin and lungs. In addition to the insulin-like effects, IGF-1 can also regulate cell growth. IGF-1 and IGF-2 are regulated by a family of gene products known as the IGF-binding proteins. These proteins help to modulate IGF action in complex ways that involve both inhibiting IGF action by preventing binding to the IGF receptors as well as promoting IGF action through aiding delivery to the receptors and increasing IGF half life in the blood stream. There are at least six characterized binding proteins (IGFBP1-6).

[0004] In its mature form, human IGF-1 (gpetlcgaelvdalgfvcgdrgfyfnkptgygsssrrapgtgivdeccfrscdlrrlem ycaplkpaksa; SEQ ID NO:1), also called somatomedin, is a small protein of 70 amino acids that has been shown to stimulate growth of a wide range of cells in culture. The mature protein is initially encoded by three known splice variant mRNAs. The open reading frame of each mRNA encodes a precursor protein containing the 70 amino acid IGF-1 and a particular E-peptide at the C-terminus, depending on the particular IGF-1 mRNA. These E-peptides have been termed the Ea (rsvraqrhtdmpktqkevhlknasrgsagnknyrm; SEQ ID NO:2), Eb (rsvraqrhtdmpktqkyqppstnknt ksqrrkgwpkthpggeqkegteaslqrgkkkeqrreigsrnaecrgkkgk; SEQ ID NO:3), and Ec (rsvraqrhtdm pktqkyqppstnkntksqrrkgstfeerk; SEQ ID NO:4) peptides and range from 35 to 87 amino acids in length and encompass a common sequence region at the N-terminus and a variable sequence region at the C-terminus. For example, the wild-type open reading frame for the IGF-1-Ea encodes a polypeptide of 105 amino acids (gpeticgaelvdalqfvcgdrgfyfnkptgygsssrrapqtgivde ccfrscdlrrlemycaplkpaksa rsvraqrhtdmpktqkevhlknasrgsagnknyrm; SEQ ID NO:5). In physiological expression, the E-peptides are cleaved off of the precursor by endogenous proteases to yield the mature 70 amino acid IGF-1 known to be bioactive. In certain contexts, one to three of the N-terminal amino acids of IGF-1 are known to be cleaved under physiological conditions, yielding active IGF-1 having between 67-70 amino acids. IGF-2 gene expression and processing is characterized by similar attributes except that only one E-peptide (rdvstpptvlpdnfprypvgkffqydtwkqstqrl rrglpallrarrghvlakeleafreakrhrplialptqdpahggappemasnrk; SEQ ID NO:6) for human IGF-2 has been identified for the 156 amino acid precursor (ayrpsetlcggelvdtlqfvcgdrgfyfsr pasrvsrrsrgiveeccfrscdlalletycatpakserdvstpptvlpdnfprypvg kffqydt wkqstqrlrrglpallrarrghvlakeleafreakrhrpli-alptqdpahggappemasnrk; SEQ ID NO:7). Both IGF-1 and IGF-2 appear to be poor drug candidates, since these proteins are quickly degraded by endogenous proteases in the serum of patients. One strategy that has been contemplated is to stabilize IGF-1 as a drug by forming a complex with one of its binding proteins.

SUMMARY OF THE INVENTION

[0005] The invention is based on the discovery that a precursor IGF-1 or IGF-2 protein containing substantially its E-peptide is bioactive and stabilized in the presence of serum, resulting in an IGF-1 or IGF-2 polypeptide that is useful as a pharmaceutical. In the compositions of the invention, the normal cleavage of the E-peptide from IGF-1 is avoided, for example, by mutating or deleting either of the arginine at position 1 or the serine at position 2 of the E-peptides (corresponding to positions 71 and 72 in the wild-type precursor IGF-1). In IGF-2, the cleavage is avoided, for example, by mutating or deleting either the arginine at position 1 or the aspartic acid at position 2 of the E-peptide (corresponding to positions 68 and 69 in the wild-type precursor IGF-2). Other modifications of an IGF precursor protein can avoid or reduce this cleavage.

[0006] In addition, further modifications of the IGF-1 precursor amino acid sequence can confer additional pharmaceutical benefits. For example, the polypeptides of the invention can exhibit increased affinity for the IGF-1 receptor or decreased binding ability to an inhibitory IGF-1 or IGF-2 binding protein.

[0007] For the sake of clarity and consistency, the numbering of amino acid residues in IGF-1 or IGF-2 precursor or mature proteins throughout this application and in the claims is based on the wild-type precursor protein sequence numbering without signal peptide.

[0008] Accordingly, the invention includes a polypeptide containing a human IGF-1 precursor protein, where the cleavage of the E-peptide from IGF-1 by a protease is reduced by modification of the precursor protein. The E-peptide can be the Ea, Eb, or Ec peptide. At the N-terminus of the precursor, amino acids G1, P2, or E3 of the precursor protein can be deleted or mutated, as can R36 (e.g., R36A) and R37 (e.g., R37A).

[0009] The precursor protein can further include the N-linked glycosylation consensus sequence NXS/T, for example by insertion of amino acids 93-102 of Ea between amino acids N95 and T96 of the Eb. In general, the precursor protein can include an oligosaccharide covalently linked to an amino acid side chain of the precursor protein, such as an arginine side chain of the precursor protein.

[0010] In addition, a residue of the precursor protein can be replaced by a non-natural amino acid (e.g., one that includes an acetylene or azido group). Such non-natural amino acids can facilitate linkage of a poly(ethylene glycol)

moiety to a side-chain of the precursor protein, though typical protein pegylation strategies are well known in the art.

[0011] The precursor protein can further include one or more additional E-peptides linked to the C-terminus of the precursor protein. For example, a polypeptide can include, from N-terminus to C-terminus, (1) an IGF-1 precursor protein having a first Eb peptide, where G1, P1, and El are deleted, either R36 or R37 or both are mutated, R71 and S72 are deleted, and the last seven C-terminal amino acids of the first Eb peptide are deleted; (2) a second Eb peptide, where R71, S72, and the last seven C-terminal amino acids of the second Eb peptide are deleted; (3) a third Eb peptide, where R71, S72, and the last seven C-terminal amino acids of the third Eb peptide are deleted; and (4) a fourth Eb peptide, where R71 and S72 are deleted.

[0012] An effective means of preventing cleavage of the E-peptide from the IGF-1 is the deletion or mutation of R71 or S72.

[0013] Similarly, the invention includes a human IGF-2 precursor protein where the cleavage of the E-peptide from IGF-2 by a protease is reduced by modification of the precursor protein. In particular, deletion or mutation of R68 or D69 can be an effective means of avoiding protease digestion of the IGF-2 precursor protein.

[0014] In addition, any E-peptide of IGF-1 can be combined with an IGF-2 and any E-peptide of IGF-2 can be combined with IGF-1 to provide the benefits described herein.

[0015] The invention further includes a method of treating a musculoskeletal disease, diabetes, neuronal cell death by administering a therapeutically effective amount of a polypeptide of the invention. Likewise, the invention includes the use of a polypeptide of the invention for the manufacture of a medicament for the treatment of a musculoskeletal disease, diabetes, neuronal cell death, or anemia.

[0016] In another embodiment, the invention includes a pegylated IGF-1 without an E-peptide but having introduced therein a non-natural amino acid as the site of pegylation. Any of the modified, pegylated IGF-1 containing a non-natural amino acid as disclosed herein, without an E-peptide, is also included in the invention.

[0017] The invention also includes veterinary methods and uses of administering an effective amount of the polypeptide of the invention to obtain a desired effect.

[0018] The veterinary uses include (i) enhancing the rate and/or extent of growth in an animal, (ii) enhancing the efficiency of their conversion of feed into body tissue, (iii) enhancing milk production in lactating animals, (iv) treating animal wasting symptoms associated with cachexia, trauma, or other consumption diseases, and (v) treating lactating animals for improvement in neonatal health.

[0019] All cited references or documents are hereby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIGS. **1**A-**1**C are Western blots of polypeptides of the invention and wild-type IGF-1 precursor after zero or 16-hour incubation in the presence or absence of 10% human serum at 37° C. Expression vectors encoding various IGF-1 constructs were transfected into Cos7 cells, and the conditioned culture medium obtained. The "3mut" refers to a hIGF-1-E-peptide precursor having the following three sets of modifications: deletion of G1, P2, and E3; mutation of Arg 37 to Ala (R37A); and deletion of R71 and S72. FIG. **1**A shows the Western blot results (using antibody to IGF-1) for the wild-type and 3mut precursor containing Ea. FIG. **1**B shows the Western blot results (using antibody to hIGF-1) for the wild-type and 3mut precursor containing Eb. FIG. **1**C shows the Western blot results (using antibody to hIGF-1) for the wild-type and 3mut precursor containing Ec.

[0021] FIGS. **2**A-**2**D are line graphs showing the biological activity of various IGF-1 polypeptides ("ligands"). Biological activity was measured by stimulation of C2C12 myoblasts with Cos7-expressed polypeptides. The stimulated C2C12 cells were then assayed for the relative amounts of total AKT and phosphorylated AKT. Long-R3-IGF-1 is a commercially available reagent (Sigma Product No. 1-1271) that consists of the mature human IGF-1 amino acid sequence, with an E3R mutation and an additional 13 amino acid N-terminal extension peptide. FIG. **2**A shows the activity of IGF-1-Ea3mut. FIG. **2**B shows the activity of IGF-1-Eb3mut. FIG. **2**C shows the activity of IGF-1-Eab3mut, which is a 3mut construct in which Ea amino acids 93 to 102 were inserted between amino acids 95 and 96 of Eb. FIG. **2**D shows the activity of IGF-1-Ec3mut.

[0022] FIGS. **3**A-**3**D and **4**A-**4**D are line graphs showing whether IGF-1 precursor polypeptides of the invention maintain selectivity to the appropriate receptor by assaying for receptor phosphorylation in response to ligand binding. FIGS. **3**A and **3**B test the receptor selectivity of IGF-1-Ea3mut against the IGF-1 receptor (FIG. **3**A) and the insulin receptor (FIG. **3**B). FIGS. **3**C and **3**D tests the receptor selectivity of IGF-1-Eb3mut against the IGF-1 receptor (FIG. **3**C) and the insulin receptor (FIG. **3**D). FIGS. **4**A and **4**B test the receptor selectivity of IGF-1-Ec3mut against the IGF-1 receptor (FIG. **4**A) and the insulin receptor (FIG. **4**B). FIGS. **4**C and **4**D tests the receptor selectivity of IGF-1-Eab3mut against the IGF-1 receptor (FIG. **4**C) and the insulin receptor (FIG. **4**D). "IGF1-R3" refers to the Long-R3-IGF-1 described above. The polypeptide listed as "IGF1Eab" refers to construct in which Ea amino acids 93 to 102 were inserted between amino acids 95 and 96 of Eb.

[0023] FIG. **5** is a Western blot showing relative AKT phosphorylation upon stimulation of C2C12 myotubes (as a result of 3 to 4 days of differentiation of C2C12 myocytes) by different ligands. The IGF-1 Eb multimer refers to the construct schematically shown in FIG. **6**A.

[0024] FIGS. **6**A and **6**B are schematic representations of two of the polypeptides of the invention. FIG. **6**A shows an IGF-1-Eb precursor polypeptide with four sets of modifications: deletion of G1, P2, and E3; mutation of R37 to A; deletion of R71 and S72; and deletion of the last seven C-terminal amino acids. In addition, the polypeptide is lengthened by the addition of two more Eb peptides (but without R71 and S72 and without the last seven C-terminal amino acids) and the addition of a final Eb peptide (buth without R71 and S72) at the C-terminus of the polypeptide. This construct is often referred to as the IGF-1-Eb multimer. FIG. **6**B shows an IGF-1-Eab precursor polypeptide with four sets of modifications: deletion of G1, P2, and E3; mutation of R37 to A; deletion of R71 and S72; and insertion of Ea amino acids 93 to 102 between amino acids 95 and 96 of Eb.

[0025] FIG. **7**A is a sequence alignment of the human IGF-1 (SEQ ID NO:1) with corresponding animal IGF-1. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. G1, P2,

E3 is conserved in all analyzed species except Sterlet (where S2 replaces P2). R36 and R37 are conserved in all analyzed species.

[0026] FIG. **7**B is a graph showing the phylogeny of the analyzed amino acid sequences compared to human IGF-1 (SEQ ID NO:1). Below the tree is a scale indicating the number of "Amino Acid Substitutions" per 100 residues for protein sequences. The Kimura distance formula is used to calculate distance values, derived from the number of non-gap mismatches and corrected for silent substitutions. The values computed are the mean number of differences per site and fall between zero and 1. Zero represents complete identity and 1 represents no identity. The phylogenetic tree scale uses these values multiplied by 100.

[0027] FIG. **8**A is a sequence alignment of the human Ea peptide (SEQ ID NO:2) with various animal Ea peptides. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. R71 and S72 are conserved in all analyzed species.

[0028] FIG. **8**B is a graph showing the phylogeny of the analyzed amino acid sequences compared to human IGF-1 Ea peptide (SEQ ID NO:2).

[0029] FIG. **9**A is a sequence alignment of the human Eb peptide (SEQ ID NO:3) with various animal Eb peptides. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. R71 and S72 are conserved in all analyzed species.

[0030] FIG. **9**B is a graph showing the phylogeny of the analysed amino acid sequences compared to human IGF-1 Eb peptide (SEQ ID NO:3).

[0031] FIG. **10**A is a sequence alignment of the human Ec peptide (SEQ ID NO:4) with various animal Ec peptides. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. R71 and S72 are conserved in all analyzed species.

[0032] FIG. **10**B is a graph showing the phylogeny of the analyzed amino acid sequences compared to human IGF-1 Ec peptide (SEQ ID NO:4).

[0033] FIG. **11**A is a sequence alignment of the human IGF-2 (SEQ ID NO:7) with corresponding animal IGF-2. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. R68 is conserved in all analyzed species; D69 is conserved except for chimpanzee, where a histidine resides in that position.

[0034] FIG. **11**B is a graph showing the phylogeny of the analyzed amino acid sequences compared to human IGF-2 (SEQ ID NO:7).

[0035] FIG. **12**A is a sequence alignment of the human IGF-2 E-peptide (SEQ ID NO:6) with various animal IGF-2 E-peptides. All animal species analyzed and their corresponding GenBank accession numbers for the sequence are given. R68 is conserved in all analyzed species; D69 is conserved except for Chimpanzee, where a histidine resides in that position.

[0036] FIG. **12**B is a graph showing the phylogeny of the analyzed amino acid sequences compared to human IGF-2 E peptide (SEQ ID NO:6).

DETAILED DESCRIPTION OF THE INVENTION

[0037] The invention relates to new IGF-1 and IGF-2 precursor polypeptides containing substantially an E-peptide that has been modified to prevent, reduce, or avoid the typical protease cleavage responsible for releasing the active IGF-1 or IGF-2 from its E-peptides. The utility of the polypeptides of the invention is based on the surprising discovery that such precursor polypeptides are biologically active, stable and beneficial as pharmaceuticals.

[0038] Screening for Active IGF Precursor Polypeptides

[0039] The usefulness of any polypeptide of the invention can be assessed using the following assays.

[0040] Stability A polypeptide of the invention should have sufficient stability in the presence of endogenous proteases, such as in human serum, to be an effective drug. To assess stability, an expression vector encoding the polypeptide can be transfected into Cos7 cells (ATCC) in a DMEM medium containing 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin. The culture medium containing secreted polypeptides can be applied to further analysis, or in the alternative, the expression vector can encode readily available tags, such as a hexa-histidine tag, in the polypeptide to facilitate efficient purification of the expressed polypeptides in the Cos7 cultures. However prepared, the polypeptide sample is incubated in normal human serum (Sigma) or in PBS for various times (e.g., 0, 1, 5, 10, and 16 hours), subjected to polyacrylamide gel electrophoresis, blotted onto nitrocellulose, and the relevant proteins visualized using a primary antibody against human IGF-1 or IGF-2 and a secondary antibody, e.g., conjugated to horseradish peroxidase. Any number of similar blotting and detection techniques, some using fluorescent dyes or even radionuclides, can be used. The intensity of the precursor band versus the intensity of the IGF-1 or IGF-2 band should indicate the degree to which the precursor polypeptide is cleaved under various conditions. A polypeptide of the invention that is exposed to human serum for 16 hours at 37° C. can exhibit a ratio of uncleaved precursor to cleaved mature IGF of about 1:2 to 1:0.1, e.g., about 1:1 to 1:0.5, particularly a ratio of about 1:1 or a ratio of about 1:0.5. Typically, the precursor should exhibit a ratio of at least 1:1.

[0041] AKT Phosphorylation A polypeptide of the invention should maintain the ability to signal through the IGF-1 receptor. (Both IGF-1 and IGF-2 signal through the IGF-1 receptor.) To determine this signaling ability, one can assess whether a downstream intracellular target, AKT, is phosphorylated in response to ligand binding at the cell surface. For analysis of AKT phosphorylation, C2C12 myoblasts are starved in serum-free medium and then stimulated with different ligands. Cells are lysed and cleared by centrifugation. AKT phosphorylation and total AKT levels are analyzed by ELISA using PathScan phospho AKT (Ser473) sandwich ELISA kit and PathScan AKT sandwich ELISA kit (Cell Signaling), respectively.

[0042] IGF-1 Receptor Specificity A polypeptide of the invention preferably maintains the specificity for the IGF-1 receptor and should bind to the related insulin receptor with low affinity. To assess receptor specificity, polypeptide samples are added to serum-starved NIH3T3 cells overexpressing the IGF-1 receptor or the insulin receptor, and the level of IGF-1 receptor phosphorylation or insulin receptor phosphorylation is determined by lysing the cells and subjecting the lysates to ELISA using the DuoSet IC human phosphor-IGF-1 receptor and insulin receptor ELISA kit (R&D Systems).

[0043] In Vivo Testing in Mouse Models of Hypertrophy To determine whether a polypeptide of the invention can act to increase skeletal muscle mass under a context that already

leads to muscle hypertrophy, one can subject treated and untreated animals to exercise and determine whether animals receiving the polypeptide have developed larger muscles than untreated animals.

[0044] Exercise Models

[0045] One model known in the art is based on the use of a voluntary running wheel with user-variable loads (see, e.g., Konhilas et al., Am J Physiol Heart Circ Physiol 289:H455-H465, 2005). The voluntary cage wheel eliminates physical and psychological insults that are common in forced exercised models, and are therefore more appropriate for evaluating candidate drugs that are used in relatively healthy individuals for whom increases in muscle mass is desirable.

[0046] Any suitable mouse strain can be used. For example, male C57B1/6J mice can be randomly assigned to experimental (e.g., receiving IGF precursor polypeptide) and control groups. Animals are individually housed in a cage containing an exercise wheel; sedentary control animals are housed in identical cages without a wheel. The exercise wheels are described in Allen et al., J Appl Physiol 90:1900-1908, 2001. Briefly, the system consists of an 11.5 cm-diameter wheel with a 5.0 cm-wide running surface (model 6208, Petsmart, Phoenix, Ariz.) equipped with a digital magnetic counter (model BC 600, Sigma Sport, Olney, Ill.) that is activated by wheel rotation. In addition, each wheel is engineered with a resistance mechanism allowing adjustment of the load. This is accomplished by attaching stainless steel fishing line to the cage top and wrapping the wire around an immovable pulley that is secured to the cage wheel at the axis of rotation so as to not contribute to the wheel load. The wire is again secured to the cage top with a spring and screw. This design permits fine adjustments of the wheel load, which is evenly distributed throughout the rotation of the wheel. Daily exercise values for time and distance run are recorded for each exercised animal throughout the duration of the exercise period. All animals are given water and standard hard rodent chow ad libitum. Voluntary running (cage wheel exposure) can begin at an average age of about 12 weeks for all groups. Each group continues running under varying resistance, depending on experimental group, for 50 days until the animals are about 19 weeks of age. The load on the wheel is determined by hanging known weights on the wheel until the wheel was slightly displaced. All exercise groups begin with no load on the cage wheel for the first week. However, the "no-load" condition is actually 2 g, which is determined as the load necessary to maintain wheel inertia and frictional load. Considering a wheel acclimatization period of 1 week, wheel loads can be changed at one-week intervals, except for higher loads, which can be changed after 2 weeks. The range of loads can be anywhere from 2 g to up to 12 g. Exercised and sedentary control animals are euthanized by cervical dislocation under inhaled anesthesia immediately after the end of the specific exercise period. Body mass is measured, and specific muscles are rapidly excised, washed, and frozen for histological or biochemical assays at a future date.

[0047] Alternative exercise hypertrophy models are also available to the skilled artisan. See, e.g., the treadmill exercise model described in Lerman et al., J Appl Physiol 92:2245-2255, 2002.

[0048] Clenbuterol Injection Model

[0049] Clenbuterol is a β_2-adrenergic agonist with growth-promoting properties that cause a documented increase in muscle mass. The precise mechanism of clenbuterol action remains unclear, although a reduction in muscle protein degradation has been proposed. In the clinic, clenbuterol is used as an anti-asthma drug, but it appears to be mostly misused as a body-building agent to increase muscle mass in both humans and show animals.

[0050] Five mice are given a daily injection of clenbuterol (3 mg/kg, subcutaneous (s.c.)) for 3, 7, or 14 days to induce muscle hypertrophy. Mice injected with PBS serves as negative control. The animals are monitored daily (visual inspection) for any adverse reactions (i.e. unkempt coat, lethargic) to the treatment. Clenbuterol treatment has the potential to make mice more fearful or aggressive, so mice should be especially monitored for fighting if housed in groups. Mice are mobile, and can eat and drink normally. Mice are monitored daily until they are euthanized on day 3, 7, or 14, and tissue collected for further analysis.

[0051] In Vivo Testing in Muscle Atrophy Models In various skeletal muscle atrophy models, an IGF precursor polypeptide of the invention can be tested for the ability to maintain muscle mass under conditions that generally reduce muscle mass. With the example models described below, the skilled artisan can readily design and implement controlled experiments involving the administration and use of IGF precursor polypeptides to determine whether such polypeptides can increase muscle mass.

[0052] For example, C57Bl6/2 male mice are purchased from The Jackson Laboratories. Mice are purchased so that they are about 9 weeks at the start of each experiment. Generally mice are housed in microisolator cages with normal rodent chow. At the start of each experiment mice are weighed. At the end of each experiment, generally mice are euthanized by CO_2 inhalation followed by cervical dislocation, and muscle tissues harvested for further processing. Mice are weighed to provide "end body weight." Skeletal muscles that can be harvested are tibialis anterior, extensor digitorum longus, soleus, and gastrocnemius muscles. Other tissues harvested occasionally are: heart, liver, spleen, kidneys, testes, and brain. All muscles and tissues are completely dissected and weighed on a balance capable of measuring to 0.0001 g. Tissues are then snap-frozen in liquid nitrogen for later RNA and protein extraction, or snap-frozen embedded in OCT on a cork disc. Muscles frozen on a cork disc for later cryosectioning are immersed in isopentane cooled to a thick slush by liquid nitrogen. All samples are stored at −80° C.

[0053] Dexamethasone Treatment

[0054] A pharmacological method of inducing muscle wasting in mice is daily intraperitoneal injection with dexamethasone at 20 mg/kg. Dexamethasone is a synthetic member of the glucocorticoid class of hormones. It acts as an anti-inflammatory and immunosuppressant, with a potency of about 40 times that of hydrocortisone. Dexamethasone is used to treat many inflammatory and autoimmune conditions, e.g. rheumatoid arthritis. It is also given to cancer patients undergoing chemotherapy, to counteract certain side-effects of their antitumor treatment. Dexamethasone causes muscle atrophy both in mice and in human patients.

[0055] Mice are injected intraperitoneally (ip) with dexamethasone for 3, 7, or 14 days. On the terminal day subjects are euthanized using CO_2, and the leg muscles harvested. The animals are monitored daily (visual inspection) for any adverse reactions (i.e. unkempt coat, lethargic) to the treatment. Mice are usually mobile, and can eat and drink normally. Mice injected with PBS are the negative control.

[0056] Cast Immobilization

[0057] Physical disuse of various muscle groups results in atrophy of those muscles. Ankle joint fixation ("pinned heel" or casting) has proven to be a highly useful and reproducible way to induce physical immobilization of rat and mouse hindlimb musculature.

[0058] Mice are anesthetized with isofluorane for immobilization. The ankle and knee joints are fixed at 90 degrees with a light-weight casting material (VET-LITE) around the joints. The material is soaked in warm water and then wrapped around the limb, leaving the toes and hip joint free. The joints are maintained in at 90° positions until the casting material has dried. The contralateral leg serves as control. The mice are then allowed to recover from anesthesia and housed in normal micro isolator cages. Casting has not been observed to cause excessive stress, and animals freely move about the cage to feed and drink. The mice are however monitored daily for any adverse events affecting body weight, activity, and irritations.

[0059] Once a cast is applied to a mouse, the animal is monitored daily to make sure that the cast remains in place, as chewing can occur. The animals can move, drink, and feed after recovery of anesthesia, and they do not require special bedding, caging or other assistance.

[0060] Denervation

[0061] Generally, mice are anesthetized with isofluorane gas for denervation. Using aseptic surgical procedures (three washes of betadine with a final ethanol wash), the right sciatic nerve is isolated in the mid-thigh and a 2 to 5 mm piece cut out. The contralateral leg serves as control.

[0062] More specifically, the skin incision is closed with a suture clip, and the animals injected with a single dose of buprenorphine before being allowed to recover from the anesthesia. Three, seven, or 14 days after surgery animals are euthanized by CO_2 inhalation followed by cervical dislocation, and muscles (gastrocnemius complex, tibialis anterior, extensor digitorum longus, soleus) are removed for histological and biochemical analyses.

[0063] Given that the sciatic nerve is transected, the effected limb is rendered immobile to induce skeletal muscle atrophy of the muscles involved. The animal can otherwise move, drink, and feed after recovery of anesthesia and they do not require special bedding, caging or other assistance. Nonetheless, animals are monitored immediately post-surgery and through recovery (1-2 hrs). In addition, the incision sites and general animal health are monitored for 3 days post-surgery. The suture clip is removed 7 to 10 days after surgery.

[0064] Genetic Models

[0065] Genetically manipulated transgenic mice can also be used as models of muscle atrophy. For example, the so-called Mini Mice (The Jackson Laboratory, Stock No. 003258) contains a knock out mutation in the IGF-1 gene that results in abnormally decreased postnatal growth, as well as low body weight and size. For additional information, see Powell-Braxton et al., Genes Dev 7:2609-2617, 1993. In addition, the so-called Midi Mice (The Jackson Laboratory, Stock No. 003259) contains a different mutation in the IGF-1 gene that results in a hypomorph exhibiting low adult body weight and other cardiovascular phenotypes. For additional information, see Lembo et al., J Clin Invest 98:2648-2655, 1996.

[0066] Critical and Optional Mutations or Modifications in the IGF Precursors

[0067] Critical Mutations The invention is based in part on the observation that an IGF precursor polypeptide that contains substantially its E-peptide remains bioactive and stable in the presence of serum. To ensure that the E-peptide is not cleaved by endogenous proteases targeting the dibasic protease site, in general either of the two N-terminal dibasic amino acids of the E-peptide in the precursor is deleted, mutated, or otherwise masked. In the case of hIGF-1, these two amino acids are R71 and S72, while in the case of hIGF-2, these first two amino acids are R68 and D69.

[0068] A variety of modifications enables this prevention of cleavage:

[0069] (1) Deletion of one or both dibasic residues

[0070] (2) Mutate one or both dibasic residues to a non-basic amino acid, such as alanine

[0071] (3) Insert one or more non-basic amino acids between the dibasic residues

[0072] (4) Place a glycosylation site near the dibasic residues sufficient to mask the protease site

[0073] (5) Site-directed pegylation using replacement of either dibasic residue, or insertion near or between the dibasic residues, with a non-natural amino acid, as described below.

[0074] In addition, residues K68 and K65 appear to play a role in IGF-1/E-peptide cleavage; accordingly, mutations or deletions of these residues can be incorporated into any tactic directed to the dibasic amino acids as described above.

[0075] Mutations at the N-terminus of Mature IGF In certain embodiments of the invention, the IGF precursor polypeptides have deletions or mutations of the first few N-terminal amino acids. In the case of IGF-1, any of the first three N-terminal amino acids can be deleted or mutated, whereas in the case of IGF-2, any of the first six N-terminal amino acids can be deleted or mutated. It has been observed that certain N-terminal amino acids are naturally cleaved in vivo, and the introduction of these mutations or deletions minimizes the in vivo associations of the polypeptides of the invention with IGF binding proteins (IGFBPs). The interaction of IGF-1 and IGF-2 with the IGF-1 receptor is regulated by IGFBPs. All six IGFBPs have been shown to inhibit IGF action (particularly IGFBP5), but in some instances a stimulatory effect has been observed. At least 99% of the IGF in the circulation is normally bound to IGFBPs. The most abundant IGFBP in the circulation after the neonatal period is IGFBP3 which can bind both IGF-1 and IGF-2 with similar affinities. The naturally occurring truncated IGF-1 (bearing deletion of G1, P2, and E3) binds to IGFBP3 with several times lower affinity than natural IGF-1. In addition, G3 is important for IGFBP binding, and G6 plays a similar role in the IGF-2 peptide.

[0076] Accordingly, in the case of the hIGF-1 precursor, any of G1, P2, or E3 can be deleted or mutated either alone or in combination. When a mutation is desired, a mutation to alanine can be introduced. In another example, in the case of hIGF-2 precursor, any of P4, S5, and E6 can be deleted or mutated either alone or in combination. When a mutation is desired, a mutation to alanine can be introduced.

[0077] Mutations at Residues 36 and 37 IGF-1 can e cleaved by serine proteases present in human serum. Mutation of either R36 or R37 to A can prevent cleavage of IGF-1 at this predicted cleavage site between R36 and R37. In the case of hIGF-2, R38 can be mutated or deleted to prevent this deleterious cleavage.

[0078] Use of Glycosylation The in vivo half-life of the polypeptides of the invention can be improved by the addition of N-linked glycosylation sites into either the IGF

or the E-peptide portions of the precursor when expressed in mammalian or other eukaryotic cells capable of N-linked glycosylation. It has been shown in vitro that human IGF-1 Ea is glycosylated at N92 and N100, as these portions of Ea fits the consensus N-linked glycosylation sequence of N-X-S/T, where X can be any amino acid and the third amino acid of the triplet is either S or T. It is also know that the adjacent amino acid context of the consensus will affect how strongly the asparagine is glycosylated. Therefore, one strategy to introduce a glycosylation site into Eb or Ec is to insert Ea amino acids around the consensus sequence into roughly the same part of Eb or Ec. A particular implementation of this strategy is illustrated in the Examples below. In any event, any other consensus N-linked glycosylation site, including surrounding context amino acids, known to the skilled artisan can be inserted into a precursor polypeptide of the invention. In addition, O-linked glycosylation of a polypeptide of the invention can be accomplished by choosing the particular host used for production of the polypeptide. For example, use of certain yeast strains for IGF-1 expression results in the addition of oligosaccharides on a serines or threonines. See, e.g., U.S. Pat. No. 5,273,966.

[0079] Addition of Poly(ethylene glycol) Conjugation to poly(ethylene glycol) (PEG; pegylation) have proven to be beneficial in prolonging the half-life of therapeutic proteins drugs. It is expected that pegylation of the IGF precursor polypeptides of the invention may result in similar pharmaceutical advantages. Methods of pegylation of IGF-1 are well known in the art. See, for example, US Patent Application Publication 2006/0154865, which describes the beneficial properties of lysine-monopegylated IGF-1. Such lysine-monopegylation can be adapted for the precursor IGF polypeptides of the invention. In addition, pegylation can be achieved in any part of a polypeptide of the invention by the introduction of a nonnatural amino acid. Certain nonnatural amino acids can be introduced by the technology described in Deiters et al., J Am Chem Soc 125:11782-11783, 2003; Wang and Schultz, Science 301:964-967, 2003; Wang et al., Science 292:498-500, 2001; Zhang et al., Science 303:371-373, 2004 or in U.S. Pat. No. 7,083,970. Briefly, some of these expression systems involve site-directed mutagenesis to introduce a nonsense codon, such as an amber TAG, into the open reading frame encoding a polypeptide of the invention. Such expression vectors are then introduced into a host that can utilize a tRNA specific for the introduced nonsense codon and charged with the nonnatural amino acid of choice. Particular nonnatural amino acids that are beneficial for purpose of conjugating moieties to the polypeptides of the invention include those with acetylene and azido side chains. The IGF precursor polypeptides containing these novel amino acids can then be pegylated at these chosen sites in the protein. In addition, such pegylated IGF molecules without the E-peptide are also useful as therapeutics.

[0080] Multimers of E-Peptides In certain pharmacological contexts, it is beneficial to increase the size of a peptide or protein drug to ensure that the drug remains on one side of the blood—brain barrier or the other. Since mature IGF molecules are relatively short peptides, even if the E-peptide remains attached, it can be beneficial to increase the size of the polypeptides of the invention. One means of doing so is to provide multimers of E-peptides at the C-terminus of the IGF precursor polypeptide, as illustrated in certain Examples described below.

[0081] C-Terminal Deletion of E-Peptides It is suspected that the free cysteine at position 81 of Eb may result in homodimerization or other effects that, when present in the polypeptides of the invention, might lead to lower activity drugs. Thus, deletion or mutation of C81 in Eb can optimize drug activity. In a particular example, deletion of the last seven amino acids of Eb (i.e., amino acids 81-87) is beneficial.

[0082] Other Mutations or Modifications Additional mutations or modifications of IGF that can be incorporated into the IGF precursor polypeptides of the invention are described in U.S. Pat. No. 5,077,276; and US Patent Application Publication Nos. 2005/0287151, 2006/0211606, and 2006/0166328.

[0083] The invention should be construed, in addition to human IGF-1 and IGF-2, to include all known and unknown non-human animal precursor IGF-1 or IGF-2 sequences containing substantially its E-peptide wherein the normal cleavage of the E-peptide is avoided or reduced according to modifications of the present invention.

[0084] The preferred type of IGF to be used depends upon the species of the subject being treated.

[0085] It is preferred that the IGF is species-matched, for example, when a cow is being treated, the preferred type of IGF is bovine IGF.

[0086] Although all forms of IGF are likely to have an effect in different subjects due to the high sequence homologies, species matching will avoid potential adverse immunological complications stemming from the induction of an immune response to an IGF from a different species.

[0087] In one embodiment of the invention, modified non-human animal precursor IGF-1 sequences are provided.

[0088] Preferred are precursor IGF-1 sequences containing substantially its E-peptide wherein the normal cleavage of the E-peptide is avoided or reduced according to modifications of the present invention from a vertebrate animal.

[0089] For example, such sequences include but are not limited to sequences from a mouse, rat, cow, pig, horse, sheep, goat, bird, dog, cat, fish and the like, from any source whether natural, synthetic, or recombinant.

[0090] In another embodiment of the invention, modified non-human animal precursor IGF-2 sequences are provided.

[0091] Preferred are precursor IGF-2 sequences containing substantially its E-peptide wherein the normal cleavage of the E-peptide is avoided or reduced according to modifications of the present invention from a vertebrate animal.

[0092] For example, such sequences include but are not limited to sequences from a mouse, rat, cow, pig, horse, sheep, goat, bird, dog, cat, fish and the like from any source, whether natural, synthetic, or recombinant.

[0093] Therapeutic Use of IGF Precursor Polypeptides

[0094] Indications The invention also includes the use of an IGF precursor polypeptide of the invention in the manufacture of a medicament for the treatment or prevention of a musculoskeletal disease. In addition, the invention includes use of IGF precursor polypepides to increase muscle or bone mass in an individual, whether or not such an individual is at risk for or has a musculoskeletal disease.

[0095] In particular, the musculoskeletal disease can be muscle atrophy. There are many causes of muscle atrophy, including as a result of treatment with a glucocorticoid such as cortisol, dexamethasone, betamethasone, prednisone, methylprednisolone, or prednisolone. The muscle atrophy can also be a result of denervation due to nerve trauma or a

result of degenerative, metabolic, or inflammatory neuropathy (e.g., Guillian-Barré syndrome, peripheral neuropathy, or exposure to environmental toxins or drugs). In addition, the muscle atrophy can be a result of an adult motor neuron disease, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, autoimmune motor neuropathy with multifocal conductor block, paralysis due to stroke or spinal cord injury, skeletal immobilization due to trauma, prolonged bed rest, voluntary inactivity, involuntary inactivity, metabolic stress or nutritional insufficiency, cancer, AIDS, fasting, rhabdomyolysis, a thyroid gland disorder, diabetes, benign congenital hypotonia, central core disease, nemalene myopathy, myotubular (centronuclear) myopathy, burn injury, chronic obstructive pulmonary disease, liver disease, sepsis, renal failure, congestive heart failure, or ageing.

[0096] The musculoskeletal disease can also be a muscular dystrophy syndrome, such as Duchenne, Becker, myotonic, fascioscapulohumeral, Emery-Deifuss, oculopharyngeal, scapulohumeral, limb girdle, a congenital muscular dystrophy, or hereditary distal myopathy. The musculoskeletal disease can also be osteoporosis, a bone fracture, short stature, or dwarfism.

[0097] IGF-1 is suggested as a treatment for insulin-insensitive diabetes, since IGF-1 can also bind heterodimers of IGF-1 receptor and insulin receptor. Accordingly, the polypeptides of the invention can be used to treat diabetes.

[0098] IGF-1 is neurotrophic and increases survival of neurons. It has been suggested that IGF-1 can be used to treat instances of motor-neuron death such as seen in amyotrophic lateral sclerosis (ALS), brain atrophy, ageing, and dementia. Accordingly, the polypeptides of the invention can be used to treat conditions associated with neuronal death, such as ALS, brain atrophy, or dementia.

[0099] IGF-1 increases both white and red blood cell populations and has an additive effect to administration of erythropoietin. Accordingly, the polypeptides of the invention can be used to treat anemia.

[0100] Since IGF-1 and IGF-2 are ubiquitous and essential regulators of cell division and vertebrate growth, they may be advantageously used in a variety of veterinary methods to exogenously enhance or maintain growth in an animal. Some examples include, but are not limited to:

[0101] (i) enhancing rate and/or extent of growth in an animal, for example, enhancing muscle growth in swine, cattle, poultry and fish;

[0102] (ii) enhancing the efficiency of their conversion of feed into body tissue (lean to fat ratio), for example, in swine, cattle, sheep, poultry and fish; and

[0103] (iii) enhancing milk production in lactating animals, for example, dairy cattle, sheep, goats.

[0104] Other veterinary therapeutic applications include, but are not limited to:

[0105] (iv) treating animal wasting symptoms associated with cachexia, trauma or other consumption diseases, for example, in companion animals such as dogs, cats, and horses; and

[0106] (v) treating lactating animals for improvement in neonatal health, for example, lactating sows for improvement in neonatal performance.

[0107] Methods of Administration The polypeptides of the invention can be delivered in a variety of ways, including the use of gene delivery vehicles. Methods known in the art for the therapeutic delivery of agents such as proteins or nucleic acids can be used for the therapeutic delivery of a polypeptide of the invention, e.g., cellular transfection, gene therapy, direct administration with a delivery vehicle, or pharmaceutically acceptable carrier, indirect delivery by providing recombinant cells containing a nucleic acid encoding the polypeptide.

[0108] Various delivery systems are known and can be used to administer the polypeptide of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the protein, receptor-mediated endocytosis (see, e.g., Wu and Wu, J Biol

[0109] Chem 262:4429-4432, 1987), construction of a nucleic acid as part of a retroviral, adeno-associated viral, adenoviral, poxviral (e.g., avipoxviral, particularly fowlpoxviral) or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, pulmonary, intranasal, intraocular, epidural, and oral routes. The polypeptides can be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0110] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, e.g., by injection, by means of a catheter, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, or commercial skin substitutes.

[0111] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533, 1990). In yet another embodiment, the active agent can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used (see Howard et al., J Neurosurg 71:105, 1989). In another embodiment where the active agent of the invention is a nucleic acid encoding a polypeptide of the invention, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see, for example, U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see, e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868, 1991), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0112] Cellular Transfection and Gene Therapy The present invention encompasses the use of nucleic acids encoding polypeptides of the invention for transfection of cells in vitro and in vivo. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells ex vivo and in vivo, through the interaction of the vector and the target cell. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response.

[0113] In another aspect, the invention provides a method of treating a target site, i.e., a target cell or tissue, in a human or other animal including transfecting a cell with a nucleic acid encoding a polypeptide of the invention, wherein the nucleic acid includes an inducible promoter operably linked to the nucleic acid encoding the targeting fusion polypeptide. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt Biotechnology 6:1149-1154, 1998.

[0114] Combination Therapies In numerous embodiments, the polypeptides of the present invention can be administered in combination with one or more additional compounds or therapies. For example, multiple polypeptides can be co-administered in conjunction with one or more therapeutic compounds. The combination therapy may encompass simultaneous or alternating administration. In addition, the combination may encompass acute or chronic administration. The polypeptides of the invention can be administered in combination with anabolic agents such as testosterone or specific androgen receptor modulators (SARMs). Additional anabolic agents include growth hormone (GH) or molecules that induce GH release. Ghrelin is particularly useful in a combination therapy for cachexia, since Ghrelin can cause an increase in appetite. In a similar vein, the polypeptides of the invention can be combined with protein supplements to increase anabolism, or combined with physical therapy or exercise to increase body weight. Any molecule that inhibits myostatin is also a candidate for combination therapy.

[0115] Pharmaceutical Compositions The present invention also provides pharmaceutical compositions comprising a IGF precursor protein of the invention and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals or humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0116] In some embodiments, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0117] The polypeptides of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0118] The amount of a polypeptide of the invention which will be effective in the treatment of a condition or disease can be determined by standard clinical techniques based on the present description. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each subject's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20-5000 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. In particular, a possible dosage regimen can be about 60 to 120 μg/kg body weight, subcutaneous injection, twice daily.

[0119] Veterinary Uses

[0120] In addition to the aforementioned methods of administration in humans, there may be additional considerations for veterinary administration.

[0121] The dosage may differ when administered to a healthy animal versus those animals suffering from a disease. An assessment of the appropriate dosage can easily be made by those skilled in the art using assays known in the art, for example, the myoblast proliferation assay (Example 79) or the mammary epithelial tissue assay (Example 80) as described below. General assays to measure IGF are also known in the art, such as those in Example 81.

[0122] Those skilled in the art will recognize that some species of animal exhibit seasonal fertility influenced by the length of the photoperiod. Any embodiment of a veterinary method or use may optionally include starting the treatment method at a specific time within the animal's reproductive cycle in order to achieve the desired effect. Those skilled in the art will know that reproductive status and cycle can easily be determined, and, if desired, synchronized by the use of an appropriate regimen.

[0123] When used for veterinary indications, in addition to methods previously mentioned for human use, the IGF-1 or IGF-2 peptide of the present invention can also be used as an oral drench, or a supplement to oral or solid feeds for animals.

[0124] The invention is further described but not limited by the following Examples.

EXAMPLES

Example 1

[0125] A DNA expression vector encoding the hIGF-1-Ea precursor polypeptide containing the following modifications was constructed: deletion of G1, deletion of P2, and deletion of E3; mutation of R37 to A; and deletion of R71 and deletion of S72. These mutations are sometimes referred to as "3mut" throughout the present disclosure. This results in the following secreted protein sequence:

(SEQ ID NO: 8)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnkny

rm

[0126] Cos7 cells (available from ATCC) were maintained in DMEM containing 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin and plated at a density of 1×10^6 cells per 10-cm plate. These cell cultures were transfected with 8 μg of expression plasmid using Fugene (Roche) according to manufacturer's instructions. Twenty-four hours post-transfection, cells were washed once and cultured in serum-free medium for 48 hours. Supernatants were collected and stored at −80° C.

[0127] In order to assess polypeptide stability in human serum, supernatants collected from the Cos7 cells transfected with wild-type (wt) hIGF-1 Ea, and hIGF-1 Ea3mut were incubated for 16 hours at 37° C. either in the absence or presence of 10% human serum (Sigma). Samples were separated by 18% SDS-PAGE, and imunoblotting was performed using goat polyclonal antibody to human IGF-1. The results in FIG. **1**A indicate that, while the wt hIGF-1 Ea was substantially degraded after incubation with serum for 16 hours, the hIGF-1 Ea3mut was stabilized. Densitometry indicated that the ratio of uncleaved to cleaved IGF-1 was about 1:6.2, while the ratio for hIGF-1 Ea3mut was about 1:0.68, showing that these mutations result in a stabilized polypeptide.

[0128] To confirm that the hIGF-1 Ea3mut was able to signal through the IGF-1R, AKT phosphorylation of cells in contact with the polypeptide was measured. C2C12 were purchased from ATCC and maintained in Dulbecco's modified Eagle's medium (DMEM) with high glucose (Invitrogen) containing 10% fetal bovine serum (AMIMED), 100 U/ml penicillin (Invitrogen), 100 μg/ml streptomycin (Invitrogen) and 2 mM glutamine (Invitrogen). For analysis of AKT phosphorylation, the C2C12 cells were plated at a density of 0.15×10^6 cells per well of a 6-well plate and were cultured in growth medium for 72 hours. Cells were starved for four hours in serum-free medium and then stimulated with different ligands at 37° C. for 30 minutes. Cells were lysed with PhosphoSafe buffer (Cell Signaling) containing various protease inhibitors and cleared by centrifugation at 14,000×g for 15 minutes at 4° C. AKT phosphorylation and total AKT levels were analyzed by ELISA using PathScan phospho AKT (Ser473) sandwich ELISA kit and PathScan AKT sandwich ELISA kit (Cell Signaling), respectively. The AKT phosphorylation results are summarized in FIG. **2**A, which indicate that the hIGF-1 Ea3mut was able to activate the IGF-1 R cellular pathway to a similar extent as the long-R3-IGF-1 positive control reagent and the recombinant IGF-1. In addition, the data in FIG. **5** directly shows that hIGF-1 Ea3mut led to AKT phosphorylation.

[0129] Next, to ensure that the receptor specificity of the hIGF-1 Ea3mut remained with the IGF-1 R, various ligands were added to cultures of NIH3T3 overexpressing either IGF-1 R or insulin receptor (InsR). These cells were cultured under the same conditions as described above for Cos7 cells. For analysis of IGF-1 R and InsR phosphorylation, NIH3T3-IGF1 R and NIH3T3-InsR cells were plated at a density of 0.2×10^6 cells per well of a 6-well plate and were cultured in growth medium for 24 hours. Cells were starved for 18 hours in serum-free medium and then stimulated with different ligands at 37° C. for 10 minutes. Cells were lysed as described above for the AKT experiment, and IGF-1 R and InsR phosphorylation levels were analyzed by ELISA using DuoSet IC human phosphor-IGF1R and -InsR ELISA kit (R&D Systems). The results summarized in FIGS. **3**A and **3**B indicate that this IGF-1 precursor polypeptide retains specificity for the IGF-1 receptor and should bind to the related insulin receptor with low affinity.

Example 2

[0130] A DNA expression vector encoding the hIGF-1-Eb precursor polypeptide containing the following mutations was constructed: deletion of G1, deletion of P2, and deletion of E3; mutation of R37 to A; and deletion of R71 and deletion of S72 (i.e., the "3mut"). This results in the following secreted protein sequence:

(SEQ ID NO: 9)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrr

kgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0131] The polypeptide was assayed in accordance with the procedures described in Example 1 above. FIG. **1**B and use of densitometry indicated that the ratio of uncleaved to cleaved IGF-1 was about 1:9, while the ratio for hIGF-1 Eb3mut was about 1:1, showing that these modifications result in a stabilized polypeptide. FIG. **2**B indicates that the hIGF-1 Eb3mut was able to activate the IGF-1 R cellular pathway to a similar extent as the long-R3-IGF-1 positive control reagent and the recombinant IGF-1. In addition, the data in FIG. **5** directly shows that hIGF-1 Eb3mut led to AKT phosphorylation. The results summarized in FIGS. **3**C and **3**D indicate that this IGF-1 precursor polypeptide retains specificity for the IGF-1 receptor and should bind to the related insulin receptor with low affinity.

Example 3

[0132] A DNA expression vector encoding the hIGF-1-Ec precursor polypeptide containing the following mutations was constructed: deletion of G1, deletion of P2, and deletion of E3; mutation of R37 to A; and deletion of R71 and

deletion of S72 (i.e., the "3mut"). This results in the following secreted protein sequence:

(SEQ ID NO: 10)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg

stfeerk

[0133] The polypeptide was assayed in accordance with the procedures described in Example 1 above. FIG. **1**C and use of densitometry indicated that the ratio of uncleaved to cleaved IGF-1 was about 1:5, while the ratio for hIGF-1 Ec3mut was about 1:0.96, showing that these modifications result in a stabilized polypeptide. FIG. **2**D indicates that the hIGF-1 Ec3mut was able to activate the IGF-1 R cellular pathway to a similar extent as the long-R3-IGF-1 positive control reagent and the recombinant IGF-1. In addition, the data in FIG. **5** directly shows that hIGF-1 Ec3mut led to AKT phosphorylation. The results summarized in FIGS. **4**A and **4**B indicate that this IGF-1 precursor polypeptide retains specificity for the IGF-1 receptor and should bind to the related insulin receptor with low affinity.

Example 4

[0134] A DNA expression vector encoding the hIGF-1-Eab chimeric precursor polypeptide containing the following modifications to the hIGF-1-Eb peptide was constructed: deletion of G1, deletion of P2, and deletion of E3; mutation of R37 to A; deletion of R71 and deletion of S72 (i.e., the "3mut"); and insertion of Ea amino acids 93 to 102 between amino acids 95 and 96 of Eb. The insertion creates a putative N-linked glycosylation signal at N92. This results in the following secreted protein sequence:

(SEQ ID NO: 11)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnkn

tksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkk

gk

[0135] The polypeptide was assayed in accordance with some of the procedures described in Example 1 above. FIG. **2**C indicates that the hIGF-1 Eab3mut was able to activate the IGF-1 R cellular pathway to a similar extent as the long-R3-IGF-1 positive control reagent and the recombinant IGF-1. The results summarized in FIGS. **4**C and **4**D indicate that this IGF-1 precursor polypeptide retains specificity for the IGF-1 receptor and does not activate the insulin receptor.

Example 5

[0136] A DNA expression vector encoding the hIGF-1-Eb multimer precursor polypeptide containing the following mutations was constructed: deletion of G1, deletion of P2, deletion of E3, deletion of R36, deletion of R37, deletion of R71, deletion of S72, deletion of the last seven C-terminal amino acids of Eb; and insertion to the C-terminus of this precursor of two additional Eb peptides both without the R71 and S72 and last seven C-terminal amino acids and a fourth and final Eb peptide without the R71 and S72. FIG. **6**A shows a schematic drawing of this construct. This results in the following secreted protein sequence:

(SEQ ID NO: 12)

tlcgaelvdalqfvcgdrgfyfnkptgygsssapqtgivdeccfrscdlr

rlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwpkt

hpggeqkegteaslqirgkkkeqrreigsrnaersvraqrhtdmpktqky

qppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsr

naersvraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegt

easlqirgkkkeqrreigsrnaersvraqrhtdmpktqkyqppstnkntk

sqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0137] This polypeptide was subjected to an AKT phosphorylation assay as described in Example 1. FIG. **5** indicates that this hIGF-1-Eb multimer was able to signal through the IGF-1R pathway.

Example 6

[0138] A hIGF-1-Eb precursor polypeptide of the invention as shown schematically in FIG. **6**B can be expressed. This construct contains the following modifications: deletion of G1, deletion of P2, deletion of E3, deletion of R36, deletion of R37, deletion of R71, deletion of S72; and the insertion of Ea amino acids 93-102 between amino acids 95 and 96 of Eb, thereby creating an N-linked glycosylation site at position N92 and N100. This results in the following secreted protein sequence:

(SEQ ID NO: 13)

tlcgaelvdalqfvcgdrgfyfnkptgygsssapqtgivdeccfrscdlr

rlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnkntk

sqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

Example 7

[0139] A hIGF-2-E precursor polypeptide of the invention having the following modifications can be expressed: deletion of P4, deletion of S5, and deletion of E6; mutation of R38 to A; and deletion of R68 and deletion of D69. This results in the following secreted protein sequence:

(SEQ ID NO: 14)

ayrtlcggelvdtlqfvcgdrgfyfsrpasrvsrasrgiveeccfrscdl

alletycatpaksevstpptvlpdnfprypvgkffqydtwkqstqrlrrg

lpallrarrghvlakeleafreakrhrplialptqdpahggappemasnr

k

Example 8

[0140] A hIGF-1-Ea precursor polypeptide of the invention having the following mutations can be expressed:

deletion of G1 and deletion of P2; mutation of E3 to X where X is a nonnatural amino acid that is pegylated; mutation of R37 to A; and deletion of R71 and deletion of S72. This results in the following secreted protein sequence:

(SEQ ID NO: 15)

Xtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnknyr

m

Examples 9-78

Δ=Deletion

[0141] 9) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R36A; ΔR71

(SEQ ID NO: 16)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksasvraqrhtdmpktqkevhlknasrgsagnknyr

m

[0142] 10) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R36A; ΔS72

(SEQ ID NO: 17)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkevhlknasrgsagnknyr

m

[0143] 10) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R36A; ΔR71, ΔS72

(SEQ ID NO: 18)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnknyrm

[0144] 11) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R37A; ΔR71

(SEQ ID NO: 19)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksasvraqrhtdmpktqkevhlknasrgsagnknyr

m

[0145] 12) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R37A; ΔS72

(SEQ ID NO: 20)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkevhlknasrgsagnknyr

m

[0146] 13) hIGF-1-Ea: ΔG1, ΔP2, ΔE3, ΔR37; ΔR71

(SEQ ID NO: 21)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksasvraqrhtdmpktqkevhlknasrgsagnknyrm

[0147] 14) hIGF-1-Ea: ΔG1, ΔP2, ΔE3, ΔR37; ΔS72

(SEQ ID NO: 22)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksarvraqrhtdmpktqkevhlknasrgsagnknyrm

[0148] 15) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; ΔR37; ΔR71, ΔS72

(SEQ ID NO: 23)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnknyrm

[0149] 16) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R36A; ΔR71

(SEQ ID NO: 24)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0150] 17) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R36A; ΔS72

(SEQ ID NO: 25)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0151] 18) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R37A; ΔR71

(SEQ ID NO: 26)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0152] 19) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R37A; ΔS72

(SEQ ID NO: 27)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0153] 20) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 28)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwp

kthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0154] 21) hIGF-1-Eb: ΔG1, ΔP2, ΔE3, ΔR37; ΔR71

(SEQ ID NO: 29)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgwp
kthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0155] 22) hIGF-1-Eb: ΔG1, ΔP2, ΔE3, ΔR37; ΔS72

(SEQ ID NO: 30)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgwp
kthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0156] 23) hIGF-1-Eb: ΔG1, ΔP2, ΔE3, ≠R37; ΔR71, ΔS72

(SEQ ID NO: 31)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwpk
thpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0157] 24) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R36A; ΔR71

(SEQ ID NO: 32)
tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd
lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgs
tfeerk

[0158] 25) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R36A; ΔS72

(SEQ ID NO: 33)
tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd
lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgs
tfeerk

[0159] 26) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R36A; ΔR71, ΔS72

(SEQ ID NO: 34)
tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd
lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgst
feerk

[0160] 27) hIGF-1-Ec: ΔG1, ΔP2, ΔE2; R37A; ΔR71

(SEQ ID NO: 35)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd
lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgs
tfeerk

[0161] 28) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R37A; ΔS72

(SEQ ID NO: 36)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd
lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgs
tfeerk

[0162] 29) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 37)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd
lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgst
feerk

[0163] 30) hIGF-1-Ec: ΔG1, ΔP2, ΔE3, ΔR37, ΔR71

(SEQ ID NO: 38)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksasvraqrhtdmpktqkyqppstnkntksqrrkgst
feerk

[0164] 31) hIGF-1-Ec: ΔG1, ΔP2, ΔE3, ΔR37, ΔS72

(SEQ ID NO: 39)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksarvraqrhtdmpktqkyqppstnkntksqrrkgst
feerk

[0165] 32) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R36A; ΔR71; insertion of Ea aa 93-102 between aa 95 and 96 of Eb (i.e., "Eab")

(SEQ ID NO: 40)
tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd
lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnknasrgsagnk
ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk
kgk

[0166] 33) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R37A; ΔR71

(SEQ ID NO: 41)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd
lrrlemycaplkpaksasvraqrhtdmpktqkyqppstnknasrgsagnk
ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk
kgk

[0167] 34) hIGF-1-Eab: ΔG1, ΔP2, ΔE3, ΔR37, ΔR71

(SEQ ID NO: 42)
tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl
rrlemycaplkpaksasvraqrhtdmpktqkyqppstnknasrgsagnkn

-continued

tksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkk

gk

[0168] 35) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R36A; ΔS72

(SEQ ID NO: 43)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnknasrgsagnk

ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk

kgk

[0169] 36) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R37A; ΔS72

(SEQ ID NO: 44)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksarvraqrhtdmpktqkyqppstnknasrgsagnk

ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk

kgk

[0170] 37) hIGF-1-Eab: ΔG1, ΔP2, ΔE3, ΔR37, ΔS72

(SEQ ID NO: 45)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksarvraqrhtdmpktqkyqppstnknasrgsagnkn

tksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkk

gk

[0171] 38) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R36A; ΔR71, ΔS72

(SEQ ID NO: 46)

tlcgaelvdalqfvcgdrgfyfnkptgygsssarapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnkn

tksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkk

gk

[0172] 39) hIGF-1-Eab: ΔG1, ΔP2, ΔE3, ΔR37, ΔR71, ΔS72

(SEQ ID NO: 47)

tlcgaelvdalqfvcgdrgfyfnkptgygsssrapqtgivdeccfrscdl

rrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnknt

ksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkg

k

[0173] **40**) hIGF-1-Ea: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 48)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnknyr

m

[0174] 41) hIGF-1-Eb: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 49)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0175] 42) hIGF-1-Eb multimer: (ΔG1, ΔP2, ΔE3; R37A)-3xEb(ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 50)

tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnknksqrrkgwp

kthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqky

qppstnknksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsr

naevraqrhtdmpktqkyqppstnknksqrrkgwpkthpggeqkegtea

slqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnknksqrr

kgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0176] 43) hIGF-1-Eb multimer: (ΔP2, ΔE3; R37A)-3xEb (ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 51)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqk

yqppstnknksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigs

rnaevraqrhtdmpktqkyqppstnknksqrrkgwpkthpggeqkegte

aslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnknksqr

rkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0177] 44) hIGF-1-Ec: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 52)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknksqrrkgs

tfeerk

[0178] 45) hIGF-1-Ea: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 53)

gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs

cdlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnkny

rm

[0179] 46) hIGF-1-Eb: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 54)

gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs

cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknksqrrkg

wpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0180] 47) hIGF-1-Eb multimer: (ΔG1, ΔP2, ΔE3; R37A)-3xEb(ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 55)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd
lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwp
kthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqky
qppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsr
naevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegtea
slqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqrr
kgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0181] 48) hIGF-1-Eb multimer: (ΔE3; R37A)-3xEb (ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 56)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg
wpkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktq
kyqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreig
srnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegt
easlqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksq
rrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0182] 49) hIGF-1-Ec: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 57)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg
stfeerk

[0183] 50) hIGF-1-Ea: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 58)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnkny
rm

[0184] 51) hIGF-1-Eb: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 59)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg
wpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0185] 52) hIGF-1-Ec: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 60)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg
stfeerk

[0186] 53) hIGF-1-Eab: ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 61)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagn
kntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrg
kkgk

[0187] 54) hIGF-1-Eb multimer: (ΔE3; R37A)-3xEb (ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 62)
gptlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrs
cdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkg
wpkthpggeqkegteaslqirgkkkeqrreigsmaevraqrhtdmpktqk
yqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigs
rnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegte
aslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqr
rkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0188] 55) hIGF-1-Ea: E3A; R37A; ΔR71, ΔS72

(SEQ ID NO: 63)
gpatlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfr
scdlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnkn
yrm

[0189] 56) hIGF-1-Eb: E3A; R37A; ΔR71, ΔS72

(SEQ ID NO: 64)
gpatlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfr
scdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrk
gwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0190] 57) hIGF-1-Ec: E3A; R37A; ΔR71, ΔS72

(SEQ ID NO: 65)
gpatlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfr
scdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrk
gstfeerk

[0191] 58) hIGF-1-Eab: E3A; R37A; ΔR71, ΔS72

(SEQ ID NO: 66)
gpatlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfr
scdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsag
nkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecr
gkkgk

[0192] 59) hIGF-1-Eb multimer: (E3A; R37A)-3xEb (ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 67)

gpatlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfr

scdlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrk

gwpkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpkt

qkyqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrrei

gsrnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkeg

teaslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntks

qrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0193] 60) hIGF-1-Ea: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 68)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkevhlknasrgsagnknyr

m

[0194] 61) hIGF-1-Eb: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 69)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0195] 62) hIGF-1-Ec: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 181)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgs

tfeerk

[0196] 63) hIGF-1-Eab: ΔP2, ΔE3; R37A; ΔR71, ΔS72

(SEQ ID NO: 70)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnk

ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk

kgk

[0197] 64) hIGF-1-Eb multimer: (ΔP2, ΔE3; R37A)-3xEb (ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 71)

gtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqk

yqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigs

rnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegte

-continued

aslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqr

rkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0198] 65) hIGF-1-Eb: ΔG1, ΔP2; E3X; R37A; ΔR71, ΔS72

(SEQ ID NO: 72)

Xtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0199] 66) hIGF-1-Ec: ΔG1, ΔP2; E3X; R37A; ΔR71, ΔS72

(SEQ ID NO: 73)

Xtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgs

tfeerk

[0200] 67) hIGF-1-Eab: ΔG1, ΔP2; E3X; R37A; ΔR71, ΔS72

(SEQ ID NO: 74)

Xtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnk

ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk

kgk

[0201] 68) hIGF-1-Eb multimer: (ΔG1, ΔP2; E3X; R37A)-3xEb(ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 75)

Xtlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrsc

dlrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqk

yqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigs

rnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegte

aslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqr

rkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0202] 69) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R37A; ΔR71; S72X

(SEQ ID NO: 76)

tlcgaelvdalqfycgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksaXvraqrhtdmpktqkevhlknasrgsagnknyr

m

[0203] 70) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R37A; ΔR71; S72X

(SEQ ID NO: 77)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksaXvraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0204] 71) hIGF-1-Ec: ΔG1, ΔP2, ΔE3; R37A; ΔR71; S72X

(SEQ ID NO: 78)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksaXvraqrhtdmpktqkyqppstnkntksqrrkgs

tfeerk

[0205] 72) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R37A; ΔR71; S72X

(SEQ ID NO: 79)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksaXvraqrhtdmpktqkyqppstnknasrgsagnk

ntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgk

kgk

[0206] 73) hIGF-1-Eb multimer: (ΔG1, ΔP2, ΔE3; R37A)-Eb(ΔR71; S72X; ΔC-term 7 aa)-2xEb(ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72)

(SEQ ID NO: 80)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpakXsavraqrhtdmpktqkyqppstnkntksqrrkgw

pkthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqk

yqppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigs

rnaevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegte

aslqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqr

rkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaecrgkkgk

[0207] 74) hIGF-1-Ea: ΔG1, ΔP2, ΔE3; R37A; ΔR71, ΔS72; N92X

(SEQ ID NO: 81)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkevhlkXasrgsagnknyrm

[0208] 75) hIGF-1-Eb: ΔG1, ΔP2, ΔE3; R37A; ΔR71, ΔS72; C142X

(SEQ ID NO: 82)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwp

kthpggeqkegteaslqirgkkkeqrreigsrnaeXrgkkgk

[0209] 76) hIGF-1-Eab: ΔG1, ΔP2, ΔE3; R37A; ΔR71, ΔS72; C151X

(SEQ ID NO: 83)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnknasrgsagnkn

tksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsrnaeXrgkk

gk

[0210] 78) hIGF-1-Eb multimer (ΔG1, ΔP2, ΔE3; R37A)-3xEb(ΔR71, ΔS72, ΔC-term 7 aa)-Eb(ΔR71, ΔS72; C71X)

(SEQ ID NO: 84)
tlcgaelvdalqfvcgdrgfyfnkptgygsssraapqtgivdeccfrscd

lrrlemycaplkpaksavraqrhtdmpktqkyqppstnkntksqrrkgwp

kthpggeqkegteaslqirgkkkeqrreigsrnaevraqrhtdmpktqky

qppstnkntksqrrkgwpkthpggeqkegteaslqirgkkkeqrreigsr

naevraqrhtdmpktqkyqppstnkntksqrrkgwpkthpggeqkegtea

slqirgkkkeqrreigsrnaevraqrhtdmpktqkyqppstnkntksqrr

kgwpkthpggeqkegteaslqirgkkkeqrreigsrnaeXrgkkgk

Example 79

Myoblast Proliferation Assay

[0211] The myoblast proliferation assay provides a reliable in vitro indicator of IGF activity and is used as a model for factors affecting embryonic myoblasts and adult satellite cells. Factors active in this system behave similarly in primary cultures of myoblasts. The enhancement of myoblast proliferation in vitro by a peptide of this invention indicates its activity in causing increased myoblast proliferation and, therefore, an increase in ultimate myofiber number in utero. In addition, similar enhancement of myoblast proliferation indicates that peptides of this invention can be used to enhance adult muscle hypertrophy, e.g. via stimulation of satellite muscle cell proliferation.

Example 80

Mammary Epithelial Tissue Assay

[0212] In lactating animals, the amount of mammary epithelial tissue is a limiting factor in milk production, as these are the cells which produce and secrete milk. Employing in vitro systems, epithelial cells obtained from mammary glands of animals can be stimulated by the modified IGF-1 or IGF-2 of the present invention to proliferate and produce increased quantities of milk constituents. It can further be demonstrated that mammary epithelial cells stimulated to proliferate in one such in vitro cell system can be reimplanted in cleared mammary fat pads and be stimulated to proliferate and/or produce milk in lactating female animals.

Example 81

Measurement of IGF-1 or IGF-2 in Blood or Other Body Fluids

[0213] The effective amount of the peptide administered parenterally per dose can be measured by a dose-response

curve. For example, modified IGF peptides of the invention can be measured in the blood or body fluids of the subject to be treated to determine the dosing. Alternatively, one can administer increasing amounts of the peptide to the subject and check the serum levels of the subject for modified IGF-1 and IGF-2. The amount of peptide to be employed can be calculated on a molar basis based on these serum levels of modified IGF-1 or IGF-2.

[0214] One method for determining appropriate dosing of the peptide entails measuring an IGF peptide of the invention in a biological fluid such as a body or blood fluid. Measuring such levels can be done by any means, including RIA and ELISA. After measuring IGF levels, the fluid is contacted with the peptide using single or multiple doses. After this contacting step, the IGF levels are re-measured in the fluid. If the fluid IGF levels have fallen by an amount sufficient to produce the desired efficacy for which the molecule is to be administered, then the dose of the molecule can be adjusted to produce maximal efficacy. This method may be carried out in vitro or in vivo. Preferably, this method is carried out in vivo, i.e., after the fluid is extracted from a subject and the IGF levels measured, the peptide herein is administered to the mammal using single or multiple doses (that is, the contacting step is achieved by administration to an animal), and then the IGF levels are re-measured from fluid extracted from the animal.

[0215] Another method for determining dosing is to use antibodies to the peptide or another detection method for the peptide in the LIFA format.

Example 82

In Vivo Pharmacokinetics of hIGF-1-Ec 3mut

[0216] Adult male mice (n=3/group) received an intravenous (i.v.) bolus injection of rhIGF-1 at 1 mg/kg, and hIGF-1-Ec 3mut (described in Example 3) at 1.55 mg/kg. Serial blood specimens were collected at 5, 15, 30 and 60 minutes after administration of test material. Serum concentrations of rhIGF-1 and hIGF-1-Ec 3mut were determined by ELISA. This assay is specific for hIGF-1.

[0217] Equimolar doses of rhIGF-1 and hIGF-1-Ec 3mut were administered i.v. in mice. The results show significantly higher levels of the hIGF-1-Ec 3mut protein as compared to rhIGF-1 at all examined time points, indicating that the hIGF-1-Ec 3mut is metabolically more stable than the 70 amino acid-long IGF-1.

time (min)	IGF-1-Ec 3mut (nM)	IGF-1 (nM)
5	201.4	54.7
15	65.3	14.3
30	12	2.4
60	0.76	0.2

SEQUENCE LISTING

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<213> ORGANISM: Homo sapiens

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Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
50 55 60

Lys Pro Ala Lys Ser Ala
65 70

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

<400> SEQUENCE: 2

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Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys Asn
20 25 30

Tyr Arg Met

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35

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

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Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
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Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
20 25 30

Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu
35 40 45

Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile
50 55 60

Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
65 70 75

<210> SEQ ID NO 4
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
20 25 30

Gly Ser Thr Phe Glu Glu Arg Lys
35 40

<210> SEQ ID NO 5
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
50 55 60

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
65 70 75 80

Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly
85 90 95

Ser Ala Gly Asn Lys Asn Tyr Arg Met
100 105

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Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Thr
20 25 30

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
35 40 45

His Val Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His
50 55 60

Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His Gly Gly Ala
65 70 75 80

Pro Pro Glu Met Ala Ser Asn Arg Lys
85

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

<400> SEQUENCE: 7

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

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

Ser Arg Val Ser Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
50 55 60

Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn
65 70 75 80

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

Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
100 105 110

Arg Arg Gly His Val Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala
115 120 125

Lys Arg His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His
130 135 140

Gly Gly Ala Pro Pro Glu Met Ala Ser Asn Arg Lys Ala Tyr Arg
145 150 155

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Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

-continued

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Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys
                85                  90                  95

Asn Tyr Arg Met
            100


<210> SEQ ID NO 9
<211> LENGTH: 142
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


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<213> ORGANISM: Homo sapiens

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Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
65                  70                  75                  80

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
                85                  90                  95

Gly Ser Thr Phe Glu Glu Arg Lys
            100
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<210> SEQ ID NO 11
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala
85 90 95

Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
100 105 110

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
115 120 125

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
130 135 140

Glu Cys Arg Gly Lys Lys Gly Lys
145 150

<210> SEQ ID NO 12
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp
35 40 45

Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys Ser
50 55 60

Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr
65 70 75 80

Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly
85 90 95

Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala
100 105 110

Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly
115 120 125

Ser Arg Asn Ala Glu Arg Ser Val Arg Ala Gln Arg His Thr Asp Met
130 135 140

Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys
145 150 155 160

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Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln
                165                 170                 175

Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu
            180                 185                 190

Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Arg Ser Val Arg Ala
        195                 200                 205

Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser
    210                 215                 220

Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
225                 230                 235                 240

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
                245                 250                 255

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
            260                 265                 270

Glu Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
        275                 280                 285

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
    290                 295                 300

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
305                 310                 315                 320

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
                325                 330                 335

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345                 350


<210> SEQ ID NO 13
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: CARBOHYD
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: CARBOHYD

<400> SEQUENCE: 13

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp
        35                  40                  45

Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys Ser
    50                  55                  60

Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr
65                  70                  75                  80

Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85                  90                  95

Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro
            100                 105                 110

Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly
        115                 120                 125
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Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Cys
    130                 135                 140

Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 14
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Ala Tyr Arg Thr Leu Cys Gly Gly Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ala Ser Arg Val
            20                  25                  30

Ser Arg Ala Ser Arg Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala Lys Ser Glu
    50                  55                  60

Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg Tyr Pro
65                  70                  75                  80

Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Thr Gln Arg
                85                  90                  95

Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly His Val
            100                 105                 110

Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His Arg Pro
        115                 120                 125

Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His Gly Gly Ala Pro Pro
    130                 135                 140

Glu Met Ala Ser Asn Arg Lys
145                 150


<210> SEQ ID NO 15
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 15

Xaa Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85                  90                  95

Lys Asn Tyr Arg Met
            100
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<210> SEQ ID NO 16
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20 25 30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50 55 60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85 90 95

Lys Asn Tyr Arg Met
            100

<210> SEQ ID NO 17
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20 25 30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50 55 60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85 90 95

Lys Asn Tyr Arg Met
            100

<210> SEQ ID NO 18
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20 25 30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35 40 45

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Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys
85 90 95

Asn Tyr Arg Met
100

<210> SEQ ID NO 19
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
85 90 95

Lys Asn Tyr Arg Met
100

<210> SEQ ID NO 20
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
85 90 95

Lys Asn Tyr Arg Met
100

<210> SEQ ID NO 21
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 21

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
35 40 45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
50 55 60

Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys
85 90 95

Asn Tyr Arg Met
100

<210> SEQ ID NO 22
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
35 40 45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
50 55 60

Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys
85 90 95

Asn Tyr Arg Met
100

<210> SEQ ID NO 23
<211> LENGTH: 99
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
35 40 45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
50 55 60

Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
65 70 75 80

Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys Asn

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                85                  90                  95

Tyr Arg Met


<210> SEQ ID NO 24
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 25
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 26
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<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
85 90 95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
100 105 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 27
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
85 90 95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
100 105 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 28
<211> LENGTH: 142
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 29
<211> LENGTH: 142
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 30
<211> LENGTH: 142
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30
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Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 31
<211> LENGTH: 141
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
65                  70                  75                  80

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
                85                  90                  95

Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu
            100                 105                 110

Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile
        115                 120                 125

Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 32
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60
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Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 33
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 34
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 35
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
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1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 36
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 37
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Ser Thr Phe Glu Glu Arg Lys
```

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100 105

<210> SEQ ID NO 38
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
35 40 45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
50 55 60

Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
85 90 95

Lys Gly Ser Thr Phe Glu Glu Arg Lys
100 105

<210> SEQ ID NO 39
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
35 40 45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
50 55 60

Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
85 90 95

Lys Gly Ser Thr Phe Glu Glu Arg Lys
100 105

<210> SEQ ID NO 40
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

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```
Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 41
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 42
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45
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```
Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala
                85                  90                  95

Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
            100                 105                 110

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
        115                 120                 125

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
    130                 135                 140

Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 43
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 44
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45
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```
Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 45
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Arg Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala
                85                  90                  95

Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
            100                 105                 110

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
        115                 120                 125

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
    130                 135                 140

Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 46
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Ala Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45
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```
Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala
                85                  90                  95

Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
            100                 105                 110

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
        115                 120                 125

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
    130                 135                 140

Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 47
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys
        35                  40                  45

Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys
    50                  55                  60

Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
65                  70                  75                  80

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala Gly
                85                  90                  95

Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His
            100                 105                 110

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

Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu
    130                 135                 140

Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 48
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45
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```
Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85                  90                  95

Lys Asn Tyr Arg Met
            100


<210> SEQ ID NO 49
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 50
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110
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```
Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp Met
    130                 135                 140

Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys
145                 150                 155                 160

Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln
                165                 170                 175

Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu
            180                 185                 190

Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg
        195                 200                 205

His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn
    210                 215                 220

Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro
225                 230                 235                 240

Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly
                245                 250                 255

Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val
            260                 265                 270

Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro
        275                 280                 285

Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro
    290                 295                 300

Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu
305                 310                 315                 320

Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg
                325                 330                 335

Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 51
<211> LENGTH: 347
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp
    130                 135                 140

Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
145                 150                 155                 160

Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu
                165                 170                 175

Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys
            180                 185                 190

Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln
        195                 200                 205

Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr
    210                 215                 220

Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His
225                 230                 235                 240

Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg
                245                 250                 255

Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu
            260                 265                 270

Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln
        275                 280                 285

Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp
    290                 295                 300

Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser
305                 310                 315                 320

Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser
                325                 330                 335

Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 52
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 53
<211> LENGTH: 102
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-continued

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

<400> SEQUENCE: 53

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly
85 90 95

Asn Lys Asn Tyr Arg Met
100

<210> SEQ ID NO 54
<211> LENGTH: 144
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
85 90 95

Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu
100 105 110

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

Arg Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 55
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser

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        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp Met
    130                 135                 140

Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys
145                 150                 155                 160

Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln
                165                 170                 175

Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu
            180                 185                 190

Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg
        195                 200                 205

His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn
    210                 215                 220

Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro
225                 230                 235                 240

Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly
                245                 250                 255

Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val
            260                 265                 270

Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro
        275                 280                 285

Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro
    290                 295                 300

Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu
305                 310                 315                 320

Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg
                325                 330                 335

Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 56
<211> LENGTH: 348
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1               5                   10                  15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
            20                  25                  30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
        35                  40                  45
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```
Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
    50                  55                  60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65                  70                  75                  80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
                85                  90                  95

Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu
            100                 105                 110

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

Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr
    130                 135                 140

Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn
145                 150                 155                 160

Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly
                165                 170                 175

Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys
            180                 185                 190

Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala
        195                 200                 205

Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser
    210                 215                 220

Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
225                 230                 235                 240

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
                245                 250                 255

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
            260                 265                 270

Glu Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr
        275                 280                 285

Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly
    290                 295                 300

Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala
305                 310                 315                 320

Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly
                325                 330                 335

Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 57
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1               5                   10                  15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
            20                  25                  30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
    50                  55                  60
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Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
85 90 95

Arg Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
100 105

<210> SEQ ID NO 58
<211> LENGTH: 102
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly
85 90 95

Asn Lys Asn Tyr Arg Met
100

<210> SEQ ID NO 59
<211> LENGTH: 144
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
85 90 95

Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu
100 105 110

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

Arg Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 60

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<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
85 90 95

Arg Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
100 105

<210> SEQ ID NO 61
<211> LENGTH: 154
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
20 25 30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
50 55 60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65 70 75 80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly
85 90 95

Ser Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro
100 105 110

Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu
115 120 125

Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg
130 135 140

Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
145 150

<210> SEQ ID NO 62
<211> LENGTH: 348
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Gly Pro Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val
1 5 10 15

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```
Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser
            20                  25                  30

Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys
    50                  55                  60

Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys
65                  70                  75                  80

Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln
                85                  90                  95

Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu
            100                 105                 110

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

Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr
    130                 135                 140

Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn
145                 150                 155                 160

Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly
                165                 170                 175

Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys
            180                 185                 190

Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala
        195                 200                 205

Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser
    210                 215                 220

Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
225                 230                 235                 240

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
                245                 250                 255

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
            260                 265                 270

Glu Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr
        275                 280                 285

Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly
    290                 295                 300

Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala
305                 310                 315                 320

Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly
                325                 330                 335

Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 63
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Gly Pro Ala Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30
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```
Ser Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro
65                  70                  75                  80

Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala
                85                  90                  95

Gly Asn Lys Asn Tyr Arg Met
            100


<210> SEQ ID NO 64
<211> LENGTH: 145
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Gly Pro Ala Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro
65                  70                  75                  80

Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser
                85                  90                  95

Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys
            100                 105                 110

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

Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly
    130                 135                 140

Lys
145


<210> SEQ ID NO 65
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Gly Pro Ala Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro
65                  70                  75                  80
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Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser
                85                  90                  95

Gln Arg Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 66
<211> LENGTH: 155
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Gly Pro Ala Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro
65                  70                  75                  80

Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg
                85                  90                  95

Gly Ser Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp
            100                 105                 110

Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser
        115                 120                 125

Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser
    130                 135                 140

Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150                 155


<210> SEQ ID NO 67
<211> LENGTH: 349
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Gly Pro Ala Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro
65                  70                  75                  80

Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser
                85                  90                  95

Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys
            100                 105                 110

Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln
        115                 120                 125
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```
Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His
    130                 135                 140

Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys
145                 150                 155                 160

Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly
                165                 170                 175

Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys
            180                 185                 190

Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg
        195                 200                 205

Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro
    210                 215                 220

Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
225                 230                 235                 240

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
                245                 250                 255

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
            260                 265                 270

Ala Glu Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
        275                 280                 285

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
    290                 295                 300

Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu
305                 310                 315                 320

Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile
                325                 330                 335

Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 68
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85                  90                  95

Lys Asn Tyr Arg Met
            100


<210> SEQ ID NO 69
<211> LENGTH: 143
<212> TYPE: PRT
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-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1 5 10 15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
20 25 30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
35 40 45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
50 55 60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
85 90 95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
100 105 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 70
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1 5 10 15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
20 25 30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
35 40 45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
50 55 60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
85 90 95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
100 105 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
115 120 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
130 135 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145 150

<210> SEQ ID NO 71
<211> LENGTH: 347
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

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Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                  10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp
    130                 135                 140

Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
145                 150                 155                 160

Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu
                165                 170                 175

Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys
            180                 185                 190

Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln
        195                 200                 205

Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr
    210                 215                 220

Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His
225                 230                 235                 240

Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg
                245                 250                 255

Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu
            260                 265                 270

Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln
        275                 280                 285

Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp
    290                 295                 300

Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser
305                 310                 315                 320

Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser
                325                 330                 335

Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 72
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated
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<400> SEQUENCE: 72

Xaa Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1 5 10 15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
20 25 30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
35 40 45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
50 55 60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
85 90 95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
100 105 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
130 135 140

<210> SEQ ID NO 73
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 73

Xaa Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1 5 10 15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
20 25 30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
35 40 45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
50 55 60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65 70 75 80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
85 90 95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
100 105

<210> SEQ ID NO 74
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 74

Xaa Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys

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```
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 75
<211> LENGTH: 347
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 75

Xaa Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1               5                   10                  15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser
            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp
    130                 135                 140

Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
145                 150                 155                 160

Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu
                165                 170                 175

Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys
            180                 185                 190
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```
Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln
        195                 200                 205

Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr
    210                 215                 220

Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His
225                 230                 235                 240

Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg
                245                 250                 255

Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu
            260                 265                 270

Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln
        275                 280                 285

Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp
    290                 295                 300

Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser
305                 310                 315                 320

Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser
                325                 330                 335

Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 76
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 76

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Xaa Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn
                85                  90                  95

Lys Asn Tyr Arg Met
            100


<210> SEQ ID NO 77
<211> LENGTH: 143
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 77
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```
Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Xaa Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 78
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 78

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Xaa Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 79
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 79

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
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-continued

```
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Xaa Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser
                85                  90                  95

Ala Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys
            100                 105                 110

Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln
        115                 120                 125

Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn
    130                 135                 140

Ala Glu Cys Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 80
<211> LENGTH: 347
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (66)..(66)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 80

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Xaa Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly
            100                 105                 110

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

Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp
    130                 135                 140

Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
145                 150                 155                 160

Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu
                165                 170                 175

Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys
            180                 185                 190

Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln
        195                 200                 205
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```
Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr
    210                 215                 220

Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His
225                 230                 235                 240

Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg
                245                 250                 255

Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu
            260                 265                 270

Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln
        275                 280                 285

Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp
    290                 295                 300

Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser
305                 310                 315                 320

Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser
                325                 330                 335

Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
            340                 345


<210> SEQ ID NO 81
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 81

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Glu Val His Leu Lys Xaa Ala Ser Arg Gly Ser Ala Gly Asn Lys
                85                  90                  95

Asn Tyr Arg Met
            100


<210> SEQ ID NO 82
<211> LENGTH: 142
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (136)..(136)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 82

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

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
                85                  90                  95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
            100                 105                 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
        115                 120                 125

Ile Gly Ser Arg Asn Ala Glu Xaa Arg Gly Lys Lys Gly Lys
    130                 135                 140


<210> SEQ ID NO 83
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (146)..(146)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated

<400> SEQUENCE: 83

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1               5                   10                  15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
            20                  25                  30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
        35                  40                  45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
    50                  55                  60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65                  70                  75                  80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Ala Ser Arg Gly Ser Ala
                85                  90                  95

Gly Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr
            100                 105                 110

His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile
        115                 120                 125

Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala
    130                 135                 140

Glu Xaa Arg Gly Lys Lys Gly Lys
145                 150


<210> SEQ ID NO 84
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (340)..(340)
<223> OTHER INFORMATION: Any non-natural amino acid that is pegylated
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<400> SEQUENCE: 84

Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly
1 5 10 15

Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser
20 25 30

Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser
35 40 45

Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala
50 55 60

Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln
65 70 75 80

Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg
85 90 95

Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
100 105 110

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
115 120 125

Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg His Thr Asp Met
130 135 140

Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys
145 150 155 160

Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro Gly Gly Glu Gln
165 170 175

Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu
180 185 190

Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val Arg Ala Gln Arg
195 200 205

His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn
210 215 220

Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro Lys Thr His Pro
225 230 235 240

Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu Gln Ile Arg Gly
245 250 255

Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg Asn Ala Glu Val
260 265 270

Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Tyr Gln Pro
275 280 285

Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys Gly Trp Pro
290 295 300

Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr Glu Ala Ser Leu
305 310 315 320

Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu Ile Gly Ser Arg
325 330 335

Asn Ala Glu Xaa Arg Gly Lys Lys Gly Lys
340 345

<210> SEQ ID NO 85
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 85

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Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Ala Ala Lys Ser Ala
65                  70


<210> SEQ ID NO 86
<211> LENGTH: 61
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 86

Leu Val Asp Ala Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe
1               5                   10                  15

Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr
            20                  25                  30

Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp Leu Arg Arg Leu
        35                  40                  45

Glu Met Tyr Cys Ala Pro Leu Lys Ala Ala Lys Ser Ala
    50                  55                  60


<210> SEQ ID NO 87
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Capra hircus

<400> SEQUENCE: 87

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Thr Lys Ser Ala
65                  70


<210> SEQ ID NO 88
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Ailuropoda melanoleuca

<400> SEQUENCE: 88

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
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    50                  55                  60

Lys Pro Ala Lys Ser Ala
65                  70


<210> SEQ ID NO 89
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Cervus elaphus

<400> SEQUENCE: 89

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Ser Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Thr Lys Ala Ala
65                  70


<210> SEQ ID NO 90
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 90

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
    50                  55                  60

Lys Pro Ala Lys Ala Ala
65                  70


<210> SEQ ID NO 91
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 91

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1               5                   10                  15

Val Cys Gly Pro Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ser Ser Ile Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Val Arg Cys
    50                  55                  60

Lys Pro Thr Lys Ser Ala
65                  70


<210> SEQ ID NO 92
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<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 92

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Pro Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ile Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
50 55 60

Lys Pro Thr Lys Ser Ala
65 70

<210> SEQ ID NO 93
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 93

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Pro Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ile Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
50 55 60

Lys Pro Thr Lys Ala Ala
65 70

<210> SEQ ID NO 94
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Anser anser

<400> SEQUENCE: 94

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ser Arg Arg Leu His His Lys Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Ile
50 55 60

Lys Pro Pro Lys Ser Ala
65 70

<210> SEQ ID NO 95
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Oncorhynchus tshawytscha

<400> SEQUENCE: 95

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe

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```
1               5                   10                  15

Val Cys Gly Glu Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Ser Gly Lys Ala Ala
65                  70


<210> SEQ ID NO 96
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Acipenser ruthenus

<400> SEQUENCE: 96

Gly Ser Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Glu Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Ala Ser Ser Arg Arg Pro His His Arg Gly Ile Val Asn Glu Cys Cys
        35                  40                  45

Phe Gln Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Pro Ala Lys Ala Ser
65                  70


<210> SEQ ID NO 97
<211> LENGTH: 68
<212> TYPE: PRT
<213> ORGANISM: Paralichthys olivaceus

<400> SEQUENCE: 97

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Glu Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Asn Ala Arg Arg Ser Arg Gly Ile Val Asp Glu Cys Cys Phe Gln
        35                  40                  45

Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Ala Lys Thr
    50                  55                  60

Ser Lys Ala Ala
65


<210> SEQ ID NO 98
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Oncorhynchus mykiss

<400> SEQUENCE: 98

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Glu Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
        35                  40                  45
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Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Ser Gly Lys Ala Ala
65                  70


<210> SEQ ID NO 99
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Ictalurus punctatus

<400> SEQUENCE: 99

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Asn Ser Arg Arg Leu His Asn Arg Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Gln Ser Cys Glu Leu Lys Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Ser Gly Lys Ala Pro
65                  70


<210> SEQ ID NO 100
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Cyprinus carpio

<400> SEQUENCE: 100

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Pro Gly Lys Thr Pro
65                  70


<210> SEQ ID NO 101
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Cyprinus carpio

<400> SEQUENCE: 101

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1               5                   10                  15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
            20                  25                  30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
    50                  55                  60

Lys Thr Gly Lys Thr Pro
65                  70
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<210> SEQ ID NO 102
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 102

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
50 55 60

Lys Thr Gly Lys Ser Pro
65 70

<210> SEQ ID NO 103
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Myxocyprinus asiaticus

<400> SEQUENCE: 103

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Pro Ser Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
50 55 60

Lys Pro Gly Lys Ala Pro
65 70

<210> SEQ ID NO 104
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Pimephales promelas

<400> SEQUENCE: 104

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Ala Gly Tyr Gly
20 25 30

Ser Asn Ser Arg Arg Ser Asn Asn Tyr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
50 55 60

Lys Thr Gly Lys Thr Pro
65 70

<210> SEQ ID NO 105
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Carassius auratus

<400> SEQUENCE: 105

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Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Pro Asn Ser Arg Arg Ser His Asn Arg Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Glu Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Val
50 55 60

Lys Pro Gly Lys Thr Pro
65 70

<210> SEQ ID NO 106
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Xenopus laevis

<400> SEQUENCE: 106

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Asn Asn Arg Arg Ser His His Arg Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Asp Phe Arg Arg Leu Glu Met Tyr Cys Ala Pro Ala
50 55 60

Lys Pro Ala Lys Ser Ala
65 70

<210> SEQ ID NO 107
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Xenopus laevis

<400> SEQUENCE: 107

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Thr Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Asn Asn Arg Arg Ser His His Arg Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Gln Ser Cys Asp Phe Arg Arg Leu Glu Met Tyr Cys Ala Pro Ala
50 55 60

Lys Gln Ala Lys Ser Ala
65 70

<210> SEQ ID NO 108
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Monodelphis domestica

<400> SEQUENCE: 108

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Glu Arg Gly Phe Tyr Phe Ser Lys Pro Thr Gly Tyr Gly
20 25 30

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```
Ser Ser Ser Arg Arg Leu His His Thr Gly Ile Val Asp Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Ile
    50                  55                  60

Lys Pro Ala Lys Ser Ala
65                  70


<210> SEQ ID NO 109
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 109

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1               5                   10                  15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Ser Gly Asn Lys Asn
            20                  25                  30

Tyr Arg Met
        35


<210> SEQ ID NO 110
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 110

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Arg Lys
1               5                   10                  15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Ser Gly Asn Lys Asn
            20                  25                  30

Tyr Arg Met
        35


<210> SEQ ID NO 111
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 111

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1               5                   10                  15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Ala Gly Asn Lys Asn
            20                  25                  30

Tyr Arg Met
        35


<210> SEQ ID NO 112
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 112

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1               5                   10                  15

Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys Thr
            20                  25                  30

Tyr
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<210> SEQ ID NO 113
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 113

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 114
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 114

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Ala Gly Asn Lys Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 115
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 115

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Ala Gly Asn Lys Thr
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 116
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 116

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Asn Thr Gly Asn Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 117
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Meleagris gallopavo

<400> SEQUENCE: 117

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Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Leu His Leu Lys Asn Thr Ser Arg Gly Asn Thr Gly Asn Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 118
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Anser anser

<400> SEQUENCE: 118

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Asn Thr Glu Asn
20 25 30

<210> SEQ ID NO 119
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Oncorhynchus tshawytscha

<400> SEQUENCE: 119

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Arg Thr Pro Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

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

<400> SEQUENCE: 120

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Ser Lys Asn Ser Ser Arg Gly Asn Thr Gly Asn Arg Asn
20 25 30

Tyr Arg Ile
35

<210> SEQ ID NO 121
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Perca fluviatilis

<400> SEQUENCE: 121

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Arg Ala Pro Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 122

-continued

<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Paralichthys olivaceus

<400> SEQUENCE: 122

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Arg Ala Pro Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Thr Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 123
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Ictalurus punctatus

<400> SEQUENCE: 123

Arg Ser Val Arg Glu Gln Arg His Thr Asp Thr Pro Lys Thr Pro Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 124
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Cirrhinus molitorella

<400> SEQUENCE: 124

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Ser Pro Lys Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 125
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Cirrhinus molitorella

<400> SEQUENCE: 125

Arg Ser Val Arg Ala Gln Arg His Thr Asp Ser Pro Arg Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Ile
35

<210> SEQ ID NO 126
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Devario aequipinnatus

<400> SEQUENCE: 126

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ile Pro Arg Thr Ala Lys
1 5 10 15

-continued

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 127
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 127

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ile Pro Arg Thr Pro Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 128
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Myxocyprinus asiaticus

<400> SEQUENCE: 128

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ile Pro Arg Thr Pro Lys
1 5 10 15

Asp Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 129
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Barbus barbus

<400> SEQUENCE: 129

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ser Pro Arg Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Ile
35

<210> SEQ ID NO 130
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Pimephales promelas

<400> SEQUENCE: 130

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ile Thr Arg Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Ile Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

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<210> SEQ ID NO 131
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Carassius auratus

<400> SEQUENCE: 131

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Gly Thr Arg Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Met
35

<210> SEQ ID NO 132
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Xenopus laevis

<400> SEQUENCE: 132

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Pro Lys Asn Thr Ser Arg Gly Asn Thr Gly Ser Arg Gly
20 25 30

Phe Arg Met
35

<210> SEQ ID NO 133
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Kuhlia rupestris

<400> SEQUENCE: 133

Arg Ser Leu Arg Ala Gln Arg His Thr Asp Ile Thr Arg Thr Ala Lys
1 5 10 15

Glu Val His Gln Lys Asn Ser Ser Arg Gly Asn Thr Gly Gly Arg Asn
20 25 30

Tyr Arg Ile
35

<210> SEQ ID NO 134
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Xenopus laevis

<400> SEQUENCE: 134

Arg Ser Val Arg Thr Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Pro Lys Asn Thr Ser Arg Gly Asn Thr Gly Ser Arg Gly
20 25 30

Phe Arg Met
35

<210> SEQ ID NO 135
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
majority consensus polypeptide

-continued

<400> SEQUENCE: 135

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Thr Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Gly Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu
35 40 45

<210> SEQ ID NO 136
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 136

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Thr Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu His Lys
35 40

<210> SEQ ID NO 137
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Bos indicus

<400> SEQUENCE: 137

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met Lys Ser Gln Arg Arg Arg
1 5 10 15

Lys Gly Gly Pro Lys Lys Arg Pro Gly Gly Glu Gln Lys Glu
20 25 30

<210> SEQ ID NO 138
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 138

His Ala Gln Gly Ser Glu Gly Lys Pro Ala Arg Gly Gly Gly Glu Gly
1 5 10 15

Arg Pro Ser Ser Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met Lys Ser
20 25 30

Gln Arg Arg Arg Lys Gly Gly Pro Lys Lys Arg Pro Gly Gly Glu Gln
35 40 45

Lys Glu
50

<210> SEQ ID NO 139
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Bubalus bubalis

<400> SEQUENCE: 139

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met Lys Ser Gln Arg Arg Arg
1 5 10 15

Lys Gly Gly Pro Lys Lys His Pro Gly Gly Glu Gln Lys Glu
20 25 30

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<210> SEQ ID NO 140
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 140

Tyr Gln Leu Pro Ser Thr Asn Lys Lys Met Lys Ser Gln Arg Arg Arg
1 5 10 15

Lys Gly Gly Pro Lys Lys His Pro Gly Gly Glu Gln Lys Glu
20 25 30

<210> SEQ ID NO 141
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 141

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Tyr His Pro Pro Ser Thr Thr Lys Arg Met Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu Cys Lys
35 40

<210> SEQ ID NO 142
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 142

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu His Lys
35 40

<210> SEQ ID NO 143
<211> LENGTH: 78
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 143

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Gly Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
35 40 45

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
50 55 60

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys
65 70 75

<210> SEQ ID NO 144
<211> LENGTH: 90
<212> TYPE: PRT
<213> ORGANISM: Macaca mulatta

-continued

<400> SEQUENCE: 144

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Gly Pro Lys Thr His Pro Gly Gly Glu Gln Lys Glu Gly Thr
35 40 45

Glu Ala Ser Leu Gln Ile Arg Gly Lys Lys Lys Glu Gln Arg Arg Glu
50 55 60

Ile Gly Ser Arg Asn Ala Glu Cys Arg Gly Lys Lys Gly Lys Trp Arg
65 70 75 80

Thr Gly Gly Leu Ser Arg Gln Arg Gln Gly
85 90

<210> SEQ ID NO 145
<211> LENGTH: 63
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 145

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Ser Pro Ser Leu Ser Thr Asn Lys Lys Thr Lys Leu Gln Arg Arg Arg
20 25 30

Lys Gly Glu Pro Lys Thr His Pro Glu Gly Glu Gln Glu Glu Val Thr
35 40 45

Glu Ala Thr Arg Lys Ile Arg Gly Pro Arg Glu Lys Arg Leu Gly
50 55 60

<210> SEQ ID NO 146
<211> LENGTH: 63
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 146

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Ser Gln Pro Leu Ser Thr His Lys Lys Arg Lys Leu Gln Arg Arg Arg
20 25 30

Lys Gly Glu Ser Lys Ala His Pro Gly Gly Glu Gln Glu Glu Gly Ala
35 40 45

Glu Ala Thr Gln Lys Ile Arg Gly Asp Arg Glu Arg Arg Pro Ser
50 55 60

<210> SEQ ID NO 147
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 147

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Ser Pro Ser Leu Ser Thr Asn Lys Lys Thr Lys Leu Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu His Lys

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        35                  40


<210> SEQ ID NO 148
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      majority consensus polypeptide

<400> SEQUENCE: 148

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1               5                   10                  15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Thr Lys Ser Gln Arg Arg Arg
            20                  25                  30

Lys Gly Ser Thr Phe Glu Glu His
        35                  40


<210> SEQ ID NO 149
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1               5                   10                  15

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
            20                  25                  30

Gly Ser Thr Phe Glu Glu Arg
        35


<210> SEQ ID NO 150
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 150

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1               5                   10                  15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Thr Lys Ser Gln Arg Arg Arg
            20                  25                  30

Lys Gly Ser Thr Phe Glu Glu His
        35                  40


<210> SEQ ID NO 151
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 151

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1               5                   10                  15

Tyr His Pro Pro Ser Thr Thr Lys Arg Met Lys Ser Gln Arg Arg Arg
            20                  25                  30

Lys Gly Ser Thr Phe Glu Glu Cys
        35                  40


<210> SEQ ID NO 152
<211> LENGTH: 40
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-continued

<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 152

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu His
35 40

<210> SEQ ID NO 153
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 153

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu Arg
35 40

<210> SEQ ID NO 154
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 154

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Ser Pro Ser Leu Ser Thr Asn Lys Lys Thr Lys Leu Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Phe Glu Glu His
35 40

<210> SEQ ID NO 155
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 155

Arg Ser Ile Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys
1 5 10 15

Ser Gln Pro Leu Ser Thr His Lys Lys Arg Lys Leu Gln Arg Arg Arg
20 25 30

Lys Gly Ser Thr Leu Glu Glu His
35 40

<210> SEQ ID NO 156
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
majority consensus polypeptide

<400> SEQUENCE: 156

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```
Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

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

Ser Arg Val Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn
65                  70                  75                  80

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

Gln Ser Ala Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
            100                 105                 110

Arg Arg Gly Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala
        115                 120                 125

Lys Arg His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His
    130                 135                 140

Gly Gly Ala Ser Pro Glu Ala Ser Ser Asn Arg Lys
145                 150                 155


<210> SEQ ID NO 157
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

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

Ser Arg Val Ser Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn
65                  70                  75                  80

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

Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
            100                 105                 110

Arg Arg Gly His Val Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala
        115                 120                 125

Lys Arg His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His
    130                 135                 140

Gly Gly Ala Pro Pro Glu Met Ala Ser Asn Arg Lys
145                 150                 155


<210> SEQ ID NO 158
<211> LENGTH: 157
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 158
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```
Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

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

Ser Arg Val Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn
65                  70                  75                  80

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

Gln Ser Ala Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
            100                 105                 110

Arg Arg Gly Arg Thr Leu Ala Lys Glu Leu Glu Ala Val Arg Glu Ala
        115                 120                 125

Lys Arg His Arg Pro Leu Thr Ala Arg Pro Thr Arg Asp Pro Ala Ala
    130                 135                 140

His Gly Gly Ala Ser Pro Glu Ala Ser Gly His Arg Lys
145                 150                 155


<210> SEQ ID NO 159
<211> LENGTH: 155
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 159

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ser
            20                  25                  30

Ser Arg Ile Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Ala Ser Thr Thr Val Leu Pro Asp Asp
65                  70                  75                  80

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

Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala Phe Leu Arg Ala
            100                 105                 110

Arg Arg Gly Arg Thr Leu Ala Lys Glu Leu Glu Ala Leu Arg Glu Ala
        115                 120                 125

Lys Ser His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala Thr
    130                 135                 140

His Gly Gly Ala Ser Ser Lys Ala Ser Ser Asp
145                 150                 155


<210> SEQ ID NO 160
<211> LENGTH: 155
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 160
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```
Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ser
            20                  25                  30

Ser Arg Ile Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Ala Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Ala Ser Thr Thr Val Leu Pro Asp Asp
65                  70                  75                  80

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

Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala Phe Leu Arg Ala
            100                 105                 110

Arg Arg Gly Arg Thr Leu Ala Lys Glu Leu Glu Ala Leu Arg Glu Ala
        115                 120                 125

Lys Ser His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala Thr
    130                 135                 140

His Gly Gly Ala Ser Ser Glu Ala Ser Ser Asp
145                 150                 155


<210> SEQ ID NO 161
<211> LENGTH: 158
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 161

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

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

Ser Arg Val Thr Arg Arg Ser Ser Arg Gly Ile Val Glu Glu Cys Cys
        35                  40                  45

Phe Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro
    50                  55                  60

Ala Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp
65                  70                  75                  80

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

Lys Gln Ser Ala Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg
            100                 105                 110

Ala Arg Arg Gly Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu
        115                 120                 125

Ala Lys Arg His Arg Pro Leu Ile Ala Leu Pro Thr His Asp Pro Ala
    130                 135                 140

Thr His Gly Gly Ala Ser Pro Glu Ala Ser Gly Asn Gln Lys
145                 150                 155


<210> SEQ ID NO 162
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 162
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```
Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Asp Leu Ser
            20                  25                  30

Arg Pro Ala Ser Arg Val Thr Arg Arg Ser Ser Arg Gly Ile Val Glu
        35                  40                  45

Glu Cys Cys Phe Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys
    50                  55                  60

Ala Thr Pro Ala Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val
65                  70                  75                  80

Leu Pro Asp Asn Phe Pro Arg Tyr Pro Val Gly Lys Phe Phe Gln Tyr
                85                  90                  95

Asp Thr Trp Lys Gln Ser Ala Gln Arg Leu Arg Arg Gly Leu Pro Ala
            100                 105                 110

Leu Leu Arg Ala Arg Arg Gly Arg Met Leu Ala Lys Glu Leu Glu Ala
        115                 120                 125

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

Asp Pro Ala Thr His Gly Gly Ala Ser Pro Glu Ala Ser Gly Asn Gln
145                 150                 155                 160

Lys


<210> SEQ ID NO 163
<211> LENGTH: 170
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 163

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Asp Ala Ala
            20                  25                  30

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

Arg Arg Ser Ser Arg Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys
    50                  55                  60

Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala Lys Ser Glu
65                  70                  75                  80

Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg
                85                  90                  95

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Ala
            100                 105                 110

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
        115                 120                 125

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

Arg Pro Leu Ile Ala Leu Pro Thr His Asp Pro Ala Thr His Gly Gly
145                 150                 155                 160

Ala Ser Pro Glu Ala Ser Gly Asn Gln Lys
                165                 170


<210> SEQ ID NO 164
<211> LENGTH: 164
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-continued

<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 164

Ala Tyr Gly Thr Ala Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Arg Pro Val
20 25 30

Gly Arg Asn Asn Arg Arg Ile Asn Arg Gly Ile Val Glu Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Lys Ser
50 55 60

Val Lys Ser Glu Arg Asp Leu Ser Ala Thr Ser Leu Ala Gly Leu Pro
65 70 75 80

Ala Leu Asn Lys Glu Ser Phe Gln Lys Pro Ser His Ala Lys Tyr Ser
85 90 95

Lys Tyr Asn Val Trp Gln Lys Lys Ser Ser Gln Arg Leu Gln Arg Glu
100 105 110

Val Pro Gly Ile Leu Arg Ala Arg Arg Tyr Arg Trp Gln Ala Glu Gly
115 120 125

Leu Gln Ala Ala Glu Glu Ala Arg Ala Met His Arg Pro Leu Ile Ser
130 135 140

Leu Pro Ser Gln Arg Pro Pro Ala Pro Arg Ala Ser Pro Glu Ala Thr
145 150 155 160

Gly Pro Gln Glu

<210> SEQ ID NO 165
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 165

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

Leu Gln Phe Val Cys Ser Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ser
20 25 30

Ser Arg Ala Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
50 55 60

Lys Ser Glu Arg Asp Val Ser Thr Ser Gln Ala Val Leu Pro Asp Asp
65 70 75 80

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

Gln Ser Ala Gly Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
100 105 110

Arg Arg Gly Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala
115 120 125

Lys Arg His Arg Pro Leu Ile Val Leu Pro Pro Lys Asp Pro Ala His
130 135 140

Gly Gly Ala Ser Ser Glu Met Ser Ser Asn His Gln
145 150 155

-continued

<210> SEQ ID NO 166
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 166

Ala Tyr Gly Pro Gly Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

Leu Gln Phe Val Cys Ser Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ser
20 25 30

Ser Arg Ala Asn Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
35 40 45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
50 55 60

Lys Ser Glu Arg Asp Val Ser Thr Ser Gln Ala Val Leu Pro Asp Asp
65 70 75 80

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

Gln Ser Ala Gly Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
100 105 110

Arg Arg Gly Arg Met Leu Ala Lys Glu Leu Lys Glu Phe Arg Glu Ala
115 120 125

Lys Arg His Arg Pro Leu Ile Val Leu Pro Pro Lys Asp Pro Ala His
130 135 140

Gly Gly Ala Ser Ser Glu Met Ser Ser Asn His Gln
145 150 155

<210> SEQ ID NO 167
<211> LENGTH: 160
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 167

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Lys Ala Ser
20 25 30

Thr Pro Ala Ala Phe Pro Ile Thr Arg Pro Leu Arg Arg Val Gly Gln
35 40 45

Arg Cys Cys Arg Gly Gly Cys Pro Pro Ala Asp Leu Arg Asp Ala Ser
50 55 60

Ala Phe Pro Arg Arg Glu Ser Arg His Leu Leu Thr Ser Pro Phe Pro
65 70 75 80

Ser Gln Asp Asn Phe Pro Arg Tyr Pro Val Gly Lys Phe Phe Gln Tyr
85 90 95

Asp Thr Trp Lys Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala
100 105 110

Leu Leu Arg Ala Arg Arg Gly His Met Leu Ala Lys Glu Leu Glu Ala
115 120 125

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

Asp Pro Ala His Gly Gly Ala Pro Pro Glu Met Ala Ser Asn Arg Lys
145 150 155 160

-continued

<210> SEQ ID NO 168
<211> LENGTH: 167
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 168

Glu Val Ala Ser Ala Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Ala
1 5 10 15

Leu Gln Phe Val Cys Glu Asp Arg Gly Phe Tyr Phe Ser Arg Pro Thr
20 25 30

Ser Arg Ser Asn Ser Arg Arg Ser Gln Asn Arg Gly Ile Val Glu Glu
35 40 45

Cys Cys Phe Ser Ser Cys Asn Leu Ala Leu Leu Glu Gln Tyr Cys Ala
50 55 60

Lys Pro Ala Lys Ser Glu Arg Asp Val Ser Ala Thr Ser Leu Gln Val
65 70 75 80

Ile Pro Val Met Pro Ala Leu Lys Gln Glu Val Pro Arg Lys His Val
85 90 95

Thr Val Lys Tyr Ser Lys Tyr Asp Val Trp Gln Arg Lys Ala Ala Gln
100 105 110

Arg Leu Arg Arg Gly Ile Pro Ala Ile Leu Arg Ala Lys Lys Phe Arg
115 120 125

Arg Gln Ala Glu Arg Ile Lys Ala Gln Glu Gln Leu Leu His His Arg
130 135 140

Pro Leu Ile Thr Leu Pro Ser Lys Leu Pro Pro Ile Leu Leu Pro Thr
145 150 155 160

Glu Asn Tyr Val Ser His Lys
165

<210> SEQ ID NO 169
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 169

Asn Val Thr Ala Gly Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1 5 10 15

Leu Gln Phe Val Cys Gly Glu Asp Gly Phe Tyr Ile Ser Arg Pro Asn
20 25 30

Arg Ser Asn Ser Arg Arg Pro Gln Arg Gly Ile Val Glu Glu Cys Cys
35 40 45

Phe Arg Ser Cys Glu Leu His Leu Leu Gln Gln Tyr Cys Ala Lys Pro
50 55 60

Val Lys Ser Glu Arg Asp Val Ser Ser Thr Ser Leu Gln Val Phe Pro
65 70 75 80

Val Ser Gln Ala Leu His Lys Asp Thr Ile Asn Val Lys Tyr Ser Lys
85 90 95

Tyr Glu Val Trp Gln Gln Lys Ala Ala Gln Arg Leu Arg Arg Gly Val
100 105 110

Pro Ser Ile Leu Leu Ala Arg Lys Phe Arg Arg Gln Met Glu Lys Ile
115 120 125

Gln Asp Glu Glu Gln Thr Ser Phe His Arg Pro Leu Met Thr Leu Pro
130 135 140

Asn Arg Gln Pro Ala Ile Val Pro His Val Gln Ile Ser Thr Ser Arg

-continued

145 150 155 160

Lys

<210> SEQ ID NO 170
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Ala
20 25 30

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
35 40 45

Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His
50 55 60

Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His Gly Gly Ala
65 70 75 80

Ser Pro Glu Ala Ser Ser Asn Arg Lys
85

<210> SEQ ID NO 171
<211> LENGTH: 90
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 171

Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Arg Tyr Asp Thr Trp Lys Gln Ser Ala
20 25 30

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
35 40 45

Arg Thr Leu Ala Lys Glu Leu Glu Ala Val Arg Glu Ala Lys Arg His
50 55 60

Arg Pro Leu Thr Ala Arg Pro Thr Arg Asp Pro Ala Ala His Gly Gly
65 70 75 80

Ala Ser Pro Glu Ala Ser Gly His Arg Lys
85 90

<210> SEQ ID NO 172
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 172

Arg Asp Val Ser Ala Ser Thr Thr Val Leu Pro Asp Asp Val Thr Ala
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Ile Trp Lys Gln Ser Thr
20 25 30

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

Arg Thr Leu Ala Lys Glu Leu Glu Ala Leu Arg Glu Ala Lys Ser His
50 55 60

-continued

Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala Thr His Gly Gly
65 70 75 80

Ala Ser Ser Lys Ala Ser Ser Asp
85

<210> SEQ ID NO 173
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Ovis aries

<400> SEQUENCE: 173

Arg Asp Val Ser Ala Ser Thr Thr Val Leu Pro Asp Asp Phe Thr Ala
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Gln Ser Asp Thr Trp Lys Gln Ser Thr
20 25 30

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

Arg Thr Leu Ala Lys Glu Leu Glu Ala Leu Arg Glu Ala Lys Ser His
50 55 60

Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala Thr His Gly Gly
65 70 75 80

Ala Ser Ser Glu Ala Ser Ser Asp
85

<210> SEQ ID NO 174
<211> LENGTH: 90
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 174

Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg
1 5 10 15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Ala
20 25 30

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
35 40 45

Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His
50 55 60

Arg Pro Leu Ile Ala Leu Pro Thr His Asp Pro Ala Thr His Gly Gly
65 70 75 80

Ala Ser Pro Glu Ala Ser Gly Asn Gln Lys
85 90

<210> SEQ ID NO 175
<211> LENGTH: 96
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 175

Arg Asp Leu Ser Ala Thr Ser Leu Ala Gly Leu Pro Ala Leu Asn Lys
1 5 10 15

Glu Ser Phe Gln Lys Pro Ser His Ala Lys Tyr Ser Lys Tyr Asn Val
20 25 30

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

Leu Arg Ala Arg Arg Tyr Arg Trp Gln Ala Glu Gly Leu Gln Ala Ala

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    50                  55                  60

Glu Glu Ala Arg Ala Met His Arg Pro Leu Ile Ser Leu Pro Ser Gln
65                  70                  75                  80

Arg Pro Pro Ala Pro Arg Ala Ser Pro Glu Ala Thr Gly Pro Gln Glu
                85                  90                  95


<210> SEQ ID NO 176
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 176

Arg Asp Val Ser Thr Ser Gln Ala Val Leu Pro Asp Asp Phe Pro Arg
1               5                   10                  15

Tyr Pro Val Gly Lys Phe Phe Lys Phe Asp Thr Trp Arg Gln Ser Ala
            20                  25                  30

Gly Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
        35                  40                  45

Arg Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His
    50                  55                  60

Arg Pro Leu Ile Val Leu Pro Pro Lys Asp Pro Ala His Gly Gly Ala
65                  70                  75                  80

Ser Ser Glu Met Ser Ser Asn His Gln
                85


<210> SEQ ID NO 177
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 177

Arg Asp Val Ser Thr Ser Gln Ala Val Leu Pro Asp Asp Phe Pro Arg
1               5                   10                  15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Arg Gln Ser Ala
            20                  25                  30

Gly Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
        35                  40                  45

Arg Met Leu Ala Lys Glu Leu Lys Glu Phe Arg Glu Ala Lys Arg His
    50                  55                  60

Arg Pro Leu Ile Val Leu Pro Pro Lys Asp Pro Ala His Gly Gly Ala
65                  70                  75                  80

Ser Ser Glu Met Ser Ser Asn His Gln
                85


<210> SEQ ID NO 178
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 178

Arg His Leu Leu Thr Ser Pro Phe Pro Ser Gln Asp Asn Phe Pro Arg
1               5                   10                  15

Tyr Pro Val Gly Lys Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Thr
            20                  25                  30

Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly
        35                  40                  45
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-continued

His Met Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His
50 55 60

Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His Gly Gly Ala
65 70 75 80

Pro Pro Glu Met Ala Ser Asn Arg Lys
85

<210> SEQ ID NO 179
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 179

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

Leu Lys Gln Glu Val Pro Arg Lys His Val Thr Val Lys Tyr Ser Lys
20 25 30

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

Pro Ala Ile Leu Arg Ala Lys Lys Phe Arg Arg Gln Ala Glu Arg Ile
50 55 60

Lys Ala Gln Glu Gln Leu Leu His His Arg Pro Leu Ile Thr Leu Pro
65 70 75 80

Ser Lys Leu Pro Pro Ile Leu Leu Pro Thr Glu Asn Tyr Val Ser His
85 90 95

Lys

<210> SEQ ID NO 180
<211> LENGTH: 93
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 180

Arg Asp Val Ser Ser Thr Ser Leu Gln Val Phe Pro Val Ser Gln Ala
1 5 10 15

Leu His Lys Asp Thr Ile Asn Val Lys Tyr Ser Lys Tyr Glu Val Trp
20 25 30

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

Leu Ala Arg Lys Phe Arg Arg Gln Met Glu Lys Ile Gln Asp Glu Glu
50 55 60

Gln Thr Ser Phe His Arg Pro Leu Met Thr Leu Pro Asn Arg Gln Pro
65 70 75 80

Ala Ile Val Pro His Val Gln Ile Ser Thr Ser Arg Lys
85 90

<210> SEQ ID NO 181
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Gly Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys
1 5 10 15

Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser

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            20                  25                  30

Ser Arg Ala Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg
        35                  40                  45

Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro
    50                  55                  60

Ala Lys Ser Ala Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr
65                  70                  75                  80

Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg
                85                  90                  95

Arg Lys Gly Ser Thr Phe Glu Glu Arg Lys
            100                 105


<210> SEQ ID NO 182
<211> LENGTH: 156
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Ala Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr
1               5                   10                  15

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

Ser Arg Val Ser Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe
        35                  40                  45

Arg Ser Cys Asp Leu Ala Leu Leu Glu Thr Tyr Cys Ala Thr Pro Ala
    50                  55                  60

Lys Ser Glu Arg Asp Val Ser Thr Pro Pro Thr Val Leu Pro Asp Asn
65                  70                  75                  80

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

Gln Ser Thr Gln Arg Leu Arg Arg Gly Leu Pro Ala Leu Leu Arg Ala
            100                 105                 110

Arg Arg Gly His Val Leu Ala Lys Glu Leu Glu Ala Phe Arg Glu Ala
        115                 120                 125

Lys Arg His Arg Pro Leu Ile Ala Leu Pro Thr Gln Asp Pro Ala His
    130                 135                 140

Gly Gly Ala Pro Pro Glu Met Ala Ser Asn Arg Lys
145                 150                 155


<210> SEQ ID NO 183
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      6xHis tag

<400> SEQUENCE: 183

His His His His His His
1               5


<210> SEQ ID NO 184
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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-continued

majority consensus peptide

<400> SEQUENCE: 184

Arg Ser Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Ala Gln Lys
1 5 10 15

Glu Val His Leu Lys Asn Thr Ser Arg Gly Ser Thr Gly Asn Lys Asn
20 25 30

Tyr Arg Met
35

What is claimed:

1. A polypeptide comprising the sequence of any one of SEQ ID NO: 8-84.

2. A polypeptide of claim **1**, which is pegylated.

3. A polypeptide of claim **1**, which is glycosylated.

4. A polynucleotide encoding a polypeptide of claim **1**.

5. A method of treating a musculoskeletal disease, diabetes, neuronal cell death, or anemia, the method comprising the step of administering a therapeutically effective amount of a polypeptide comprising the sequence of any one of SEQ ID NO: 8-84 to a subject in need thereof.

6. The method of claim **5**, wherein the polypeptide is pegylated.

7. The method of claim **5**, wherein the polypeptide is glycosylated.

8. The method of claim **5**, wherein the musculoskeletal disease is muscle atrophy.

9. The method of claim **8**, wherein the muscle atrophy is the result of burn, injury, or a chronic obstructive pulmonary disease.

10. A method of treating a musculoskeletal disease, the method comprising administering a therapeutically effective amount of a polypeptide of claim **1** to a subject in need thereof.

11. The method of claim **10**, wherein the musculoskeletal disease is muscle atrophy.

12. The method of claim **11**, wherein the muscle atrophy is the result of burn, injury, or a chronic obstructive pulmonary disease.

13. The method of claim **10**, wherein the polypeptide is pegylated.

14. The method of claim **10**, wherein the polypeptide is glycosylated.

15. A method of increasing muscle mass in a subject, the method comprising the step of:

Administering to the subject a therapeutically effective amount of a polypeptide comprising the sequence of any one of SEQ ID NO: 8-84.

16. The method of claim **15**, wherein the polypeptide is pegylated.

17. The method of claim **15**, wherein the polypeptide is glycosylated.

* * * * *