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(54) Title: C-MET KINASE BINDING PROTEINS

(57) Abstract: Polypeptides comprising monomer domains that bind to c-MET, or portions thereof, are provided.

C-MET KINASE BINDING PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

[01] This application is a continuation-in-part of U.S. Patent Application No. 10/957,351, filed September 30, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/871,602, filed June 17, the disclosures of each of which are incorporated by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[02] Hepatocyte Growth Factor/Scatter Factor (HGF/SF) is a mesenchyme-derived pleiotropic factor, which regulates cell growth, cell motility, and morphogenesis of various types of cells and mediates epithelial-mesenchymal interactions responsible for morphogenic tissue interactions during embryonic development and organogenesis. Although HGF was originally identified as a potent mitogen for hepatocytes, it has also been identified as an angiogenic growth factor.

[03] Met was first identified in the 1980s as an oncogene and is the receptor for HGF. The proto-oncogene c-MET, was found to encode a receptor tyrosine kinase. In response to HGF treatment a range of activities are observed: phosphorylation of receptor, docking of signaling intermediates Gab-1/Grb2, culminating in activation of kinases such as PI3K, ERK1 and 2, and AKT. These activities aid in cell growth, survival, migration, and neovascularisation.

[04] Inappropriate expression or signaling of the receptor tyrosine kinase Met and its ligand Hepatocyte Growth Factor/Scatter Factor (HGF/SF) is associated with an aggressive phenotype and poor clinical prognosis for a wide variety of solid human tumors.

[05] Four lines of evidence cement the case for a role of c-MET in cancer:

[06] First, mouse and human cell lines that ectopically overexpress HGF and/or Met become tumorigenic and metastatic in athymic nude mice. Secondly, downregulation of Met or HGF expression in human tumour cells decreases their tumorigenic potential. Mouse models that express the receptor or ligand as a transgene develop various types of tumour and metastatic tumors. Third, a large number of studies show that HGF and/or Met are frequently expressed in carcinomas, in other types of human solid tumours and in their metastases, and that HGF and/or Met over- or misexpression often correlates with poor prognosis. Fourth, unequivocal evidence that implicates Met in human cancer is provided by the activating mutations that have been discovered in both sporadic and inherited forms of human renal papillary carcinomas.

BRIEF SUMMARY OF THE INVENTION

According to a first aspect, the present invention provides an isolated polypeptide comprising at least one monomer domain that binds to c-MET, wherein the at least one monomer domain comprises a sequence selected from the group consisting of (i) SEQ ID NO:7, (ii) SEQ ID NO:12, (iii) and at least amino acids 1-34 of SEQ ID NO:14 and (iv) a sequence that is at least 95% identical to a sequence defined by any of (i), (ii) or (iii), as defined herein:

Cxxx[EQ]FxCxSTxRC[IV]xxxWxCDGDNDCEDxSDEx (SEQ ID NO:7),
wherein the first x is an amino acid chosen from A, L, E, R, P, and Q,
the second x is an amino acid chosen from P, A, and S,
the third x is an amino acid chosen from S, N, and G,
the fourth x is an amino acid chosen from T, Q, and K,
the fifth x is an amino acid chosen from N, R, S, and H,
the sixth x is an amino acid chosen from G, N, D, and E,
the seventh x is an amino acid chosen from P and S,
the eighth x is an amino acid chosen from Q, L, and A,
the ninth x is an amino acid chosen from E, T, Q, A, S, G, and D .
the tenth x is an amino acid chosen from V and L,
the eleventh x is an amino acid chosen from S and G,
the twelfth x is an amino acid chosen from A, S, and K,
and amino acids in brackets are alternative amino acids at a single position;
Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO:12),
wherein the first x is an amino acid chosen from A, E, V, R, L, P, and Q,

the second x is an amino acid chosen from A, S, P, T, and L,
the third x is an amino acid chosen from D, S, N, and G,
the fourth x is an amino acid chosen from Q, T, and R,
the fifth x is an amino acid chosen from N, H, and R,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from V, Q, L, R, A, and G,
the eighth x is an amino acid chosen from S, E, D, Q, and A,
the ninth x is any amino acid,
the tenth x is an amino acid chosen from D and H,
the eleventh x is an amino acid chosen from V and D,
the twelfth x is an amino acid chosen from S and G,
the thirteenth x is an amino acid chosen from A, T, S, and E,
and amino acids in brackets are alternative amino acids at a single position; and at least amino acids 1-34 of
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid,
the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position.

According to a second aspect, the present invention provides an isolated polypeptide comprising at least one monomer domain that binds to c-MET, wherein the at least one monomer domain comprises the amino acids of SEQ ID NO:14 as defined herein:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,
the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,

the twenty-first x is an amino acid chosen from S, H, G and N,

and amino acids in brackets are alternative amino acids at a single position or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein.

According to a third aspect, the present invention provides an isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein one monomer domain comprises a sequence selected from the group consisting of

(1) Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO:12),

wherein the first x is an amino acid chosen from A, E, V, R, L, P, and Q,

the second x is an amino acid chosen from A, S, P, T, and L,

the third x is an amino acid chosen from D, S, N, and G,

the fourth x is an amino acid chosen from Q, T, and R,

the fifth x is an amino acid chosen from N, H, and R,

the sixth x is any amino acid, the seventh x is an amino acid chosen from V, Q, L, R, A, and G,

the eighth x is an amino acid chosen from S, E, D, Q, and A,

the ninth x is any amino acid,

the tenth x is an amino acid chosen from D and H,

the eleventh x is an amino acid chosen from V and D,

the twelfth x is an amino acid chosen from S and G,

the thirteenth x is an amino acid chosen from A, T, S, and E,

and amino acids in brackets are alternative amino acids at a single position, and

(ii) a sequence that is at least 95% identical to a sequence defined by (i);

another monomer domain comprises a sequence selected from the group consisting of

(iii) at least amino acids 1-34 of:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),

wherein the first x is an amino acid chosen from P, Q, V, L, and E,

the second x is an amino acid chosen from A, S, and P,

the third x is an amino acid chosen from G, S, N, and D, the fourth x is an amino acid chosen from Q, R, T, and M,

the fifth x is an amino acid chosen from any amino acid,

the sixth x is any amino acid,

the seventh x is an amino acid chosen from T, G, and N,

the eighth x is any amino acid,

the ninth x is an amino acid chosen from R and Q,

the tenth x is an amino acid chosen from P and S,

the eleventh x is any amino acid,

the twelfth x is an amino acid chosen from T, P, N, D, A, and H,

the thirteenth x is an amino acid chosen from L, G, and V,

the fourteenth x is an amino acid chosen from D, V, and E,

the fifteenth x is an amino acid chosen from E and G,

the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,

the eighteenth x is any amino acid,

the nineteenth x is any amino acid,

the twentieth x is any amino acid,

the twenty-first x is any amino acid,

and amino acids in brackets are alternative amino acids at a single position, and

(iv) a sequence that is at least 95% identical to a sequence defined by (iii); and yet another monomer domain comprises a sequence selected from the group consisting of

(v) at least amino acids 1-34 of:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),

wherein the first x is an amino acid chosen from P, Q, V, L, and E,

the second x is an amino acid chosen from A, S, and P,

the third x is an amino acid chosen from G, S, N, and D,

the fourth x is an amino acid chosen from Q, R, T, and M,

the fifth x is an amino acid chosen from any amino acid,

the sixth x is any amino acid,

the seventh x is an amino acid chosen from T, G, and N,

the eighth x is any amino acid, the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid,
the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position; and
(vi) a sequence that is at least 95% identical to a sequence defined by (v).

According to a fourth aspect, the present invention provides an isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein one monomer domain comprises at least amino acids 1-38 of: CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHT (SEQ ID NO:389); another monomer domain comprises a sequence selected from the group consisting of

(i) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid,

the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid, the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position,
and (ii) a sequence that is at least 95% identical to a sequence defined by (i); and yet another monomer domain comprises a sequence selected from the group consisting of (iii) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14), wherein the first x is an amino acid chosen from P, Q, V, L, and E, the second x is an amino acid chosen from A, S, and P, the third x is an amino acid chosen from G, S, N, and D, the fourth x is an amino acid chosen from Q, R, T, and M, the fifth x is an amino acid chosen from any amino acid, the sixth x is any amino acid, the seventh x is an amino acid chosen from T, G, and N, the eighth x is any amino acid, the ninth x is an amino acid chosen from R and Q, the tenth x is an amino acid chosen from P and S, the eleventh x is any amino acid, the twelfth x is an amino acid chosen from T, P, N, D, A, and H, the thirteenth x is an amino acid chosen from L, G, and V, the fourteenth x is an amino acid chosen from D, V, and E, the fifteenth x is an amino acid chosen from E and G, the sixteenth x is an amino acid chosen from G and S, the seventeenth x is any amino acid, the eighteenth x is any amino acid, the nineteenth x is any amino acid, the twentieth x is any amino acid, the twenty-first x is any amino acid, and amino acids in brackets

are alternative amino acids at a single position; and (iv) a sequence that is at least 95% identical to a sequence defined by (iii).

According to a fifth aspect, the present invention provides an isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein each of the at least three monomer domains comprises the amino acids of the following sequence

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),

wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,
the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,
the twenty-first x is an amino acid chosen from S, H, G and N,
and amino acids in brackets are alternative amino acids at a single position,

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein.

According to a sixth aspect, the present invention provides an isolated polypeptide comprising at least two monomer domains that bind to c-MET, wherein one monomer domain comprises the amino acids of the following sequence:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),

wherein the first x is an amino acid chosen from P, Q, V, L and E,

the second x is an amino acid chosen from A, S and P,

the third x is an amino acid chosen from G, S, N, and D,

the fourth x is an amino acid chosen from Q, R, T and M,

the fifth x is an amino acid chosen from any amino acid,

the sixth x is any amino acid,

the seventh x is an amino acid chosen from T, G and N,

the eighth x is any amino acid,

the ninth x is an amino acid chosen from R and Q,

the tenth x is an amino acid chosen from P and S,

the eleventh x is any amino acid,

the twelfth x is an amino acid chosen from T, P, N, D, A and H,

the thirteenth x is an amino acid chosen from L, G and V,

the fourteenth x is an amino acid chosen from D, V and E,

the fifteenth x is an amino acid chosen from E and G,

the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,

the eighteenth x is any amino acid,

the nineteenth x is P or no amino acid,

the twentieth x is A or no amino acid,

the twenty-first x is an amino acid chosen from S, H, G and N,

and amino acids in brackets are alternative amino acids at a single position,

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein; and

another monomer domain comprising the amino acids of the following sequence:

CxxxⅹEQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,
the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,
the twenty-first x is an amino acid chosen from S, H, G and N,
and amino acids in brackets are alternative amino acids at a single position,
or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein; and

further comprising the following sequence:
CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHT (SEQ ID NO:389).

According to a seventh aspect, the present invention provides an isolated polypeptide that binds to c-MET, wherein the polypeptide comprises the amino acids of

SEQ ID NO:389 or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:389.

According to an eighth aspect, the present invention provides an isolated polypeptide that binds to c-MET, wherein the polypeptide comprises amino acids 1-38 of SEQ ID NO:389 or a sequence that is at least 95% identical to amino acids 1-38 of SEQ ID NO:389.

According to a ninth aspect, the present invention provides an isolated polynucleotide encoding the polypeptide of any one of the first to eighth aspects.

According to a tenth aspect, the present invention provides a method of treating cancer comprising administering the polypeptide of any one of the first to eighth aspects to a subject, wherein the subject suffers from a cancer that expresses c-MET and/or HGF.

[07] The present invention provides a polypeptide comprising a monomer domain that binds to c-MET. In some embodiments, the monomer domain:

is a non-naturally-occurring monomer domain consisting of 30 to 50 amino acids; comprises at least one disulfide bond; and optionally, binds to an ion.

[08] In some embodiments, the monomer domain is an LDL receptor class A monomer domain. In some embodiments, the monomer domain is an LDL receptor class A monomer domain comprising the following sequence:

EFXCXNGXCIPXXWXCDGXDDCGDXSDE (SEQ ID NO: 17),

wherein X is any amino acid.

[09] In some embodiments, the polypeptide comprises at least one and no more than six monomer domains that bind c-MET. In some embodiments, the polypeptide comprises at least two monomer domains that bind c-MET.

[10] In some embodiments, the polypeptide further comprises a second monomer domain, wherein the second monomer domain has a binding specificity for a blood factor, thereby increasing the serum half-life of the polypeptide when the polypeptide is injected into an animal compared to the serum half-life of a polypeptide lacking the blood factor-binding monomer domain. In some embodiments, the blood factor is serum albumin, an immunoglobulin or an erythrocyte. In some embodiments, the second monomer domain binds to immunoglobulin (IgG) and the second monomer domain is an LDL receptor class A monomer domain comprising a sequence selected from the following:

CXSSGRCIPXXWVCDGXXDCRDXSDE (SEQ ID NO: 2), and

CXSSGRCIPXXWLCDGXXDCRDXSDE (SEQ ID NO: 3),

wherein X is any amino acid.

[11] In some embodiments, the second monomer domain binds to immunoglobulin (IgG) and the second monomer domain is an LDL receptor class A monomer domain comprising the following sequence:

[EQ]FXCRX[ST]XRC[IV]XXXW[ILV]CDGXXDCXD[DN]SDE (SEQ ID NO: 4),

wherein X is any amino acid and amino acids in brackets are alternative amino acids at a single position. In some embodiments, the second monomer domain comprises

CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENCSAPASEPPGSL

(SEQ ID NO: 5). In some embodiments, the second monomer domain comprises CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENC (SEQ ID NO: 6)

[12] In some embodiments, binding of at least one monomer domain to c-MET inhibits dimerization of Met. In some embodiments, at least one monomer domain binds to the Sema domain of c-MET, thereby preventing binding of Met ligands to c-MET.

[13] In some embodiments, the polypeptide comprises at least one and no more than six monomer domains. In some embodiments, the polypeptide comprises at least two monomer domains and the monomer domains are linked by a linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is between 4 to 12 amino acids long.

[14] In some embodiments, the monomer domains are each between 35 to 45 amino acids.

[15] In some embodiments, each monomer domain comprises two disulfide bonds. In some embodiments, each monomer domain comprises three disulfide bonds.

[16] In some embodiments, the ion is a metal ion. In some embodiments, the ion is a calcium ion.

[17] In some embodiments, at least one of the monomer domains is derived from a LDL-receptor class A domain. In some embodiments, at least one of the monomer domains is derived from an EGF-like domain.

[18] In some embodiments, the monomer comprises an amino acid sequence in which at least 10% of the amino acids in the sequence are cysteine; and/or at least 25% of the amino acids are non-naturally-occurring amino acids.

[19] The present invention also provides methods for identifying a polypeptide that binds to c-MET. In some embodiments, the method comprises,

screening a library of polypeptides for affinity to c-MET; and
selecting a polypeptide comprising at least one monomer domain that binds to c-MET, wherein the monomer domain:
is a non-naturally-occurring monomer domain;
comprises at least one disulfide bond; and
binds to an ion.

[20] In some embodiments, the selected polypeptide comprises a monomer domain comprising any of the following:

Cxxx[EQ]FxCxSTxRC[IV]xxxWxCDGDNDCEDxSDEx (SEQ ID NO: 7)

Cxxxx[EQ]FECxSTxRC[IV]xxxWxCDGxNDCEDxSDEx (SEQ ID NO: 8)

Cxxxx[EQ]FxCxSTxRC[ILV]PxxWxCDGxxDCEDxSDExx (SEQ ID NO: 9)

Cxxx[EQ]FQCxSTxRC[IV]PxxWxCDGxNDCEDSSDExxC (SEQ ID NO: 10)

Cxxxx[EQ]FxCxxxxxC[ILV]xxxxxxxxxxDCxDxSDEx (SEQ ID NO: 11)

Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO: 12)

Cxxxx[EQ]FxCxSTxRC[ILV]xxxWxCxxxxDCxDxSDxxxxxCx (SEQ ID NO: 13)

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO: 14)

Cxxxx[EQ]FxCxSTxRC[ILV]PxxWxCxGxxDCxDxSDEx (SEQ ID NO: 15)

Cxxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxxDCxDxSDEx (SEQ ID NO: 16)

EFXCXNGXCIPXXWXCDGXDDCGDXSDE (SEQ ID NO: 17).

[21] In some embodiments, the selecting step comprises selecting a polypeptide that reduces HGF-mediated cell proliferation and/or migration. In some embodiments, the method further comprises selecting a polypeptide that inhibits tumor growth in an animal.

[22] In some embodiments, the monomer domain comprises an amino acid sequence in which at least 10% of the amino acids in the sequence are cysteine; and/or at least 25% of the amino acids are non-naturally-occurring amino acids.

[23] In some embodiments, the method further comprises

linking the monomer domain in the selected polypeptide to a second monomer domain to form a library of multimers, each multimer comprising at least two monomer domains;

screening the library of multimers for the ability to bind to c-MET; and

selecting a multimer that binds c-MET.

[24] In some embodiments, the method further comprises

linking the monomer domain in the selected polypeptide to a second monomer domain to form a library of multimers, each multimer comprising at least two monomer domains;

screening the library of multimers for the ability to bind to a target molecule other than the c-MET; and

selecting a multimer that binds to the target molecule.

[25] In some embodiments, the method further comprises a step of mutating at least one monomer domain, thereby providing a library comprising mutated monomer domains.

[26] In some embodiments, the library of monomer domains is expressed as a phage display, ribosome display or cell surface display.

[27] In some embodiments, the polypeptide comprises at least two monomer domains and the monomer domains are linked by a linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is between 4 to 12 amino acids long.

[28] In some embodiments, the monomer domains are each between 35 to 45 amino acids.

[29] In some embodiments, each monomer domain comprises two disulfide bonds. In some embodiments, each monomer domain comprises three disulfide bonds.

[30] In some embodiments, the ion is a metal ion. In some embodiments, the ion is a calcium ion.

[31] In some embodiments, at least one of the monomer domains is derived from a LDL-receptor class A domain. In some embodiments, at least one of the monomer domains is derived from an EGF-like domain.

[32] In some embodiments, the monomer domain comprises an amino acid sequence in which at least 10% of the amino acids in the sequence are cysteine; and/or at least 25% of the amino acids are non-naturally-occurring amino acids.

[33] The present invention also provides polynucleotides encoding a polypeptide comprising a monomer domain that binds to c-MET, wherein the monomer domain:

is a non-naturally-occurring monomer domain consisting of 30 to 50 amino acids;

comprises at least one disulfide bond.

The present invention also provides

[34] A polypeptide comprising a monomer domain that binds to immunoglobulin-G (IgG), wherein the monomer domain is an LDL receptor class A monomer domain comprising sequence selected from the following:

CXSSGRCIPXXWVCDGXXDCRDXSDE (SEQ ID NO: 2),

CXSSGRCIPXXWLCDGXXDCRDXSDE (SEQ ID NO: 3), and

[EQ]FXCRX[ST]XRC[IV]XXXW[ILV]CDGXXDCXD[DN]SDE (SEQ ID NO: 4)
wherein X is any amino acid and amino acids in brackets are alternative amino acids at a single position; and
wherein the polypeptide has an increased serum half-life when the polypeptide is injected into an animal compared to the serum half-life of a polypeptide lacking the monomer domain that binds to IgG.

[35] In some embodiments, the monomer domain comprises CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENCSAPASEPPGSL (SEQ ID NO: 5). In some embodiments, the monomer domain comprises CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENC (SEQ ID NO: 6).

[36] In some embodiments, the polypeptide comprises a second monomer domain with binding specificity for a molecule other than IgG, wherein the second monomer domain:
has between 30-100 amino acids;
is a non-naturally-occurring monomer domain;
comprises at least one disulfide bond.

[37] In some embodiments, the second monomer domain is a non-naturally-occuring LDL-receptor class A domain.

[38] The present invention also provides polynucleotides that encode the polypeptides as described above.

DEFINITIONS

[39] Unless otherwise indicated, the following definitions supplant those in the art.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[40] "Met" also referred to as "c-MET," refers to the Hepatocyte Growth Factor/Scatter Factor (HGF/SF)-binding receptor tyrosine kinase. In response to HGF treatment a range of activities are observed: phosphorylation of receptor, docking of signaling intermediates Gab-1/Grb2, culminating in activation of kinases such as PI3K, ERK1 and 2, and AKT. These activities aid in cell growth, survival, migration, and neovascularisation. *See, e.g.*, Birchmeier *et al.*, *Mol. Cell Biol.* 4:915-925 (2003). The amino acid sequence of Met is known and is displayed in SEQ ID NO:1. *See, e.g.*, Park *et al.*, *Proc. Natl. Acad. Sci. USA* 84(18):6379 (1987).

[41] The terms "monomer domain" or "monomer" are used interchangeably and herein refer to a discrete region found in a protein or polypeptide. A monomer domain forms a native three-dimensional structure in solution in the absence of flanking native amino acid sequences. Monomer domains of the invention will often bind to a target molecule. For example, a polypeptide that forms a three-dimensional structure that binds to a target molecule is a monomer domain. As used herein, the term "monomer domain" does not encompass the complementarity determining region (CDR) of an antibody.

[42] The term "loop" refers to that portion of a monomer domain that is typically exposed to the environment by the assembly of the scaffold structure of the monomer domain protein, and which is involved in target binding. The present invention provides three types of loops that are identified by specific features, such as, potential for disulfide bonding, bridging between secondary protein structures, and molecular dynamics (i.e., flexibility). The three types of loop sequences are a cysteine-defined loop sequence, a structure-defined loop sequence, and a B-factor-defined loop sequence.

[43] As used herein, the term "cysteine-defined loop sequence" refers to a subsequence of a naturally occurring monomer domain-encoding sequence that is bound at each end by a cysteine residue that is conserved with respect to at least one other naturally occurring monomer domain of the same family. Cysteine-defined loop sequences are identified by multiple sequence alignment of the naturally occurring monomer domains, followed by sequence analysis to identify conserved cysteine residues. The sequence between each consecutive pair of conserved cysteine residues is a cysteine-defined loop sequence. The cysteine-defined loop sequence does not include the cysteine residues adjacent to each terminus. Monomer domains having cysteine-defined loop sequences include the LDL receptor A-domains, EGF-like domains, sushi domains, Fibronectin type 1 domains, and the like. Thus, for example, in the case of LDL receptor A-domains represented by the consensus sequence, $CX_6CX_4CX_6CX_5CX_8C$ (SEQ ID NO: 18), wherein X_6, X_4, X_5, and X_8 each represent a cysteine-defined loop sequence comprising the designated number of amino acids.

[44] As used herein, the term "structure-defined loop sequence" refers to a subsequence of a monomer-domain encoding sequence that is bound at each end to subsequences that each form a secondary structure. Secondary structures for proteins with known three dimensional structures are identified in accordance with the algorithm STRIDE for assigning protein secondary structure as described in Frishman, D. and Argos, P. (1995) "Knowledge-based secondary structure assignment," Proteins, 23(4):566-79 (see also //hgmp.mrc.ac.uk/Registered/Option/stride.html at the World Wide Web). Secondary structures for proteins with unknown or uncharacterized three dimensional structures are identified in accordance with the algorithm described in Jones, D.T. (1999), "Protein secondary structure prediction based on position-specific scoring matrices," J. Mol. Biol., 292:195-202 (see also McGuffin, L.J., Bryson, K., Jones, D.T. (2000) "The PSIPRED protein structure prediction server," Bioinformatics, 16:404-405, and //bioinf.cs.ucl.ac.uk/psipred/ at the World Wide Web). Secondary structures include, for example, pleated sheets, helices, and the like. Examples of monomer domains having structure-defined loop sequences are the C2 domains, Ig domains, Factor 5/8 C domains, Fibronectin type 3 domains, and the like.

[45] The term "B-factor-defined loop sequence" refers to a subsequence of at least three amino acid residues of a monomer-domain encoding sequence in which the B-factors for the alpha carbons in the B-factor-defined loop are among the 25% highest alpha carbon B factors in the entire monomer domain. Typically the average alpha-carbon B-factor for the subsequence is at least about 65. As used herein, the term "B-factor" (or "temperature factor" or "Debye-Waller factor") is derived from X-ray scattering data. The B-factor is a factor that can be applied to the X-ray scattering term for each atom, or for groups of atoms, that describes the degree to which electron density is spread out B-factors employed in the practice of the present invention may be either isotropic or anisotropic. The term "average alpha-carbon B-factor" refers to:

$$(\sum_{i=1}^{n} \text{B-factor}_{C\alpha i}) / n$$

where n corresponds to the number of residues in the loop, and is at least 3, and $\text{B-factor}_{C\alpha i}$ is the B-factor for the alpha carbon of amino acid residue i of the loop.

[46] The term “multimer” is used herein to indicate a polypeptide comprising at least two monomer domains. The separate monomer domains in a multimer can be joined together by a linker. A multimer is also known as a combinatorial mosaic protein or a recombinant mosaic protein.

[47] The term “family” and “family class” are used interchangeably to indicate proteins that are grouped together based on similarities in their amino acid sequences. These similar sequences are generally conserved because they are important for the function of the protein and/or the maintenance of the three dimensional structure of the protein. Examples of such families include the LDL Receptor A-domain family, the EGF-like family, and the like. Additionally, related sequences that bind to the same target molecule can be divided into families based on common sequence motifs.

[48] The term “ligand,” also referred to herein as a “target molecule,” encompasses a wide variety of substances and molecules, which range from simple molecules to complex targets. Target molecules can be proteins, nucleic acids, lipids, carbohydrates or any other molecule capable of recognition by a polypeptide domain. For example, a target molecule can include a chemical compound (i.e., non-biological compound such as, e.g., an organic molecule, an inorganic molecule, or a molecule having both organic and inorganic atoms, but excluding polynucleotides and proteins), a mixture of chemical compounds, an array of spatially localized compounds, a biological macromolecule, a bacteriophage peptide display library, a polysome peptide display library, an extract made from a biological materials such as bacteria, plants, fungi, or animal (e.g., mammalian) cells or tissue, a protein, a toxin, a peptide hormone, a cell, a virus, or the like. Other target molecules include, e.g., a whole cell, a whole tissue, a mixture of related or unrelated proteins, a mixture of viruses or bacterial strains or the like. Target molecules can also be defined by inclusion in screening assays described herein or by enhancing or inhibiting a specific protein interaction (i.e., an agent that selectively inhibits a binding interaction between two predetermined polypeptides).

[49] The term “linker” is used herein to indicate a moiety or group of moieties that joins or connects two or more discrete separate monomer domains. The linker allows the discrete separate monomer domains to remain separate when joined together in a multimer. The linker moiety is typically a substantially linear moiety. Suitable linkers include polypeptides, polynucleic acids, peptide nucleic acids and the like. Suitable linkers also include optionally substituted alkylene moieties that have one or more oxygen atoms incorporated in the carbon backbone. Typically, the molecular weight of the linker is less than about 2000 daltons. More typically, the molecular weight of the linker is less than about 1500 daltons and usually is less than about 1000 daltons. The linker can be small enough to allow the discrete separate monomer domains to cooperate, e.g., where each of the discrete separate monomer domains in a multimer binds to the same target molecule via separate binding sites. Exemplary linkers include a polynucleotide encoding a polypeptide, or a polypeptide of amino acids or other non-naturally occurring moieties. The linker can be a portion of a native sequence, a variant thereof, or a synthetic sequence. Linkers can comprise, e.g., naturally occurring, non-naturally occurring amino acids, or a combination of both.

[50] The term “separate” is used herein to indicate a property of a moiety that is independent and remains independent even when complexed with other moieties, including for example, other monomer domains. A monomer domain is a separate domain in a protein because it has an independent property that can be recognized and separated from the protein. For instance, the ligand binding ability of the A-domain in the LDLR is an independent property. Other examples of separate include the separate monomer domains in a multimer that remain separate independent domains even when complexed or joined together in the multimer by a linker. Another example of a separate property is the separate binding sites in a multimer for a ligand.

[51] As used herein, "directed evolution" refers to a process by which polynucleotide variants are generated, expressed, and screened for an activity (e.g., a polypeptide with binding activity) in a recursive process. One or more candidates in the screen are selected and the process is then repeated using polynucleotides that encode the selected candidates to generate new variants. Directed evolution involves at least two rounds of variation generation and can include 3, 4, 5, 10, 20 or more rounds of variation generation and selection. Variation can be generated by any method known to those of skill in the art, including, e.g., by error-prone PCR, gene recombination, chemical mutagenesis and the like.

[52] The term "shuffling" is used herein to indicate recombination between non-identical sequences. In some embodiments, shuffling can include crossover via homologous recombination or via non-homologous recombination, such as via cre/lox and/or flp/frt systems. Shuffling can be carried out by employing a variety of different formats, including for example, *in vitro* and *in vivo* shuffling formats, in silico shuffling formats, shuffling formats that utilize either double-stranded or single-stranded templates, primer based shuffling formats, nucleic acid fragmentation-based shuffling formats, and oligonucleotide-mediated shuffling formats, all of which are based on recombination events between non-identical sequences and are described in more detail or referenced herein below, as well as other similar recombination-based formats. The term "random" as used herein refers to a polynucleotide sequence or an amino acid sequence composed of two or more amino acids and constructed by a stochastic or random process. The random polynucleotide sequence or amino acid sequence can include framework or scaffolding motifs, which can comprise invariant sequences.

[53] The term "pseudorandom" as used herein refers to a set of sequences, polynucleotide or polypeptide, that have limited variability, so that the degree of residue variability at some positions is limited, but any pseudorandom position is allowed at least some degree of residue variation.

[54] The terms "polypeptide," "peptide," and "protein" are used herein interchangeably to refer to an amino acid sequence of two or more amino acids.

[55] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. "Amino acid mimetics" refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[56] "Conservative amino acid substitution" refers to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, and asparagine-glutamine.

[57] The phrase "nucleic acid sequence" refers to a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end or an analog thereof.

[58] The term "encoding" refers to a polynucleotide sequence encoding one or more amino acids. The term does not require a start or stop codon. An amino acid sequence can be encoded in any one of six different reading frames provided by a polynucleotide sequence.

[59] The term "promoter" refers to regions or sequence located upstream and/or downstream from the start of transcription that are involved in recognition and binding of RNA polymerase and other proteins to initiate transcription.

[60] A "vector" refers to a polynucleotide, which when independent of the host chromosome, is capable of replication in a host organism. Examples of vectors include plasmids. Vectors typically have an origin of replication. Vectors can comprise, e.g., transcription and translation terminators, transcription and translation initiation sequences, and promoters useful for regulation of the expression of the particular nucleic acid.

[61] The term “recombinant” when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (nonrecombinant) form of the cell or express native genes that are otherwise abnormally expressed, under-expressed or not expressed at all.

[62] The phrase “specifically (or selectively) binds” to a polypeptide, when referring to a monomer or multimer, refers to a binding reaction that can be determinative of the presence of the polypeptide in a heterogeneous population of proteins (e.g., a cell or tissue lysate) and other biologics. Thus, under standard conditions or assays used in antibody binding assays, the specified monomer or multimer binds to a particular target molecule above background (e.g., 2X, 5X, 10X or more above background) and does not bind in a significant amount to other molecules present in the sample.

[63] The terms “identical” or percent “identity,” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. “Substantially identical” refers to two or more nucleic acids or polypeptide sequences having a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, or 95% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity or substantial identity exists over a region that is at least about 50 nucleotides in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides or amino acids in length.

[64] A polynucleotide or amino acid sequence is “heterologous to” a second sequence if the two sequences are not linked in the same manner as found in naturally-occurring sequences. For example, a promoter operably linked to a heterologous coding sequence refers to a coding sequence which is different from any naturally-occurring allelic variants. The term “heterologous linker,” when used in reference to a multimer, indicates that the multimer comprises a linker and a monomer that are not found in the same relationship to each other in nature (*e.g.*, they form a non-naturally occurring fusion protein).

[65] A "non-naturally-occurring amino acid" in a protein sequence refers to any amino acid other than the amino acid that occurs in the corresponding position in an alignment with a naturally-occurring polypeptide with the lowest smallest sum probability where the comparison window is the length of the monomer domain queried and when compared to a naturally-occuring sequence in the non-redundant ("nr") database of Genbank using BLAST 2.0 as described herein.

[66] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[67] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Such sequences are then said to be "substantially identical." This definition also refers to the complement of a test sequence. Optionally, the identity exists over a region that is at least about 50 amino acids or nucleotides in length, or more preferably over a region that is 75-100 amino acids or nucleotides in length.

[68] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[69] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat'l. Acad. Sci. USA* 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g.,* Ausubel *et al.*, *Current Protocols in Molecular Biology* (1995 supplement)).

[70] One example of a useful algorithm is the BLAST 2.0 algorithm, which is described in Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[71] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

BRIEF DESCRIPTION OF THE DRAWINGS

[72] Figure 1 schematically illustrates the alignment of partial amino acid sequence from a variety of the LDL-receptor class A-domains to demonstrate the conserved cysteines (SEQ ID NOS 735-748, respectively, in order or appearance). The connectivity of cysteines in the three disulfide bonds of the folded domain is illustrated schematically on the consensus sequence. Residues whose side-chains contribute to calcium binding are designated with an asterisk in the consensus sequence.

[73] Figure 2, panel A schematically illustrates an example of an A-domain. Panel A schematically illustrates conserved amino acids in an A-domain of about 40 amino acids long (SEQ ID NO: 749). The conserved cysteine residues are indicated by C, and the conserved negatively charged amino acids are indicated by a circle with a minus ("-") sign. Circles with an "H" indicate conserved hydrophobic residues. Panel B schematically illustrates two folded A-domains connected via a linker. Panel B also indicates two calcium binding sites, dark circles with Ca^{+2}, and three disulfide bonds within each folded A-domain for a total of 6 disulfide bonds.

[74] Figure 3 indicates some of the ligands recognized by naturally-occurring members of the LDL-receptor family, which include inhibitors, proteases, protease complexes, vitamin-carrier complexes, proteins involved in lipoprotein metabolism, non-human ligands, antibiotics, viruses, and others.

[75] Figure 4 schematically illustrates a general scheme for identifying monomer domains that bind to a ligand, isolating the selected monomer domains, creating multimers of the selected monomer domains by joining the selected monomer domains in various combinations and screening the multimers to identify multimers comprising more than one monomer that binds to a ligand.

[76] Figure 5 is a schematic representation of another selection strategy (guided selection). A monomer domain with appropriate binding properties is identified from a library of monomer domains. The identified monomer domain is then linked to monomer domains from another library of monomer domains to form a library of multimers. The multimer library is screened to identify a pair of monomer domains that bind simultaneously to the target. This process can then be repeated until the optimal binding properties are obtained in the multimer.

[77] Figure 6 depicts an alignment of A domains (SEQ ID NOS 750-966, respectively, in order or appearance). At the top and the bottom of the figure, small letters (a-q) indicate conserved residues.

[78] Figure 7 illustrates various possible antibody-monomer or multimer conformations. In some embodiments, the monomer or multimer replaces the Fab fragment of the antibody.

[79] Figure 8 depicts a possible conformation of a multimer of the invention comprising at least one monomer domain that binds to a half-life extending molecule and other monomer domains binding to one or optionally two or more target molecules. In the Figure, two monomer domains bind to two first target molecules. Optionally, the two monomer domains can bind to different sites on one first target molecule (not depicted).

[80] Figure 9 shows a comparison between c-METFc, a c-MET-specific monomer (M26) and a c-MET-specific dimer (RM12; RecM12) with regards to their relative abilities to block HGF-induced proliferation of serum-starved A549-SC human lung adenocarcinoma cells.

[81] Figure 10 illustrates the serum half-life in monkeys of monomers that bind to IgG.

DETAILED DESCRIPTION OF THE INVENTION

I. INTRODUCTION

[82] The present invention provides for non-naturally-occurring proteins that bind to c-MET. Generally, the proteins of the present invention comprise a domain that binds to c-MET. These domains may be readily identified using a variety of polypeptide scaffolds to generate a plurality of polypeptide variants and then selecting a variant that binds to c-MET. The present invention therefore also provides for selecting a protein that binds to c-MET. Proteins that bind c-MET are useful, e.g., for treating

individuals with solid tumors that express c-MET. The polypeptides of the invention are also useful to detect tissues in which Met is expressed and can be used to target molecules to those tissues.

[83] c-MET is inactive in its resting monomer state and dimer formation results in receptor activation (often even in absence of ligand binding). The mature form of the

the receptor consists of a solely extracellular α chain and a longer β chain encompassing the remainder of the extracellular domain, a transmembrane domain and a cytoplasmic tail. The cytoplasmic tail contains the juxtamembrane domain, a kinase domain and docking sites for signaling intermediates. The α chain and the first 212 amino acids of the β chain, also known as the Sema domain (Kong-Beltran, *et al.*, *Cancer Cell* 6:75-84 (2004), are sufficient for binding to HGF. The rest of the extracellular portion of the β chain consists of a cysteine-rich C domain and four repeats of an unusual immunoglobulin domain. Accordingly, in some embodiments, the polypeptides of the invention comprise at least one monomer domain that inhibits dimerization of c-MET α and β chains and/or functions as an antagonist to prevent ligands of c-MET from binding and/or activating c-MET.

[84] While the present invention provides for polypeptides comprising single domains, multimers of the domains may also be synthesized and used. In some embodiments, all of the domains of the multimer bind c-MET. In some of these embodiments, each of the domains are identical and bind to the same portion (i.e., "epitope") of c-MET. For example, in some embodiments, the monomer domains bind to the Sema domain of c-MET. In other embodiments, at least some of the domains in the multimer bind to different portions of c-MET. In yet other embodiments, at least some of the domains of the polypeptide bind to a molecule or molecules other than c-MET (*e.g.*, a blood factor such as serum albumin, immunoglobulin, or erythrocytes).

II. MONOMERS

[85] Monomer domains can be polypeptide chains of any size. In some embodiments, monomer domains have about 25 to about 500, about 30 to about 200, about 30 to about 100, about 35 to about 50, about 35 to about 100, about 90 to about 200, about 30 to about 250, about 30 to about 60, about 9 to about 150, about 100 to about 150, about 25 to about 50, or about 30 to about 150 amino acids. Similarly, a monomer domain of the present invention can comprise, e.g., from about 30 to about 200 amino acids; from about 25 to about 180 amino acids; from about 40 to about 150 amino acids; from about 50 to about 130 amino acids; or from about 75 to about 125 amino acids. Monomer domains can typically maintain a stable conformation in solution, and are often heat stable, e.g., stable at 95° C for at least 10 minutes without losing binding affinity. Sometimes, monomer domains can fold independently into a stable conformation. In one embodiment, the stable conformation is stabilized by ions (e.g., such as metal or calcium ions). The stable conformation can optionally contain disulfide bonds (e.g., at least one, two, or three or more disulfide bonds). The disulfide bonds can optionally be formed between two cysteine residues. In some embodiments, monomer domains, or monomer domain variants, are substantially identical to the sequences exemplified.

A. c-MET Binders

[86] In some aspects, the invention provides monomer domains that bind to a c-MET polypeptide or a portion thereof. A portion of a polypeptide can be, e.g., at least 5, 10, 15, 20, 30, 50, 100, or more contiguous amino acids of the polypeptide.

[87] A large number of c-MET binding sequences having an A domain scaffold were generated. As described in detail in the examples, ten families (*i.e.*, Families 1-10, or "Fam 1-10") of monomer domains that bind to c-MET have been identified. The consensus motifs generated based on these families indicate common amino acid residues between c-MET binders. Sequence flanking the conserved residues comprising the motif are omitted from the motif, although it is assumed that all residues comprising the A-domain structure will be present in any binding domain based on the families below. Those of skill in the art will appreciate that positions where there is no consensus (marked with an "X") can be any amino acid. In some embodiments, the amino acid at "X" positions will be selected from amino acids in the analogous position of one of the exemplified c-MET binders either from the same family or a different family.

[88] Family 1 has the following consensus motif:

Cxxx [EQ]FxCxSTxRC[IV]xxxWxCDGDNDCEDxSDEx (SEQ ID NO: 7)

[89] Exemplary sequences comprising the c-MET Family 1 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 1 sequence exemplified in the examples.

[90] Family 2 has the following motif:

Cxxxx[EQ]FECxSTxRC[IV]xxxWxCDGxNDCEDxSDEx (SEQ ID NO: 8)

[91] Exemplary sequences comprising the c-MET Family 2 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 2 sequence exemplified in the examples.

[92] Family 3 has the following motif:

Cxxxx[EQ]FxCxSTxRC[ILV]PxxWxCDGxxDCEDxSDExx (SEQ ID NO: 9)

[93] Exemplary sequences comprising the c-MET Family 3 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 3 sequence exemplified in the examples.

[94] Family 4 has the following motif:

Cxxx[EQ]FQCxSTxRC[IV]PxxWxCDGxNDCEDSSDExxC (SEQ ID NO: 10)

[95] Exemplary sequences comprising the c-MET Family 4 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 4 sequence exemplified in the examples.

[96] Family 5 has the following motif:

Cxxxx[EQ]FxCxxxxxC[ILV]xxxxxxxxxxDCxDxSDEx (SEQ ID NO: 11)

[97] Exemplary sequences comprising the c-MET Family 5 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 5 sequence exemplified in the examples.

[98] Family 6 has the following motif:

Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO: 12)

[99] Exemplary sequences comprising the c-MET Family 6 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 6 sequence exemplified in the examples.

[100] Family 7 has the following motif:

Cxxxx[EQ]FxCxSTxRC[ILV]xxxWxCxxxxDCxDxSDxxxxxCx (SEQ ID NO: 13)

[101] Exemplary sequences comprising the c-MET Family 7 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 7 sequence exemplified in the examples.

[102] Family 8 has the following motif:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO: 14)

[103] Exemplary sequences comprising the c-MET Family 8 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 8 sequence exemplified in the examples.

[104] Family 9 has the following motif:

Cxxxx[EQ]FxCxSTxRC[ILV]PxxWxCxGxxDCxDxSDEx (SEQ ID NO: 15)

[105] Exemplary sequences comprising the c-MET Family 9 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 9 sequence exemplified in the examples.

[106] Family 10 has the following motif:

Cxxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxxDCxDxSDEx (SEQ ID NO: 16)

which can be further condensed as:

EFXCXNGXCIPXXWXCDGXDDCGDXSDE (SEQ ID NO: 17)

[107] Exemplary sequences comprising the c-MET Family 10 motif are displayed in the examples. References to c-MET binding monomers or multimers encompass each Family 10 sequence exemplified in the examples.

B. IgG binders and serum half-life extension

[108] The invention further provide monomer domains that bind to a blood factor (*e.g.*, serum albumin, immunoglobulin, or erythrocytes).

[109] In some embodiments, the monomer domains bind to an immunoglobulin polypeptide or a portion thereof.

[110] Two families (*i.e.*, A domain Families 2 and 3) of monomer domains that bind to immunoglobulin have been identified.

[111] Family 2 has the following motif:

[EQ]FXCRX[ST]XRC[IV]XXXW[ILV]CDGXXDCXD[DN]SDE (SEQ ID NO: 4)

[112] Exemplary sequences comprising the IgG Family 2 motif are displayed in the examples. References to IgG binding monomers or multimers encompass each Family 2 sequence exemplified in the examples.

[113] Family 3 has either of the two following motifs:

CXSSGRCIPXXWVCDGXXDCRDXSDE (SEQ ID NO: 2); or
CXSSGRCIPXXWLCDGXXDCRDXSDE (SEQ ID NO: 3)

[114] Exemplary sequences comprising the IgG Family 3 motif are displayed in the examples. References to IgG binding monomers or multimers encompass each Family 3 sequence exemplified in the examples.

[115] Monomer domains that bind to red blood cells (RBC) or serum albumin (CSA) are described in U.S. Patent Publication No. 2005/0048512, and include, e.g.,:

RBCA

CRSSQFQ**C**NDSRI**C**IPGRWR**C**DGDND**C**QDGSDETG**C**GDSHILPFSTPGPST (SEQ ID NO: 19)

RBCB

CPAGEFP**C**KNGQ**C**LPVTWL**C**DGVND**C**LDGSDEKG**C**GRPGPGATSAPAA (SEQ ID NO: 20)

RBC11

CPPDEFP**C**KNGQ**C**IPQDWL**C**DGVND**C**LDGSDEKD**C**GRPGPGATSAPAA (SEQ ID NO: 21)

CSA-A8 **C**GAGQFP**C**KNGH**C**LPLNLL**C**DGVND**C**EDNSDEPSEL**C**KALT (SEQ ID NO: 22)

[116] The present invention provides a method for extending the serum half-life of a protein, including, e.g., a multimer of the invention or a protein of interest in an animal. The protein of interest in an ——————————

animal. The protein of interest can be any protein with therapeutic, prophylactic, or otherwise desirable functionality. This method comprises first providing a monomer domain that has been identified as a binding protein that specifically binds to a half-life extender such as a blood-carried molecule or cell, such as serum albumin (e.g., human serum albumin), IgG, red blood cells, etc. The half-life extender-binding monomer is then covalently linked to another monomer domain that has a binding affinity for the protein of interest (e.g., c-MET or a different target). This complex formation results in the half-life extension protecting the multimer and/or bound protein(s) from proteolytic degradation and/or other removal of the multimer and/or protein(s) and thereby extending the half-life of the protein and/or multimer. One variation of this use of the invention includes the half-life extender-binding monomer covalently linked to the protein of interest. The protein of interest may include a monomer domain, a multimer of monomer domains, or a synthetic drug. Alternatively, monomers that bind to either immunoglobulins or erythrocytes could be generated using the above method and could be used for half-life extension.

[117] The half-life extender-binding multimers are typically multimers of at least two domains, chimeric domains, or mutagenized domains (i.e., one that binds to Met and one that binds to the blood-carried molecule or cell). Suitable domains include all of those described herein, that are further screened and selected for binding to a half-life extender. The half-life extender-binding multimers are generated in accordance with the methods for making multimers described herein, using, for example, monomer domains pre-screened for half-life extender -binding activity. The serum half-life of a molecule can be extended to be, e.g., at least 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70 80, 90, 100, 150, 200, 250, 400, 500 or more hours.

C. Discussion of Monomer Domains

[118] Monomer domains that are particularly suitable for use in the practice of the present invention are cysteine-rich domains comprising disulfide bonds. Cysteine-rich domains employed in the practice of the present invention typically do not form an α helix, a β sheet, or a β-barrel structure. Typically, the disulfide bonds promote folding of the domain into a three-dimensional structure. Usually, cysteine-rich domains have at least two disulfide bonds, more typically at least three disulfide bonds. In some embodiments, at least 5, 10, 15 or 20% of the amino acids in a monomer domain are cysteines.

[119] Domains can have any number of characteristics. For example, in some embodiments, the domains have low or no immunogenicity in an animal (e.g., a human). Domains can have a small size. In some embodiments, the domains are small enough to penetrate skin or other tissues. Domains can have a range of *in vivo* half-lives or stabilities.

[120] Illustrative monomer domains suitable for use in the practice of the present invention include, e.g., an EGF-like domain, a Kringle-domain, a fibronectin type I domain, a fibronectin type II domain, a fibronectin type III domain, a PAN domain, a Gla domain, a SRCR domain, a Kunitz/Bovine pancreatic trypsin Inhibitor domain, a Kazal-type serine protease inhibitor domain, a Trefoil (P-type) domain, a von Willebrand factor type C domain, an Anaphylatoxin-like domain, a CUB domain, a thyroglobulin type I repeat, LDL-receptor class A domain, a Sushi domain, a Link domain, a Thrombospondin type I domain, an Immunoglobulin-like domain, a C-type lectin domain, a MAM domain, a von Willebrand factor type A domain, a Somatomedin B domain, a WAP-type four disulfide core domain, a F5/8 type C domain, a Hemopexin domain, an SH2 domain, an SH3 domain, a Laminin-type EGF domain, a C2 domain, and other such domains known to those of ordinary skill in the art, as well as derivatives and/or variants thereof.

[121] In some embodiments, suitable monomer domains (e.g. domains with the ability to fold independently or with some limited assistance) can be selected from the families of protein domains that contain β-sandwich or β-barrel three dimensional structures as defined by such computational sequence analysis tools as Simple Modular Architecture Research Tool (SMART), *see* Shultz *et al.*, *SMART: a web-based tool for the study of genetically mobile domains*, (2000) Nucleic Acids Research 28(1):231-234) or CATH (*see* Pearl *et.al.*, *Assigning genomic sequences to CATH*, (2000) Nucleic Acids Research 28(1):277-282).

[122] In another embodiment, monomer domains of the present invention include domains other than a fibronectin type III domain, an anticalin domain and a Ig-like domain from CTLA-4. Some aspects of these domains are described in WO01/64942 entitled "Protein scaffolds for antibody mimics and other binding proteins" by Lipovsek et al., published on September 7, 2001, WO99/16873 entitled "Anticalins" by Beste et al., published April 8, 1999 and WO 00/60070 entitled "A polypeptide structure for use as a scaffold" by Desmet, et al., published on October 12, 2000.

[123] As described *supra*, monomer domains are optionally cysteine rich. Suitable cysteine rich monomer domains include, e.g., the LDL receptor class A domain ("A-domain") or the EGF domain. The monomer domains can also have a cluster of negatively charged residues.

[124] Other features of monomer domains can include the ability to bind ligands or the ability to bind an ion (e.g., Ca^{2+} binding by the LDL receptor A-domain). Monomer domains that bind ions to maintain their secondary structure include, e.g., A domain, EGF domain, EF Hand (e.g., such as those found in present in calmodulin and troponin C), Cadherin domain, C-type lectin, C2 domain, Annexin, Gla-domain, Trombospondin type 3 domain, all of which bind calcium, and zinc fingers (e.g., C2H2 type C3HC4 type (RING finger), Integrase Zinc binding domain, PHD finger, GATA zinc finger, FYVE zinc finger, B-box zinc finger), which bind zinc. Without intending to limit the invention, it is believed that ion-binding provides stability of secondary structure while providing sufficient flexibility to allow for numerous binding conformations depending on primary sequence.

[125] As described herein, monomer domains may be selected for the ability to bind to targets other than the target that a homologous naturally occurring domain may bind. Thus, in some embodiments, the invention provides monomer domains (and multimers comprising such monomers) that do not bind to the target or the class or family of target proteins that a substantially identical naturally occurring domain may bind.

[126] Characteristics of a monomer domain can include the ability to fold independently and the ability to form a stable structure. Thus, the structure of the monomer domain is often conserved, although the polynucleotide sequence encoding the monomer need not be conserved. For example, the A-domain structure is conserved among the members of the A-domain family, while the A-domain nucleic acid sequence is not. Thus, for example, a monomer domain is classified as an A-domain by its cysteine residues and its affinity for calcium, not necessarily by its nucleic acid sequence. *See*, Figures 1 and 2.

[127] Specifically, the A-domains (sometimes called "complement-type repeats" or "LDL receptor type or class A domains") contain about 30-50 or 30-65 amino acids. In some embodiments, the domains comprise about 35-45 amino acids and in some cases about 40 amino acids. Within the 30-50 amino acids, there are about 6 cysteine residues. Of the six cysteines, disulfide bonds typically are found between the following cysteines: C1 and C3, C2 and C5, C4 and C6. The cysteine residues of the domain are disulfide linked to form a compact, stable, functionally independent moiety. *See*, Figure 3.

Clusters of these repeats make up a ligand binding domain, and differential clustering can impart specificity with respect to the ligand binding.

[128] Exemplary A domain sequences and consensus sequences are depicted in Figures 1 and 2. One typical consensus sequence useful to identify A domains is the following: **C**-[VILMA]-X$_{(5)}$-**C**-[DNH]-X$_{(3)}$-[DENQHT]-**C**-X$_{(3,4)}$-[STADE]- [DEH]-[DE]-X$_{(1,5)}$-**C** (SEQ ID NO: 23), where the residues in brackets indicate possible residues at one position. "X$_{(\#)}$" indicates number of residues. These residues can be any amino acid residue. Parentheticals containing two numbers refers to the range of amino acids that can occupy that position (e.g., "[DE]-X$_{(1,5)}$-**C**" means that the amino acids DE are followed by 1, 2, 3, 4, or 5 residues, followed by C). This consensus sequence only represents the portion of the A domain beginning at the third cysteine. A second consensus is as follows: **C**-X$_{(3\text{-}15)}$-**C**-X$_{(4\text{-}15)}$-**C**-X$_{(6\text{-}7)}$-**C**-[N,D]-X$_{(3)}$-[D,E,N,Q,H,S,T]-**C**-X$_{(4\text{-}6)}$-D-E-X$_{(2\text{-}8)}$-**C** (SEQ ID NO: 24). The second consensus predicts amino acid residues spanning all six cysteine residues. In some embodiments, A domain variants comprise sequences substantially identical to any of the above-described sequences. Note that reference to "LDL receptor class A" domain, for the purposes of this invention, is not intended to indicate origin or binding properties of the domain.

[129] Additional exemplary A domains include the following sequence:

$C_aX_{3\text{-}15}C_bX_{3\text{-}15}C_cX_{6\text{-}7}C_d(D,N)X_4C_eX_{4\text{-}6}DEX_{2\text{-}8}C_f$ (SEQ ID NO: 25)

wherein C is cysteine, $X_{n\text{-}m}$ represents between n and m number of independently selected amino acids, and (D,N) indicates that the position can be either D or N; and wherein C_a-C_c, C_b-C_e and C_d-C_f form disulfide bonds.

[130] To date, at least 190 naturally-occurring human A-domains are identified based on cDNA sequences. *See, e.g.*, Figure 6. Exemplary proteins containing naturally-occurring A-domains include, e.g., complement components (e.g., C6, C7, C8, C9, and Factor I), serine proteases (e.g., enteropeptidase, matriptase, and corin), transmembrane proteins (e.g., ST7, LRP3, LRP5 and LRP6) and endocytic receptors (e.g., Sortilin-related receptor, LDL-receptor, VLDLR, LRP1, LRP2, and ApoER2). A domains and A domain variants can be readily employed in the practice of the present invention as monomer domains and variants thereof. Further description of A domains can be found in the following publications and references cited therein: Howell and Hertz, *The LDL receptor gene family: signaling functions during* *development*, (2001) Current Opinion in Neurobiology 11:74-81; Herz (2001), *supra*; Krieger, *The "best" of cholesterols, the "worst" of cholesterols: A tale of two receptors*, (1998) PNAS 95: 4077-4080; Goldstein and Brown, *The Cholesterol Quartet*, (2001) Science, 292: 1310-1312; and, Moestrup and Verroust, *Megalin-and Cubilin-Mediated Endocytosis of Protein-Bound Vitamins, Lipids, and Hormones in Polarized Epithelia*, (2001) Ann. Rev. Nutr. 21:407-28.

[131] A number of other domain types can also be used to generate c-MET-binding monomer domains.

[132] Exemplary EGF monomer domains include the sequence:

$C_aX_{3-14}C_bX_{3-7}C_cX_{4-16}C_dX_{1-2}C_eX_{8-23}C_f$ (SEQ ID NO: 26)

wherein C is cysteine, X_{n-m} represents between n and m number of independently selected amino acids; and

wherein C_a-C_c, C_b-C_e and C_d-C_f form disulfide bonds.

[133] Each of the domains described below employ exemplary motifs (*i.e.*, scaffolds). Certain positions are marked x, indicating that any amino acid can occupy the position. These positions can include a number of different amino acid possibilities, thereby allowing for sequence diversity and thus affinity for different target molecules. Use of brackets in motifs indicates alternate possible amino acids within a position (e.g., "[ekq]" indicates that either E, K or Q may be at that position). Use of parentheses in a motif indicates that that the positions within the parentheses may be present or absent (e.g., "([ekq])" indicates that the position is absent or either E, K, or Q may be at that position). When more than one "x" is used in parentheses (e.g., "(xx)"), each x represents a possible position. Thus "(xx)" indicates that zero, one or two amino acids may be at that position(s), where each amino acid is independently selected from any amino acid. α represents an aromatic/hydrophobic amino acid such as, *e.g.*, W, Y, F, or L; β represents a hydrophobic amino acid such as, *e.g.*, V, I, L, A, M, or F; χ represents a small or polar amino acid such as, *e.g.*, G, A, S, or T; δ represents a charged amino acid such as, *e.g.*, K, R, E, Q, or D; ε represents a small amino acid such as, *e.g.*,; V, A, S, or T; and ϕ represents a negatively charged amino acid such as, *e.g.*, D, E, or N.

[134] Suitable domains include, *e.g.* thrombospondin type 1 domains, trefoil domains, and thyroglobulin domains.

[135] Thrombospondin type 1 ("TSP1") domains contain about 30-50 or 30-65 amino acids. In some embodiments, the domains comprise about 35-55 amino acids and in some cases about 50 amino acids. Within the 35-55 amino acids, there are typically about 4 to about 6 cysteine residues. Of the six cysteines, disulfide bonds typically are found between the following cysteines: C1 and C5, C2 and C6, C3 and C4. The cysteine residues of the domain are disulfide linked to form a compact, stable, functionally independent moiety comprising distorted beta strands. Clusters of these repeats make up a ligand binding domain, and differential clustering can impart specificity with respect to the ligand binding.

[136] Exemplary TSP1 domain sequences and consensus sequences are as follows:

(1) (xxxxxx)C_1xxxC_2xxxxx(x)xxxxxC_3xxxx(xxx)xxxxxC_4xxxxxx(x)xxxC_5(x)xxxxC_6; (SEQ ID NO: 27)

(2) (wxxWxx)C_1xxxC_2xxGxx(x)xRxxxC_3xxxx(Pxx)xxxxxC_4xxxxxx(x)xxxC_5(x)xxxxC_6 (SEQ ID NO: 28)

(3) (wxxWxx)C_1sxtC_2xxGxx(x)xRxrxC_3xxxx(Pxx)xxxxxC_4xxxxxx(x)xxxC_5(x)xxxxC_6 (SEQ ID NO: 29)

(4) (WxxWxx)C_1[Stnd][Vkaq][Tspl]C_2xx[Gq]xx(x)x[Re]x[Rktvm]x[C_3vldr]xxxx([Pq]xx)xxxxx[C_4ldae]xxxxxx(x)xxxC_5(x)xxxxC_6; (SEQ ID NO: 30)

(5) (WxxWxx)C_1[Stnd][Vkaq][Tspl]C_2xx[Gq]xx(x)x[Re]x[Rktvm]x[C_3vldr]xxxx([Pq]xx)xxxxx[C_4ldae]xxxxxx(x)xxxC_5(x)xxxxC_6; (SEQ ID NO: 31) and

(6) C_1[nst][aegiklqrstv][adenpqrst]C_2[adetgs]xgx[ikqrstv]x[aqrst]x[almrtv]xC_3xxxxxxxxx(xxxxxxx)C_4xxxxxxxxx(xx)C_5xxxxC_6 (SEQ ID NO: 32)

[137] In some embodiments, thrombospondin type 1 domain variants comprise sequences substantially identical to any of the above-described sequences.

[138] To date, at least 1677 naturally occurring thrombospondin domains have identified based on cDNA sequences. Exemplary proteins containing the naturally occurring thrombospondin domains include, *e.g.*, proteins in the complement pathway (*e.g.*, properdin, C6, C7, C8A, C8B, and C9), extracellular matrix proteins (*e.g.*, mindin, F-spondin, SCO-spondin,), circumsporozoite surface protein 2, and TRAP proteins of *Plasmodium*. Thrombospondin type 1 domains are further described in, *e.g.*, Roszmusz *et al.*, *BBRC* 296:156 (2002); Higgins *et al.*, *J Immunol.* 155:5777-85 (1995); Schultz-Cherry *et al.*, *J. Biol. Chem.* 270:7304-7310 (1995); Schultz-Cherry *et al.*, *J.*

Biol. Chem. 269:26783-8 (1994); Bork, *FEBS Lett* 327:125-30 (1993); and Leung-Hagesteijn *et al.*, *Cell* 71:289-99 (1992).

[139] Another exemplary monomer domain suitable for use in the practice of the present invention is the trefoil domain. Trefoil monomer domains are typically about about 30-50 or 30-65 amino acids. In some embodiments, the domains comprise about 35-55 amino acids and in some cases about 45 amino acids. Within the 35-55 amino acids, there are typically about 6 cysteine residues. Of the six cysteines, disulfide bonds typically are found between the following cysteines: C1 and C5, C2 and C4, C3 and C6.

[140] To date, at least 149 naturally occurring trefoil domains have identified based on cDNA sequences. Exemplary proteins containing naturally occurring trefoil domains include, *e.g.*, protein pS2 (TFF1), spasmolytic peptide SP (TFF2), intestinal trefoil factor (TFF3), intestinal surcease-isomaltase, and proteins which may be involved in defense against microbial infections by protecting the epithelia (*e.g.*, *Xenopus* xP1, xP4, integumentary mucins A.1 and C.1. Trefoil domains are further described in, *e.g.*, Sands and Podolsky, *Annu. Rev. Physiol.* 58:253-273 (1996); Carr *et al.*, *PNAS USA* 91:2206-2210 (1994); DeA *et al.*, *PNAS USA* 91:1084-1088 (1994); Hoffman *et al.*, *Trends Biochem Sci* 18:239-243 (1993).

[141] Exemplary trefoil domain sequences and consensus sequences are as follows:

(1) C_1(xx)xxxxxxxxxC_2xx(x)xxxxxxxC_3xxxxC_4C_5xxxxx(x)xxxxxC_6 (SEQ ID NO: 33)

(2) C_1(xx)xxxxxxRxxC_2xx(x)xxxxxxxC_3xxxxC_4C_5xxxxx(x)xxxxxC_6 (SEQ ID NO: 34)

(3) C_1(xx)xxxpxxRxnC_2gx(x)pxitxxxC_3xxxgC_4C_5fdxxx(x)xxxpwC_6f (SEQ ID NO: 35)

(4) C_1(xx)xxx[Pvae]xxRx[ndpm]C_2[Gaiy][ypfst]([de]x)[pskq]x[Ivap][Tsa]xx[qedk]C_3xx[krln][Gnk]C_4C_5[Fwy][Dnrs][sdpnte]xx(x)xxx[pki][Weash]C_6[Fy] (SEQ ID NO: 36)

(5) C1(xx)xxx[Pvae]xxRx[ndpm]C2[Gaiy][ypfst]([de]x)[pskq]x[Ivap][Tsa]xx[keqd]C3xx[krln][Gnk]C4C5[α][Dnrs][sdpnte]xx(x)xxx[pki][Weash]C6[Fy] (SEQ ID NO: 37)

(6) C_1([dnps])[adiklnprstv][dfilmv][adenprst][adelprv][ehklnqrs][adegknsv][kqr][fiklqrtv][dnpqs]C_2[agiy][flpsvy][dknpqs][adfghlp][aipv][st][aegkpqrs][adegkpqs][deiknqt]C_3[adefknqrt][adegknqs][gn]C_4C_5[wyfh][deinrs][adgnpst][aefgqlrstw][giknsvmq]([afmprstv][degklns][afiqstv][iknpv]w)C_6 (SEQ ID NO: 38)

[142] Another exemplary monomer domain suitable for use in the present invention is the thyroglobulin domain. Thyroglobulin monomer domains are typically about 30-85 or 30-80 amino acids. In some embodiments, the domains comprise about 35-75 amino acids and in some cases about 65 amino acids. Within the 35-75 amino acids, there are typically about 6 cysteine residues. Of the six cysteines, disulfide bonds typically are found between the following cysteines: C1 and C2, C3 and C4, C5 and C6.

[143] To date at least 251 naturally occurring thyroglobulin domains have been identified based on cDNA sequences. The N-terminal section of Tg contains 10 repeats of a domain of about 65 amino acids which is known as the Tg type-1 repeat PUBMED:3595599, PUBMED:8797845. Exemplary proteins containing naturally occurring thyroglobulin domains include *e.g.*, the HLA class II associated invariant chain, human pancreatic carcinoma marker proteins, nidogen (entactin), insulin-like growth factor binding proteins (IGFBP), saxiphilin, chum salmon egg cysteine proteinase inhibitor, and equistatin. The Thyr-1 and related domains belong to MEROPS proteinase inhibitor family I31, clan IX. Thyroglobulin domains are further described in, *e.g.*, Molina *et al.*, *Eur. J. Biochem.* 240:125-133 (1996); Guncar *et al.*, *EMBO J* 18:793-803 (1999); Chong and Speicher, *DW* 276:5804-5813 (2001).

[144] Exemplary thyroglobulin domain sequences and consensus sequences are as follows:

(1) C_1xxxxxxxxxxxxxxxxx(xxxxxxxxxxx)xxxxxxxxxxxC_2xxxxxxxxxxxC_3x(x)x(xxx)xxxxC_4
xC_5xxxx(x)xxxxxxxxxxxxxxx(xx)xC_6 (SEQ ID NO: 39)

(2) C_1xxxxxxxxxxxxxxxxx(xxxxxxxxxxx)xxxxxxxyxPxC_2xxxGxxxxxQC_3x(x)x(xxx)xxxx
C_4WC_5Vxxx(x)GxxxxGxxxxxxxx(xx)xC_6 (SEQ ID NO: 40)

(3) C_1xxxxxxxxxxxxxxxxx(xxxxxxxxxxx)xxxxxxxyxPxC_2xxxGxyxxxQC_3x(x)s(xxx)xxgx
C_4WC_5Vdxx(x)GxxxxGxxxxxgxx(xx)xC_6 (SEQ ID NO: 41)

(4) C_1[qerl]xxxxxxxxxxxxxxxx(xxxxxxxxxxx)xxxxxxx[Yfhp]xPxC_2xxxGx[Yf]xx[vkrl]QC_3
x(x[sa]xxx)xx[Gsa]xC_4[Wyf]C_5V[Dnyfl]xx(x)Gxxxx[Gdne]xxxxxgxx(xx)xC_6
(SEQ ID NO: 42)

(5) C_1[qerl]xxxxxxxxxxxxxxxx(xxxxxxxxxxx)xxxxxxx[αhp]xPxC2xxxGx[α]xx[vkrl]QC_3x(
x[sa]xxx)xx[gas]xC_4[α]C_5V[Dnα]xx(x)Gxxxx[ϕg]xxxxxgxx(xx)xC_6 (SEQ ID NO: 43)

[145] Another exemplary monomer domain that can be used in the present invention is a laminin-EGF domain. Laminin-EGF domains are typically about 30-85 or 30-80 amino acids. In some embodiments, the domains comprise about 45-65 amino acids and in some cases about 50 amino acids. Within the 45-65 amino acids, there are typically about 8 cysteine residues which interact to form 4 disulfide bonds.

Laminins are a major noncollagenous component of basement membranes that mediate cell adhesion, growth migration, and differentiation. They are composed of distinct but related alpha, beta, and gamma chains. The three chains form a cross-shaped molecule that consist of a long arm and three short globular arms. The long arm consist of a coiled coil structure contributed by all three chains and cross-linked by interchain disulphide bonds.

[146] Exemplary laminin EGF domain sequences and consensus sequences are as follows:

(1) $C_1xC_2xxxxxx(xxx)xxC_3xxx(xxxxxx)xxxxC_4xC_5xxxxxxxxC_6xxC_7xxxxxxx(xxxxx)xxxxxC_8$ (SEQ ID NO: 44)

(2) $C_1xC_2xxxxxx(xxx)xxC3xxx(xxxxxx)xxgxC_4xC_5xxxxxGxxC_6xxC_7xxxxxxx(xxxxx)xxxxxC_8$ (SEQ ID NO: 45)

(3) $C_1xC_2[ndh]xxxxx(xxx)xxC_3xxx(xxxxxx)xxgxC_4xC_5xxxxxGxxC_6[denq]xC_7xx[gn][yfht]xxx(xxxxx)xxxxxC_8$ (SEQ ID NO: 46)

In some embodiments, the monomer domain is a Notch/LNR monomer domain, a DSL monomer domain, an Anato monomer domain, an integrin beta monomer domain, and a Ca-EGF monomer domain.

[147] In some embodiments, the Ca-EGF monomer domain comprises the following sequence: $DxdEC_1xx(xx)xxxxC_2x(xx)xxxxxC_3xNxxGxfxC_4x(xxx)xC_5xxgxxxxxxx(xxxxx)xxxC_6$ (SEQ ID NO: 47).

[148] In some embodiments, the Notch/LNR monomer domain, comprises the following sequence:
$C_1xx(xx)xxxC_2xxxxxnGxC_3xxxC_4nxxxC_5xxDGxDC_6$ (SEQ ID NO: 48)

[149] In some embodiments, the DSL monomer domain comprises the following sequence: $C_1xxxYygxxC_2xxfC_3xxxxdxxxhxxC_4xxxGxxxC_5xxGWxGxxC_6$ (SEQ ID NO: 49).

[150] Anato monomer domain comprises the following sequence: $C_1C_2xdgxxxxx(x)xxxxC_3exrxxxxxx(xx)xxC_4xxxfxxC_5C_6$ (SEQ ID NO: 50).

[151] In some embodiments, the integrin beta monomer domain comprises the following sequence: $C_1xxC_2xxxxpxC_3xwC4xxxxfxxx(gx)xxxxRC_5dxxxxLxxxgC_6$ (SEQ ID NO: 51); and “x” is any amino acid.

[152] In some embodiments, C_1-C_5, C_2-C_4 and C_3-C_6 of the Notch/LNR monomer domain form disulfide bonds; and C_1-C_5, C_2-C_4 and C_3-C_6 of the DSL monomer domain form disulfide bonds.

[153] In some embodiments, the Ca-EGF monomer domain comprises the following sequence: D[β][Dn]EC_1xx(xx)xxxxC_2[pdg](dx)xxxxxC_3xNxxG[sgt][α]xC_4x(xxx)xC_5xx[Gsn][αs] xxxxxx(xxxxx)xxxC_6 (SEQ ID NO: 52).

[154] In some embodiments, the Notch/LNR monomer domain, comprises the following sequence: C_1xx(x[$\beta\alpha$])xxxC_2x[ϕs]xxx[ϕ][Gk]xC_3[nd]x[ϕsa]C_4 [ϕs]xx[aeg]C_5x[α]DGxDC_6 (SEQ ID NO: 53).

[155] In some embodiments, the DSL monomer domain comprises the following sequence: C_1xxx[α][αh][Gsna]xxC_2xx[α]C_3x[pae]xx[Da]xx[χl][Hrgk][αk]x C_4[dnsg]xxGxxxC_5xxG[α]xGxxC_6 (SEQ ID NO: 54).

[156] In some embodiments, the Anato monomer domain comprises the following sequence: C_1C_2x[Dhtl][Ga]xxxx[plant](xx)xxxxC_3[esqdat]x[Rlps]xxxxxx([ge pa]x)xxC_4xx[avfpt][Fqvy]xxC_5C_6 (SEQ ID NO: 55).

[157] In some embodiments, the integrin beta monomer domain comprises the following sequence: C_1xxC_2[β]xx[ghds][Pk]xC_3[χ][α]C_4xxxx[α]xxx([Gr]xx)x[χ]xRC_5[Dnae]xxxxL[βk]xx[Gn]C_6 (SEQ ID NO: 56); α is selected from: w, y, f, and l; β is selected from: v, I, l, a, m, and f; χ is selected from: g, a, s, and t; δ is selected from: k, r, e, q, and d; ε is selected from: v, a, s, and t; and ϕ is selected from: d, e, and n.

[158] In some embodiments, the Ca-EGF monomer domain comprises the following sequence: D[vilf][Dn]EC_1xx(xx)xxxxC_2[pdg](dx)xxxxxC_3xNxxG[sgt][fy] xC_4x(xxx)xC_5xx[Gsn][αs]xxxxxx(xxxxx)xxxC_6 (SEQ ID NO: 57).

[159] In some embodiments, the Notch/LNR monomer domain, comprises the following sequence: C_1xx(x[yiflv])xxxC_2x[dens]xxx[Nde][Gk]xC_3[nd]x[d ensa]C_4[Nsde]xx[aeg]C_5x[wyf]DGxDC6 (SEQ ID NO: 58).

[160] In some embodiments, the DSL monomer domain comprises the following sequence:C_1xxx[Ywf][Yfh][Gasn]xxC_2xx[Fy]C_3x[pae]xx[Da]xx[glast][Hrgk] [ykfw]xC_4[dsgn]xxGxxxC_5xxG[Wlfy]xGxxC_6 (SEQ ID NO: 59).

[161] In some embodiments, the Anato monomer domain comprises the following sequence: C_1C_2x[adehlt]gxxxxxxxx(x)[derst]C_3xxxxxxxxx(xx[aersv])C_4xx[apvt][fmq][eklqrtv][adehqrsk](x)C_5C_6 (SEQ ID NO: 60).

[162] In some embodiments, the integrin beta monomer domain comprises the following sequence: C_1[aegkqrst][kreqd]C_2[il][aelqrv][vilas][dghs][kp]xC_3[gast][wy]C_4xxxx[fl]xxxx(xxxx[vilar]r)C_5[and][dilrt][iklpqrv][adeps][aenq]l[iklqv]x[adknr][gn]C_6 (SEQ ID NO: 61)

[163] Polynucleotides encoding the monomer domains are typically employed to make monomer domains via expression. Nucleic acids that encode monomer domains can be derived from a variety of different sources. Libraries of monomer domains can be prepared by expressing a plurality of different nucleic acids encoding naturally occurring monomer domains, altered monomer domains (i.e., monomer domain variants), or a combinations thereof. For example, libraries may be designed in which a scaffold of amino acids remain constant (e.g., an LDL A receptor domain, EGF domain) while the intervening amino acids in the scaffold comprise randomly generated amino acids.

[164] The invention provides methods of identifying monomer domains that bind to a selected or desired ligand or mixture of ligands. In some embodiments, monomer domains are identified or selected for a desired property (e.g., binding affinity) and then the monomer domains are formed into multimers. *See*, *e.g.*, Figure 4. For those embodiments, any method resulting in selection of domains with a desired property (e.g., a specific binding property) can be used. For example, the methods can comprise providing a plurality of different nucleic acids, each nucleic acid encoding a monomer domain; translating the plurality of different nucleic acids, thereby providing a plurality of different monomer domains; screening the plurality of different monomer domains for binding of the desired ligand or a mixture of ligands; and, identifying members of the plurality of different monomer domains that bind the desired ligand or mixture of ligands.

[165] Monomer domains can be naturally-occurring or altered (non-natural variants). The term "naturally occurring" is used herein to indicate that an object can be found in nature. For example, natural monomer domains can include human monomer domains or optionally, domains derived from different species or sources, e.g., mammals, primates, rodents, fish, birds, reptiles, plants, etc. The natural occurring monomer domains can be obtained by a number of methods, e.g., by PCR amplification of genomic DNA or cDNA.

[166] Monomer domains of the present invention can be naturally-occurring domains or non-naturally occurring variants. Libraries of monomer domains employed in the practice of the present invention may contain naturally-occurring monomer domain, non-naturally occurring monomer domain variants, or a combination thereof.

[167] Monomer domain variants can include ancestral domains, chimeric domains, randomized domains, mutated domains, and the like. For example, ancestral domains can be based on phylogenetic analysis. Chimeric domains are domains in which one or more regions are replaced by corresponding regions from other domains of the same family. For example, chimeric domains can be constructed by combining loop sequences from multiple related domains of the same family to form novel domains with potentially lowered immunogenicity. Those of skill in the art will recognized the immunologic benefit of constructing modified binding domain monomers by combining loop regions from various related domains of the same family rather than creating random amino acid sequences. For example, by constructing variant domains by combining loop sequences or even multiple loop sequences that occur naturally in human LDL receptor class A-domains, the resulting domains may contain novel binding properties but may not contain any immunogenic protein sequences because all of the exposed loops are of human origin. The combining of loop amino acid sequences in endogenous context can be applied to all of the monomer constructs of the invention. Thus the present invention provides a method for generating a library of chimeric monomer domains derived from human proteins, the method comprising: providing loop sequences corresponding to at least one loop from each of at least two different naturally occurring variants of a human protein, wherein the loop sequences are polynucleotide or polypeptide sequences; and covalently combining loop sequences to generate a library of at least two different chimeric sequences, wherein each chimeric sequence encodes a chimeric monomer domain having at least two loops. Typically, the chimeric domain has at least four loops, and usually at least six loops. As described above, the present invention provides three types of loops that are identified by specific features, such as, potential for disulfide bonding, bridging between secondary protein structures, and molecular dynamics (i.e., flexibility). The three types of loop sequences are a cysteine-defined loop sequence, a structure-defined loop sequence, and a B-factor-defined loop sequence.

[168] Randomized domains are domains in which one or more regions are randomized. The randomization can be based on full randomization, or optionally, partial randomization based on natural distribution of sequence diversity.

[169] The present invention also provides recombinant nucleic acids encoding one or more polypeptides comprising one or a plurality of monomer domains that bind c-MET. For example, the polypeptide can be selected to comprise a non-naturally occuring domain from the group consisting of: an EGF-like domain, a Kringle-domain, a fibronectin type I domain, a fibronectin type II domain, a fibronectin type III domain, a PAN domain, a Gla domain, a SRCR domain, a Kunitz/Bovine pancreatic trypsin Inhibitor domain, a Kazal-type serine protease inhibitor domain, a Trefoil (P-type) domain, a von Willebrand factor type C domain, an Anaphylatoxin-like domain, a CUB domain, a thyroglobulin type I repeat, LDL-receptor class A domain, a Sushi domain, a Link domain, a Thrombospondin type I domain, an Immunoglobulin-like domain, a C-type lectin domain, a MAM domain, a von Willebrand factor type A domain, a Somatomedin B domain, a WAP-type four disulfide core domain, a F5/8 type C domain, a Hemopexin domain, an SH2 domain, an SH3 domain, a Laminin-type EGF-like domain, a C2 domain and variants of one or more thereof. In another embodiment, the naturally occuring polypeptide encodes a monomer domain found in the Pfam database and/or the SMART database.

[170] All the compositions of the present invention, including the compositions produced by the methods of the present invention, e.g., monomer domains and/or immuno-domains, as well as multimers and libraries thereof can be optionally bound to a matrix of an affinity material. Examples of affinity material include beads, a column, a solid support, a microarray, other pools of reagent-supports, and the like.

III. MULTIMERS

[171] Methods for generating multimers are a feature of the present invention. Multimers comprise at least two monomer domains. For example, multimers of the invention can comprise from 2 to about 10 monomer domains, from 2 and about 8 monomer domains, from about 3 and about 10 monomer domains, about 7 monomer domains, about 6 monomer domains, about 5 monomer domains, or about 4 monomer domains. In some embodiments, the multimer comprises 3 or at least 3 monomer domains. In some embodiments, the mutimers have no more than 2, 3, 4, 5, 6, 7, or 8 monomer domains. In view of the possible range of monomer domain sizes, the multimers of the invention may be, e.g., less than 100 kD, less than 90kD, less than 80kD, less than 70kD, less than 60kD, less than 50kd, less than 40kD, less than 30kD, less than 25kD, less than 20kD, less than 15kD, less than 10kD or may be smaller or larger. In some cases, the monomer domains have been pre-selected for binding to the target molecule of interest (e.g., Met).

[172] In some embodiments, each monomer domain specifically binds to one target molecule (e.g., c-Met). In some of these embodiments, each monomer binds to a different position (analogous to an epitope) on a target molecule. Multiple monomer domains that bind to the same target molecule results in an avidity effect resulting in improved affinity of the multimer for the target molecule compared to the affinity of each individual monomer. In some embodiments, the multimer has an avidity of at least about 1.5, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, or 1000 times the avidity of a monomer domain alone. In some embodiments, at least one, two, three, four or more (e.g., all) monomers of a multimer bind an ion such as calcium or another ion. Multimers can comprise a variety of combinations of monomer domains. For example, in a single multimer, the selected monomer domains can be identical or different. In addition, the selected monomer domains can comprise various different monomer domains from the same monomer domain family, or various monomer domains from different domain families , or optionally, a combination of both. For example, the monomer domains may be selected from Families 1-10 of c-Met binding monomer domains. In some embodiments, at least one of the monomer domains is selected from from Family 10 of the c-Met binding monomer domains. Exemplary c-MET-binding dimers (comprised of two c-MET-binding monomers) are listed in the examples.

[173] Multimers that are generated in the practice of the present invention may be any of the following:

(1) A homo-multimer (a multimer of the same domain, i.e., A1-A1-A1-A1);

(2) A hetero-multimer of different domains of the same domain class, e.g., A1-A2-A3-A4. For example, hetero-multimer include multimers where A1, A2, A3 and A4 are different non-naturally occurring variants of a particular LDL-receptor class A domains, or where some of A1, A2, A3, and A4 are naturally-occurring variants of a LDL-receptor class A domain.

(3) A hetero-multimer of domains from different monomer domain classes, e.g., A1-B2-A2-B1. For example, where A1 and A2 are two different monomer domains (either naturally occurring or non-naturally-occurring) from LDL-receptor class A, and B1 and B2 are two different monomer domains (either naturally occurring or non-naturally occurring) from class EGF-like domain).

[174] In another embodiment, the multimer comprises monomer domains with specificities for different target molecules (*e.g.*, a blood factor such as serum albumin, immunoglobulin, or erythrocytes). For example, in some embodiments, the multimers of the invention comprises 1, 2, 3, or more monomer domains that bind to Met and at least one monomer domain that binds to a second target molecule. Exemplary target molecules include, e.g., a serum molecule that extends the serum half-life of the multimer (*e.g.*, an immunoglobulin or serum albumin), EGFR gene family members, VEGF receptors, PDGF receptor, other receptor tyrosine kinases, integrins, other molecules implicated in tumorigenesis, or markers of tumor tissue. Exemplary molecule that extends the serum half-life of a multimer include, e.g., red blood cells (*i.e.*, erythrocytes), IgG, and serum albumin such as HSA. An exemplary multimer will include a monomer domain from Family 10 of the c-MET binding monomer domains and monomer domain from Family 2 or 3 of the immunoglobulin binding monomer domains.

[175] Multimer libraries employed in the practice of the present invention may contain homo-multimers, hetero-multimers of different monomer domains (natural or non-natural) of the same monomer class, or hetero-multimers of monomer domains (natural or non-natural) from different monomer classes, or combinations thereof.

[176] Monomer domains, as described herein, are also readily employed in a immuno-domain-containing heteromultimer (i.e., a multimer that has at least one immuno-domain variant and one monomer domain variant). Thus, multimers of the present invention may have at least one immuno-domain such as a minibody, a single-domain antibody, a single chain variable fragment (ScFv), or a Fab fragment; and at least one monomer domain, such as, for example, an EGF-like domain, a Kringle-domain, a fibronectin type I domain, a fibronectin type II domain, a fibronectin type III domain, a PAN domain, a Gla domain, a SRCR domain, a Kunitz/Bovine pancreatic trypsin Inhibitor domain, a Kazal-type serine protease inhibitor domain, a Trefoil (P-type) domain, a von Willebrand factor type C domain, an Anaphylatoxin-like domain, a CUB domain, a thyroglobulin type I repeat, LDL-receptor class A domain, a Sushi domain, a Link domain, a Thrombospondin type I domain, an Immunoglobulin-like domain, a C-type lectin domain, a MAM domain, a von Willebrand factor type A domain, a Somatomedin B domain, a WAP-type four disulfide core domain, a F5/8 type C domain, a Hemopexin domain, an SH2 domain, an SH3 domain, a Laminin-type EGF-like domain, a C2 domain, or variants thereof.

[177] Domains need not be selected before the domains are linked to form multimers. On the other hand, the domains can be selected for the ability to bind to a target molecule before being linked into multimers. Thus, for example, a multimer can comprise two domains that bind to one target molecule and a third domain that binds to a second target molecule.

[178] The multimers of the present invention may have the following qualities: multivalent, multispecific, single chain, heat stable, extended serum and/or shelf half-life. Moreover, at least one, more than one or all of the monomer domains may bind an ion (e.g., a metal ion or a calcium ion), at least one, more than one or all monomer domains may be derived from LDL receptor A domains and/or EGF-like domains, at least one, more than one or all of the monomer domains may be non-naturally occurring, and/or at least one, more than one or all of the monomer domains may comprise 1, 2, 3, or 4 disulfide bonds per monomer domain. In some embodiments, the multimers comprise at least two (or at least three) monomer domains, wherein at least one monomer domain is a non-naturally occurring monomer domain and the monomer domains bind calcium. In some embodiments, the multimers comprise at least 4 monomer domains, wherein at least one monomer domain is non-naturally occurring, and wherein:

a. each monomer domain is between 30-100 amino acids and each of the monomer domains comprise at least one disulfide linkage; or

b. each monomer domain is between 30-100 amino acids and is derived from an extracellular protein; or

c. each monomer domain is between 30-100 amino acids and binds to a protein target.

[179] In some embodiments, the multimers comprise at least 4 monomer domains, wherein at least one monomer domain is non-naturally occurring, and wherein:

a. each monomer domain is between 35-100 amino acids; or

b. each domain comprises at least one disulfide bond and is derived from a human protein and/or an extracellular protein.

[180] In some embodiments, the multimers comprise at least two monomer domains, wherein at least one monomer domain is non-naturally occurring, and wherein each domain is:

a. 25-50 amino acids long and comprises at least one disulfide bond; or

b. 25-50 amino acids long and is derived from an extracellular protein; or

c. 25-50 amino acids and binds to a protein target; or

d. 35-50 amino acids long.

[181] In some embodiments, the multimers comprise at least two monomer domains, wherein at least one monomer domain is non-naturally-occurring and:

a. each monomer domain comprises at least one disulfide bond; or

b. at least one monomer domain is derived from an extracellular protein; or

c. at least one monomer domain binds to a target protein.

[182] The monomer domains and/or multimers identified can have biological activity, which is meant to include at least specific binding affinity for a selected or desired ligand, and, in some instances, will further include the ability to block the binding of other compounds, to stimulate or inhibit metabolic pathways, to act as a signal or messenger, to stimulate or inhibit cellular activity, and the like. Monomer domains can be generated to function as ligands for receptors where the natural ligand for the receptor has not yet been identified (orphan receptors). These orphan ligands can be created to either block or activate the receptor top which they bind.

[183] A single ligand can be used, or optionally a variety of ligands can be used to select the monomer domains and/or multimers. A monomer domain of the present invention can bind a single ligand or a variety of ligands. A multimer of the present invention can have multiple discrete binding sites for a single ligand, or optionally, can have multiple binding sites for a variety of ligands.

[184] In some embodiments, the multimer comprises monomer domains with specificities for different proteins. The different proteins can be related or unrelated. Examples of related proteins including members of a protein family or different serotypes of a virus. Alternatively, the monomer domains of a multimer can target different molecules in a physiological pathway (e.g., different blood coagulation proteins). In yet other embodiments, monomer domains bind to proteins in unrelated pathways (e.g., two domains bind to blood factors, two other domains bind to inflammation-related proteins and a fifth binds to serum albumin). In another embodiment, a multimer is comprised of monomer domains that bind to different pathogens or contaminants of interest. Such multimers are useful as a single detection agent capable of detecting for the possibility of any of a number of pathogens or contaminants.

[185] In some embodiments, the multimers of the invention bind to the same or other multimers to form aggregates. Aggregation can be mediated, for example, by the presence of hydrophobic domains on two monomer domains, resulting in the formation of non-covalent interactions between two monomer domains. Alternatively, aggregation may be facilitated by one or more monomer domains in a multimer having binding specificity for a monomer domain in another multimer. Aggregates can also form due to the presence of affinity peptides on the monomer domains or multimers. Aggregates can contain more target molecule binding domains than a single multimer.

[186] Multimers with affinity for both a cell surface target and a second target may provide for increased avidity effects. In some cases, membrane fluidity can be more flexible than protein linkers in optimizing (by self-assembly) the spacing and valency of the interactions. In some cases, multimers will bind to two different targets, each on a different cell or one on a cell and another on a molecule with multiple binding sites.

[187] In some embodiments, the monomers or multimers of the present invention are linked to another polypeptide to form a fusion protein. Any polypeptide in the art may be used as a fusion partner, though it can be useful if the fusion partner forms multimers. For example, monomers or multimers of the invention may, for example, be fused to the following locations or combinations of locations of an antibody:

1. At the N-terminus of the VH1 and/or VL1 domains, optionally just after the leader peptide and before the domain starts (framework region 1);
2. At the N-terminus of the CH1 or CL1 domain, replacing the VH1 or VL1 domain;
3. At the N-terminus of the heavy chain, optionally after the CH1 domain and before the cysteine residues in the hinge (Fc-fusion);
4. At the N-terminus of the CH3 domain;
5. At the C-terminus of the CH3 domain, optionally attached to the last amino acid residue via a short linker;

6. At the C-terminus of the CH2 domain, replacing the CH3 domain;

7. At the C-terminus of the CL1 or CH1 domain, optionally after the cysteine that forms the interchain disulfide; or

8. At the C-terminus of the VH1 or VL1 domain. *See, e.g.*, Figure 7.

[188] In some embodiments, one or more monomer or multimer domains of the invention is linked to a molecule (e.g., a protein, nucleic acid, organic small molecule, etc.) useful as a pharmaceutical. Exemplary pharmaceutical proteins include, e.g., cytokines, antibodies, chemokines, growth factors, interleukins, cell-surface proteins, extracellular domains, cell surface receptors, cytotoxins, etc. Exemplary small molecule pharmaceuticals include toxins or therapeutic agents. In some embodiments, a metal can be bound to the polypeptides of the invention. This can be useful, e.g., as a contrast agent, e.g., for MRI.

[189] In some embodiments, the monomer or multimers are selected to bind to a tissue- or disease-specific target protein. Tissue-specific proteins are proteins that are expressed exclusively, or at a significantly higher level, in one or several particular tissue(s) compared to other tissues in an animal. As c-MET is expressed at significant levels in the liver, monomer domains that bind to Met may be used to target other molecules, including other monomer domains, to the liver. This may be used to target liver-specific diseases, for example, by targeting therapeutic or toxic molecules to the liver. An example of a liver disease that can be treated is hepatocellular carcinoma. Similarly, disease-specific proteins are proteins that are expressed exclusively, or at a significantly higher level, in one or several diseased cells or tissues compared to other non-diseased cells or tissues in an animal.

[190] In some embodiments, the monomers or multimers that bind to the target protein are linked to the pharmaceutical protein or small molecule such that the resulting complex or fusion is targeted to the specific tissue or disease-related cell(s) where the target protein (e.g., c-MET) is expressed. Monomers or multimers for use in such complexes or fusions can be initially selected for binding to the target protein and may be subsequently selected by negative selection against other cells or tissue (e.g., to avoid targeting bone marrow or other tissues that set the lower limit of drug toxicity) where it is desired that binding be reduced or eliminated in other non-target cells or tissues. By keeping the pharmaceutical away from sensitive tissues, the therapeutic window is increased so that a higher dose may be administered safely. In another alternative, *in vivo* panning can be performed in animals by injecting a library of monomers or multimers into an animal and then isolating the monomers or multimers that bind to a particular tissue or cell of interest.

[191] The fusion proteins described above may also include a linker peptide between the pharmaceutical protein and the monomer or multimers. A peptide linker sequence may be employed to separate, for example, the polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Fusion proteins can also be expressed as recombinant proteins in an expression system by standard techniques.

[192] Multimers or monomer domains of the invention can be produced according to any methods known in the art. In some embodiments, *E. coli* comprising a pET-derived plasmid encoding the polypeptides are induced to express the protein. After harvesting the bacteria, they may be lysed and clarified by centrifugation. The polypeptides may be purified using Ni-NTA agarose elution and refolded by dialysis. Misfolded proteins may be neutralized by capping free sulfhydrils with iodoacetic acid. Q sepharose elution, butyl sepharose flow-through, SP sepharose elution, DEAE sepharose elution, and/or CM sepharose elution may be used to purify the polypeptides. Equivalent anion and/or cation exchange purification steps may also be employed.

[193] In some embodiments, the polypeptide comprising a monomer or multimer of the invention is linked to itself (C-terminus to N-terminus), e.g., for proteion stability.

IV. LINKERS

[194] Monomer domains can be joined by a linker to form a multimer. For example, a linker may be positioned between each separate discrete monomer domain in a multimer.

[195] Joining the selected monomer domains via a linker can be accomplished using a variety of techniques known in the art. For example, combinatorial assembly of polynucleotides encoding selected monomer domains can be achieved by restriction digestion and re-ligation, by PCR-based, self-priming overlap reactions, or other recombinant methods. The linker can be attached to a monomer before the monomer is identified for its ability to bind to a target multimer or after the monomer has been selected for the ability to bind to a target multimer.

[196] The linker can be naturally-occurring, synthetic or a combination of both. For example, the synthetic linker can be a randomized linker, e.g., both in sequence and size. In one aspect, the randomized linker can comprise a fully randomized sequence, or optionally, the randomized linker can be based on natural linker sequences. The linker can comprise, e.g,. a non-polypeptide moiety, a polynucleotide, a polypeptide or the like.

[197] A linker can be rigid, or flexible, or a combination of both. Linker flexibility can be a function of the composition of both the linker and the monomer domains that the linker interacts with. The linker joins two selected monomer domain, and maintains the monomer domains as separate discrete monomer domains. The linker can allow the separate discrete monomer domains to cooperate yet maintain separate properties such as multiple separate binding sites for the same ligand in a multimer, or e.g., multiple separate binding sites for different ligands in a multimer.

[198] Choosing a suitable linker for a specific case where two or more monomer domains (i.e. polypeptide chains) are to be connected may depend on a variety of parameters including, e.g. the nature of the monomer domains, the structure and nature of the target to which the polypeptide multimer should bind and/or the stability of the peptide linker towards proteolysis and oxidation.

[199] The present invention provides methods for optimizing the choice of linker once the desired monomer domains/variants have been identified. Generally, libraries of multimers having a composition that is fixed with regard to monomer domain composition, but variable in linker composition and length, can be readily prepared and screened as described above.

[200] A more detailed discussion of linkers can be found in, e.g., U.S. Patent Publication No. 2005/0048512.

V. IDENTIFYING MONOMERS OR MULTIMERS WITH AFFINITY FOR A TARGET MOLECULE

[201] Those of skill in the art can readily identify monomer domains with a desired property (e.g., binding affinity). For those embodiments, any method resulting in selection of domains with a desired property (e.g., a specific binding property) can be used. For example, the methods can comprise providing a plurality of different nucleic acids, each nucleic acid encoding a monomer domain; translating the plurality of different nucleic acids, thereby providing a plurality of different monomer domains; screening the plurality of different monomer domains for binding of the desired ligand or a mixture of ligands; and, identifying members of the plurality of different monomer domains that bind the desired ligand or mixture of ligands.

[202] In addition, any method of mutagenesis, such as site-directed mutagenesis and random mutagenesis (e.g., chemical mutagenesis) can be used to produce monomer domains, e.g., for a monomer domain library. In some embodiments, error-prone PCR is employed to create variants. Additional methods include aligning a plurality of naturally occurring monomer domains by aligning conserved amino acids in the plurality of naturally occurring monomer domains; and, designing the non-naturally occurring monomer domain by maintaining the conserved amino acids and inserting, deleting or altering amino acids around the conserved amino acids to generate the non-naturally occurring monomer domain. In one embodiment, the conserved amino acids comprise cysteines. In another embodiment, the inserting step uses random amino acids, or optionally, the inserting step uses portions of the naturally occurring monomer domains. The portions could ideally encode loops from domains from the same family. Amino acids are inserted or exchanged using synthetic oligonucleotides, or by shuffling, or by restriction enzyme based recombination. Human chimeric domains of the present invention are useful for therapeutic applications where minimal immunogenicity is desired. The present invention provides methods for generating libraries of human chimeric domains. Human chimeric monomer domain libraries can be constructed by combining loop sequences from different variants of a human monomer domain, as described above. The loop sequences that are combined may be sequence-defined loops, structure-defined loops, B-factor-defined loops, or a combination of any two or more thereof.

[203] Alternatively, a human chimeric domain library can be generated by modifying naturally-occurring human monomer domains at the amino acid level, as compared to the loop level. In some embodiments, to minimize the potential for immunogenicity, only those residues that naturally occur in protein sequences from the same family of human monomer domains are utilized to create the chimeric sequences. This can be achieved by providing a sequence alignment of at least two human monomer domains from the same family of monomer domains, identifying amino acid residues in corresponding positions in the human monomer domain sequences that differ between the human monomer domains, generating two or more human chimeric monomer domains, wherein each human chimeric monomer domain sequence consists of amino acid residues that correspond in type and position to residues from two or more human monomer domains from the same family of monomer domains. Libraries of human chimeric monomer domains can be employed to identify human chimeric monomer domains that bind to a target of interest by: screening the library of human chimeric monomer domains for binding to a target molecule, and identifying a human chimeric monomer domain that binds to the target molecule. Suitable naturally-occurring human monomer domain sequences employed in the initial sequence alignment step include those corresponding to any of the naturally-occurring monomer domains described herein.

[204] Domains of human monomer variant libraries of the present invention (whether generated by varying loops or single amino acid residues) can be prepared by methods known to those having ordinary skill in the art. Methods particularly suitable for generating these libraries are split-pool format and trinucleotide synthesis format as described in WO01/23401.

[205] In some embodiments, monomer domains of the invention are screened for potential immunogenicity by:

providing a candidate protein sequence;

comparing the candidate protein sequence to a database of human protein sequences;

identifying portions of the candidate protein sequence that correspond to portions of human protein sequences from the database; and

determining the extent of correspondence between the candidate protein sequence and the human protein sequences from the database.

[206] In general, the greater the extent of correspondence between the candidate protein sequence and one or more of the human protein sequences from the database, the lower the potential for immunogenicity is predicted as compared to a candidate protein having little correspondence with any of the human protein sequences from the database. A database of human protein sequences that is suitable for use in the practice of the invention method for screening candidate proteins can be found at ncbi.nlm.nih.gov/blast/Blast.cgi at the World Wide Web (in addition, the following web site can be used to search short, nearly exact matches: cbi.nlm.nih.gov/blast/Blast.cgi?CMD =Web&LAYOUT=TwoWindows&AUTO_FORMAT=Semiauto&ALIGNMENTS=50&ALIGNMENT_VIEW=Pairwise&CLIENT=web&DATABASE=nr&DESCRIPTIONS=100&ENTREZ_QUERY=(none)&EXPECT=1000&FORMAT_OBJECT=Alignment&FORMAT_TYPE=HTML&NCBI_GI=on&PAGE=Nucleotides&PROGRAM=blastn&SERVICE=plain&SET_DEFAULTS.x=29&SET_DEFAULTS.y=6&SHOW_OVERVIEW=on&WORD_SIZE=7&END_OF_HTTPGET=Yes&SHOW_LINKOUT=yes at the World Wide Web). The method is particularly useful in determining whether a crossover sequence in a chimeric protein, such as, for example, a chimeric monomer domain, is likely to cause an immunogenic event. If the crossover sequence corresponds to a portion of a sequence found in the database of human protein sequences, it is believed that the crossover sequence is less likely to cause an immunogenic event.

[207] Information pertaining to portions of human protein sequences from the database can be used to design a protein library of human-like chimeric proteins. Such library can be generated by using information pertaining to "crossover sequences" that exist in naturally occurring human proteins. The term "crossover sequence" refers herein to a sequence that is found in its entirety in at least one naturally occurring human protein, in which portions of the sequence are found in two or more naturally occurring proteins. Thus, recombination of the latter two or more naturally occurring proteins would generate a chimeric protein in which the chimeric portion of the sequence actually corresponds to a sequence found in another naturally occurring protein. The crossover sequence contains a chimeric junction of two consecutive amino acid residue positions in which the first amino acid position is occupied by an amino acid residue identical in type and position found in a first and second naturally occurring human protein sequence, but not a third naturally occurring human protein sequence. The second amino acid position is occupied by an amino acid residue identical in type and position found in a second and third naturally occurring human protein sequence, but not the first naturally occurring human protein sequence. In other words, the "second" naturally occurring human protein sequence corresponds to the naturally occurring human protein in which the crossover sequence appears in its entirety, as described above.

[208] In some embodiments, a library of human-like chimeric proteins is generated by: identifying human protein sequences from a database that correspond to proteins from the same family of proteins; aligning the human protein sequences from the same family of proteins to a reference protein sequence; identifying a set of subsequences derived from different human protein sequences of the same family, wherein each subsequence shares a region of identity with at least one other subsequence derived from a different naturally occurring human protein sequence; identifying a chimeric junction from a first, a second, and a third subsequence, wherein each subsequence is derived from a different naturally occurring human protein sequence, and wherein the chimeric junction comprises two consecutive amino acid residue positions in which the first amino acid position is occupied by an amino acid residue common to the first and second naturally occurring human protein sequence, but not the third naturally occurring human protein sequence, and the second amino acid position is occupied by an amino acid residue common to the second and third naturally occurring human protein sequence, and generating human-like chimeric protein molecules each corresponding in sequence to two or more subsequences from the set of subsequences, and each comprising one of more of the identified chimeric junctions.

[209] Thus, for example, if the first naturally-occurring human protein sequence is, A-B-C, and the second is, B-C-D-E, and the third is, D-E-F, then the chimeric junction is C-D. Alternatively, if the first naturally-occurring human protein sequence is D-E-F-G, and the second is B-C-D-E-F, and the third is A-B-C-D, then the chimeric junction is D-E. Human-like chimeric protein molecules can be generated in a variety of ways. For example, oligonucleotides comprising sequences encoding the chimeric junctions can be recombined with oligonucleotides corresponding in sequence to two or more subsequences from the above-described set of subsequences to generate a human-like chimeric protein, and libraries thereof. The reference sequence used to align the naturally occurring human proteins is a sequence from the same family of naturally occurring human proteins, or a chimera or other variant of proteins in the family.

[210] Nucleic acids encoding fragments of naturally-occurring monomer domains can also be mixed and/or recombined (e.g., by using chemically or enzymatically-produced fragments) to generate full-length, modified monomer domains. The fragments and the monomer domain can also be recombined by manipulating nucleic acids encoding domains or fragments thereof. For example, ligating a nucleic acid construct encoding fragments of the monomer domain can be used to generate an altered monomer domain.

[211] Altered monomer domains can also be generated by providing a collection of synthetic oligonucleotides (e.g., overlapping oligonucleotides) encoding conserved, random, pseudorandom, or a defined sequence of peptide sequences that are then inserted by ligation into a predetermined site in a polynucleotide encoding a monomer domain. Similarly, the sequence diversity of one or more monomer domains can be expanded by mutating the monomer domain(s) with site-directed mutagenesis, random mutation, pseudorandom mutation, defined kernal mutation, codon-based mutation, and the like. The resultant nucleic acid molecules can be propagated in a host for cloning and amplification. In some embodiments, the nucleic acids are shuffled.

[212] The present invention also provides a method for recombining a plurality of nucleic acids encoding monomer domains and screening the resulting library for monomer domains that bind to the desired ligand or mixture of ligands or the like. Selected monomer domain nucleic acids can also be back-crossed by shuffling with polynucleotide sequences encoding neutral sequences (i.e., having insubstantial functional effect on binding), such as for example, by back-crossing with a wild-type or naturally-occurring sequence substantially identical to a selected sequence to produce native-like functional monomer domains. Generally, during back-crossing, subsequent selection is applied to retain the property, e.g., binding to the ligand.

[213] In some embodiments, the monomer library is prepared by shuffling. In such a case, monomer domains are isolated and shuffled to combinatorially recombine the nucleic acid sequences that encode the monomer domains (recombination can occur between or within monomer domains, or both). The first step involves identifying a monomer domain having the desired property, e.g., affinity for a certain ligand. While maintaining the conserved amino acids during the recombination, the nucleic acid sequences encoding the monomer domains can be recombined, or recombined and joined into multimers.

[214] A significant advantage of the present invention is that known ligands, or unknown ligands can be used to select the monomer domains and/or multimers. No prior information regarding ligand structure is required to isolate the monomer domains of interest or the multimers of interest. The monomer domains and/or multimers identified can have biological activity, which is meant to include at least specific binding affinity for a selected or desired ligand, and, in some instances, will further include the ability to block the binding of other compounds, to stimulate or inhibit metabolic pathways, to act as a signal or messenger, to stimulate or inhibit cellular activity, and the like. Monomer domains can be generated to function as ligands for receptors where the natural ligand for the receptor has not yet been identified (orphan receptors). These orphan ligands can be created to either block or activate the receptor to which they bind.

[215] A single ligand can be used, or optionally a variety of ligands can be used to select the monomer domains and/or multimers. A monomer domain of the present invention can bind a single ligand or a variety of ligands. A multimer of the present invention can have multiple discrete binding sites for a single ligand, or optionally, can have multiple binding sites for a variety of ligands.

[216] The invention also includes compositions that are produced by methods of the present invention. For example, the present invention includes monomer domains selected or identified from a library and/or libraries comprising monomer domains produced by the methods of the present invention.

[217] The present invention also provides libraries of monomer domains and libraries of nucleic acids that encode monomer domains. The libraries can include, e.g., about 100, 250, 500 or more nucleic acids encoding monomer domains, or the library can include, e.g., about 100, 250, 500 or more polypeptides that encode monomer domains.

Libraries can include monomer domains containing the same cysteine frame, e.g., A-domains or EGF-like domains.

[218] In some embodiments, variants are generated by recombining two or more different sequences from the same family of monomer domains (e.g., the LDL receptor class A domain). Alternatively, two or more different monomer domains from different families can be combined to form a multimer. In some embodiments, the multimers are formed from monomers or monomer variants of at least one of the following family classes: an EGF-like domain, a Kringle-domain, a fibronectin type I domain, a fibronectin type II domain, a fibronectin type III domain, a PAN domain, a Gla domain, a SRCR domain, a Kunitz/Bovine pancreatic trypsin Inhibitor domain, a Kazal-type serine protease inhibitor domain, a Trefoil (P-type) domain, a von Willebrand factor type C domain, an Anaphylatoxin-like domain, a CUB domain, a thyroglobulin type I repeat, LDL-receptor class A domain, a Sushi domain, a Link domain, a Thrombospondin type I domain, an Immunoglobulin-like domain, a C-type lectin domain, a MAM domain, a von Willebrand factor type A domain, a Somatomedin B domain, a WAP-type four disulfide core domain, a F5/8 type C domain, a Hemopexin domain, an SH2 domain, an SH3 domain, a Laminin-type EGF-like domain, a C2 domain and derivatives thereof. In another embodiment, the monomer domain and the different monomer domain can include one or more domains found in the Pfam database and/or the SMART database. Libraries produced by the methods above, one or more cell(s) comprising one or more members of the library, and one or more displays comprising one or more members of the library are also included in the present invention.

[219] Optionally, a data set of nucleic acid character strings encoding monomer domains can be generated e.g., by mixing a first character string encoding a monomer domain, with one or more character string encoding a different monomer domain, thereby producing a data set of nucleic acids character strings encoding monomer domains, including those described herein. In another embodiment, the monomer domain and the different monomer domain can include one or more domains found in the Pfam database and/or the SMART database. The methods can further comprise inserting the first character string encoding the monomer domain and the one or more second character string encoding the different monomer domain in a computer and generating a multimer character string(s) or library(s), thereof in the computer.

[220] The libraries can be screened for a desired property such as binding of a desired ligand or mixture of ligands. For example, members of the library of monomer domains can be displayed and prescreened for binding to a known or unknown ligand or a mixture of ligands. The monomer domain sequences can then be mutagenized (e.g., recombined, chemically altered, etc.) or otherwise altered and the new monomer domains can be screened again for binding to the ligand or the mixture of ligands with an improved affinity. The selected monomer domains can be combined or joined to form multimers, which can then be screened for an improved affinity or avidity or altered specificity for the ligand or the mixture of ligands. Altered specificity can mean that the specificity is broadened, e.g., binding of multiple related viruses, or optionally, altered specificity can mean that the specificity is narrowed, e.g., binding within a specific region of a ligand. Those of skill in the art will recognize that there are a number of methods available to calculate avidity. *See, e.g.*, Mammen *et al.*, *Angew Chem Int. Ed.* 37:2754-2794 (1998); Muller *et al.*, *Anal. Biochem.* 261:149-158 (1998).

VI. SELECTION OF MONOMER DOMAINS THAT BIND c-MET

[221] Preliminary screens can be conducted by screening for agents capable of binding to c-MET, as at least some of the agents so identified are likely c-MET modulators (e.g., antagonists or agonists). The binding assays usually involve contacting a c-MET protein (or a fragment thereof such as a fragment comprising the SEMA rdomain or the α chain) with one or more test agents (i.e., monomers or multimers of the invention) and allowing sufficient time for the protein and test agents to form a binding complex. Any binding complexes formed can be detected using any of a number of established analytical techniques. Protein binding assays include, but are not limited to, immunohistochemical binding assays, flow cytometry or other assays. The c-MET protein utilized in such assays can be naturally expressed, cloned or synthesized. Similar methods can be used to identify monomer domains or multimers that bind IgG.

[222] The screening methods of the invention can be performed as *in vitro* or cell-based assays. Cell based assays can be performed in any cells in which c-MET is expressed. Cell-based assays may involve whole cells or cell fractions containing a c-MET receptor to screen for agent binding or modulation of activity of c-MET by the agent. Exemplary cell types that can be used according to the methods of the invention include, e.g., any mammalian cells, as well as fungal cells, including yeast, and bacterial cells. Cells can be primary cells or tumor cells or other types of immortal cell lines. Of course, c-MET can be expressed in cells that do not endogenously contain c-MET.

[223] c-MET activity assays may also be used to identify a modulator (antagonist or agonist) of c-MET. In these embodiments, one or more test agents are contacted to a cell expressing c-MET and then tested for an activity of c-MET. Exemplary c-MET activities include HGF-dependent or constitutive kinase activity. *See*, *e.g.*, Christensen *et al.*, *Cancer Res.* 63:7345-7355 (2003). In other embodiments, down stream molecular events can also be monitored to determine signaling activity. For example, c-MET induces cell growth (proliferation and survival), cell motility, invasion and morphology changes. In addition, c-MET indirectly mediates phosphorylation of Gab-1, Akt, signal transducer and activator of transcription 3, phospholipase C γ, and focal adhesions kinase, among others. *See*, *e.g.*, Christensen *et al.*, *Cancer Res.* 63:7345-7355 (2003).

[224] In some embodiments, activity assays are also used to confirm that identified antagonist monomers or multimers (i.e., that compete with HGF) lack agonist activity (i.e., that they do not activate c-MET in the absence of HGF or another agonist).

[225] Agents that are initially identified by any of the foregoing screening methods can be further tested to validate the apparent activity. Such studies may be conducted with suitable animal models. The basic format of such methods involves administering a lead compound identified during an initial screen to an animal that serves as a model for humans and then determining if c-MET is in fact modulated and/or the disease or condition is ameliorated. The animal models utilized in validation studies generally are mammals of any kind. Specific examples of suitable animals include, but are not limited to, primates, mice and rats.

[226] Selection of monomer domains that bind c-MET from a library of domains can be accomplished by a variety of procedures. For example, one method of identifying monomer domains which have a desired property (e.g., binding c-MET or IgG) involves translating a plurality of nucleic acids, where each nucleic acid encodes a monomer domain, screening the polypeptides encoded by the plurality of nucleic acids, and identifying those monomer domains that, e.g., bind to a desired ligand or mixture of ligands, thereby producing a selected monomer domain. The monomer domains expressed by each of the nucleic acids can be tested for their ability to bind to the ligand by methods known in the art (i.e. panning, affinity chromatography, FACS analysis).

[227] As mentioned above, selection of monomer domains can be based on binding to a ligand such as c-MET, or a fragment therof or other target molecule (e.g., lipid, carbohydrate, nucleic acid and the like). Other molecules can optionally be included in the methods along with the target, e.g., ions such as Ca^{+2}.

[228] When a monomer domain of the invention is selected based on its ability to bind to a ligand, the selection basis can include selection based on a slow dissociation rate, which is usually predictive of high affinity. The valency of the ligand can also be varied to control the average binding affinity of selected monomer domains. The ligand can be bound to a surface or substrate at varying densities, such as by including a competitor compound, by dilution, or by other method known to those in the art. High density (valency) of predetermined ligand can be used to enrich for monomer domains that have relatively low affinity, whereas a low density (valency) can preferentially enrich for higher affinity monomer domains.

[229] A variety of reporting display vectors or systems can be used to express nucleic acids encoding the monomer domains and/or multimers of the present invention and to test for a desired activity. For example, a phage display system is a system in which monomer domains are expressed as fusion proteins on the phage surface (Pharmacia, Milwaukee Wis.). Phage display can involve the presentation of a polypeptide sequence encoding monomer domains on the surface of a filamentous bacteriophage, typically as a fusion with a bacteriophage coat protein.

[230] Generally in these methods, each phage particle or cell serves as an individual library member displaying a single species of displayed polypeptide in addition to the natural phage or cell protein sequences. The nucleic acids are cloned into the phage DNA at a site which results in the transcription of a fusion protein, a portion of which is encoded by the plurality of the nucleic acids. The phage containing a nucleic acid molecule undergoes replication and transcription in the cell. The leader sequence of the fusion protein directs the transport of the fusion protein to the tip of the phage particle. Thus, the fusion protein that is partially encoded by the nucleic acid is displayed on the phage particle for detection and selection by the methods described above and below. For example, the phage library can be incubated with a predetermined ligand such as c-MET or a fragment thereof, so that phage particles which present a fusion protein sequence that binds to the ligand can be differentially partitioned from those that do not present polypeptide sequences that bind to the predetermined ligand. For example, the separation can be provided by immobilizing the predetermined ligand. The phage particles (i.e., library members) which are bound to the immobilized ligand are then recovered and replicated to amplify the selected phage subpopulation for a subsequent round of affinity enrichment and phage replication. After several rounds of affinity enrichment and phage replication, the phage library members that are thus selected are isolated and the nucleotide sequence encoding the displayed polypeptide sequence is determined, thereby identifying the sequence(s) of polypeptides that bind to the predetermined ligand. Such methods are further described in PCT patent publication Nos. 91/17271, 91/18980, and 91/19818 and 93/08278.

[231] Examples of other display systems include ribosome displays, a nucleotide-linked display (*see, e.g.*, U.S. Patent Nos. 6,281,344; 6,194,550, 6,207,446, 6,214,553, and 6,258,558), polysome display, cell surface displays and the like. The cell surface displays include a variety of cells, e.g., E. coli, yeast and/or mammalian cells. When a cell is used as a display, the nucleic acids, e.g., obtained by PCR amplification followed by digestion, are introduced into the cell and translated. Optionally, polypeptides encoding the monomer domains or the multimers of the present invention can be introduced, e.g., by injection, into the cell.

[232] The monomer and multimer libraries of the invention can be screened for a desired property such as binding of a desired ligand (e.g., c-MET) or mixture of ligands. For example, members of the library of monomer domains can be displayed and prescreened for binding to a known or unknown ligand or a mixture of ligands. The monomer domain sequences can then be mutagenized(e.g., recombined, chemically altered, etc.) or otherwise altered and the new monomer domains can be screened again for binding to the ligand or the mixture of ligands with an improved affinity. The selected monomer domains can be combined or joined to form multimers, which can then be screened for an improved affinity or avidity or altered specificity for the ligand or the mixture of ligands. Altered specificity can mean that the specificity is broadened, e.g., binding of multiple related ligands, or optionally, altered specificity can mean that the specificity is narrowed, e.g., binding within a specific region of a ligand. Those of skill in the art will recognize that there are a number of methods available to calculate avidity. *See, e.g.*, Mammen *et al.*, *Angew Chem Int. Ed.* 37:2754-2794 (1998); Muller *et al.*, *Anal. Biochem.* 261:149-158 (1998).

[233] Those of skill in the art will recognize that the steps of generating variation and screening for a desired property can be repeated (i.e., performed recursively) to optimize results. For example, in a phage display library or other like format, a first screening of a library can be performed at relatively lower stringency, thereby selected as many particles associated with a target molecule as possible. The selected particles can then be isolated and the polynucleotides encoding the monomer or multimer can be isolated from the particles. Additional variations can then be generated from these sequences and subsequently screened at higher affinity.

[234] All the compositions of the present invention, e.g., monomer domains as well as multimers and libraries thereof can be optionally bound to a matrix of an affinity material. Examples of affinity material include beads, a column, a solid support, a microarray, other pools of reagent-supports, and the like.

[235] When multimers capable of binding relatively large targets are desired, they can be generated by a "walking" selection method. This method is carried out by providing a library of monomer domains and screening the library of monomer domains for affinity to a first target molecule. Once at least one monomer that binds to the target is identified, that monomer is covalently linked to a new library or each remaining member of the original library of monomer domains. This new library of multimers (dimers) is then screened for multimers that bind to the target with an increased affinity, and a multimer that binds to the target with an increased affinity can be identified. The "walking" monomer selection method provides a way to assemble a multimer that is composed of monomers that can act additively or even synergistically with each other given the restraints of linker length. This walking technique is very useful when selecting for and assembling multimers that are able to bind large target proteins with high affinity. The walking method can be repeated to add more monomers thereby resulting in a multimer comprising 2, 3, 4, 5, 6, 7, 8 or more monomers linked together.

[236] In some embodiments, the selected multimer comprises more than two domains. Such multimers can be generated in a step fashion, e.g., where the addition of each new domain is tested individually and the effect of the domains is tested in a sequential fashion. *See, e.g.*, Figure 5. In an alternate embodiment, domains are linked to form multimers comprising more than two domains and selected for binding without prior knowledge of how smaller multimers, or alternatively, how each domain, bind.

[237] The methods of the present invention also include methods of evolving monomers or multimers. Intra-domain recombination can be introduced into monomers across the entire monomer or by taking portions of different monomers to form new recombined units. Interdomain recombination (e.g., recombining different monomers into or between multimers) or recombination of modules (e.g., multiple monomers within a multimer) may be achieved. Inter-library recombination is also contemplated.

[238] Methods for evolving monomers or multimers can comprise, e.g., any or all of the following steps: providing a plurality of different nucleic acids, where each nucleic acid encoding a monomer domain; translating the plurality of different nucleic acids, which provides a plurality of different monomer domains; screening the plurality of different monomer domains for binding of the desired ligand (e.g., c-MET) or mixture of ligands; identifying members of the plurality of different monomer domains that bind the desired ligand or mixture of ligands, which provides selected monomer domains; joining the selected monomer domains with at least one linker to generate at least one multimer, wherein the at least one multimer comprises at least two of the selected monomer domains and the at least one linker; and, screening the at least one multimer for an improved affinity or avidity or altered specificity for the desired ligand or mixture of ligands as compared to the selected monomer domains.

[239] Variation can be introduced into either monomers or multimers. An example of improving monomers includes intra-domain recombination in which two or more (e.g., three, four, five, or more) portions of the monomer are amplified separately under conditions to introduce variation (for example by shuffling or other recombination method) in the resulting amplification products, thereby synthesizing a library of variants for different portions of the monomer. By locating the 5' ends of the middle primers in a "middle" or 'overlap' sequence that both of the PCR fragments have in common, the resulting "left" side and "right" side libraries may be combined by overlap PCR to generate novel variants of the original pool of monomers. These new variants may then be screened for desired properties, e.g., panned against a target or screened for a functional effect. The "middle" primer(s) may be selected to correspond to any segment of the monomer, and will typically be based on the scaffold or one or more consensus amino acids within the monomer (e.g., cysteines such as those found in A domains).

[240] Similarly, multimers may be created by introducing variation at the monomer level and then recombining monomer variant libraries. On a larger scale, multimers (single or pools) with desired properties may be recombined to form longer multimers. In some cases variation is introduced (typically synthetically) into the monomers or into the linkers to form libraries. This may be achieved, e.g., with two different multimers that bind to two different targets, thereby eventually selecting a multimer with a portion that binds to one target and a portion that binds a second target.

[241] Additional variation can be introduced by inserting linkers of different length and composition between domains. This allows for the selection of optimal linkers between domains. In some embodiments, optimal length and composition of linkers will allow for optimal binding of domains. In some embodiments, the domains with a particular binding affinity(s) are linked via different linkers and optimal linkers are selected in a binding assay. For example, domains are selected for desired binding properties and then formed into a library comprising a variety of linkers. The library can then be screened to identify optimal linkers. Alternatively, multimer libraries can be formed where the effect of domain or linker on target molecule binding is not known.

[242] Methods of the present invention also include generating one or more selected multimers by providing a plurality of monomer domains. The plurality of monomer domains is screened for binding of a desired ligand or mixture of ligands. Members of the plurality of domains that bind the desired ligand or mixture of ligands are identified, thereby providing domains with a desired affinity. The identified domains are joined with at least one linker to generate the multimers, wherein each multimer comprises at least two of the selected domains and the at least one linker; and, the multimers are screened for an improved affinity or avidity or altered specificity for the desired ligand or mixture of ligands as compared to the selected domains, thereby identifying the one or more selected multimers.

[243] Multimer libraries may be generated, in some embodiments, by combining two or more libraries or monomers or multimers in a recombinase-based approach, where each library member comprises as recombination site (e.g., a lox site). A larger pool of molecularly diverse library members in principle harbor more variants with desired properties, such as higher target-binding affinities and functional activities. When libraries are constructed in phage vectors, which may be transformed into *E. coli*, library size (10^9 - 10^{10}) is limited by the transformation efficiency of *E. coli*. A recombinase/recombination site system (e.g., the *Cre-lox*P system) and *in vivo* recombination can be exploited to generate libraries that are not limited in size by the transformation efficiency of *E. coli*.

[244] For example, the Cre-loxP system may be used to generate dimer libraries with 10^{10}, 10^{11}, 10^{12}, 10^{13}, or greater diversity. In some embodiments, *E. coli* as a host for one naïve monomer library and a filamentous phage that carries a second naïve monomer library are used. The library size in this case is limited only by the number of infective phage (carrying one library) and the number of infectible *E. coli* cells (carrying the other library). For example, infecting 10^{12} *E. coli* cells (1L at OD600=1) with $>10^{12}$ phage could produce as many as 10^{12} dimer combinations.

[245] Selection of multimers can be accomplished using a variety of techniques including those mentioned above for identifying monomer domains. Other selection methods include, e.g., a selection based on an improved affinity or avidity or altered specificity for the ligand compared to selected monomer domains. For example, a selection can be based on selective binding to specific cell types, or to a set of related cells or protein types (e.g., different virus serotypes). Optimization of the property selected for, e.g., avidity of a ligand, can then be achieved by recombining the domains, as well as manipulating amino acid sequence of the individual monomer domains or the linker domain or the nucleotide sequence encoding such domains, as mentioned in the present invention.

[246] One method for identifying multimers can be accomplished by displaying the multimers. As with the monomer domains, the multimers are optionally expressed or displayed on a variety of display systems, e.g., phage display, ribosome display, polysome display, nucleotide-linked display (*see, e.g.*, U.S. Patent Nos. 6,281,344; 6,194,550, 6,207,446, 6,214,553, and 6,258,558) and/or cell surface display, as described above. Cell surface displays can include but are not limited to *E. coli*, yeast or mammalian cells. In addition, display libraries of multimers with multiple binding sites can be panned for avidity or affinity or altered specificity for a ligand or for multiple ligands.

[247] Monomers or multimers can be screened for target binding activity in yeast cells using a two-hybrid screening assay. In this type of screen the monomer or multimer library to be screened is cloned into a vector that directs the formation of a fusion protein between each monomer or multimer of the library and a yeast transcriptional activator fragment (i.e., Gal4). Sequences encoding the “target” protein are cloned into a vector that results in the production of a fusion protein between the target and the remainder of the Gal4 protein (the DNA binding domain). A third plasmid contains a reporter gene downstream of the DNA sequence of the Gal4 binding site. A monomer that can bind to the target protein brings with it the Gal4 activation domain, thus reconstituting a functional Gal4 protein. This functional Gal4 protein bound to the binding site upstream of the reporter gene results in the expression of the reporter gene and selection of the monomer or multimer as a target binding protein. (see Chien et.al. (1991) *Proc. Natl. Acad. Sci.* (USA) 88:9578; Fields S. and Song O. (1989) *Nature* 340: 245) Using a two-hybrid system for library screening is further described in U.S. Patent No. 5,811,238 (see also Silver S.C. and Hunt S.W. (1993) *Mol. Biol. Rep.* 17:155; Durfee et al. (1993) *Genes Devel.* 7:555; Yang et al. (1992) *Science* 257:680; Luban et al. (1993) *Cell* 73:1067; Hardy et al. (1992) *Genes Devel.* 6:801; Bartel et al. (1993) *Biotechniques* 14:920; and Vojtek et al. (1993) *Cell* 74:205). Another useful screening system for carrying out the present invention is the *E.coli*/BCCP interactive screening system (Germino et al. (1993) *Proc. Nat. Acad. Sci.* (U.S.A.) 90:993; Guarente L. (1993) *Proc. Nat. Acad. Sci.* (U.S.A.) 90:1639).

[248] Other variations include the use of multiple binding compounds, such that monomer domains, multimers or libraries of these molecules can be simultaneously screened for a multiplicity of ligands or compounds that have different binding specificity. Multiple predetermined ligands or compounds can be concomitantly screened in a single library, or sequential screening against a number of monomer domains or multimers. In one variation, multiple ligands or compounds, each encoded on a separate bead (or subset of beads), can be mixed and incubated with monomer domains, multimers or libraries of these molecules under suitable binding conditions. The collection of beads, comprising multiple ligands or compounds, can then be used to isolate, by affinity selection, selected monomer domains, selected multimers or library members. Generally, subsequent affinity screening rounds can include the same mixture of beads, subsets thereof, or beads containing only one or two individual ligands or compounds. This approach affords efficient screening, and is compatible with laboratory automation, batch processing, and high throughput screening methods.

[249] In another embodiment, multimers can be simultaneously screened for the ability to bind multiple ligands, wherein each ligand comprises a different label. For example, each ligand can be labeled with a different fluorescent label, contacted simultaneously with a multimer or multimer library. Multimers with the desired affinity are then identified (e.g., by FACS sorting) based on the presence of the labels linked to the desired labels.

[250] Libraries of either monomer domains or multimers (referred in the following discussion for convenience as "affinity agents") can be screened (i.e., panned) simultaneously against multiple ligands in a number of different formats. For example, multiple ligands can be screened in a simple mixture, in an array, displayed on a cell or tissue (e.g., a cell or tissue provides numerous molecules that can be bound by the monomer domains or multimers of the invention), and/or immobilized. The libraries of affinity agents can optionally be displayed on yeast or phage display systems. Similarly, if desired, the ligands (e.g., encoded in a cDNA library) can be displayed in a yeast or phage display system.

[251] Initially, the affinity agent library is panned against the multiple ligands. Optionally, the resulting "hits" are panned against the ligands one or more times to enrich the resulting population of affinity agents.

[252] If desired, the identity of the individual affinity agents and/or ligands can be determined. In some embodiments, affinity agents are displayed on phage. Affinity agents identified as binding in the initial screen are divided into a first and second portion. The first portion is infected into bacteria, resulting in either plaques or bacterial colonies, depending on the type of phage used. The expressed phage are immobilized and then probed with ligands displayed in phage selected as described below.

[253] The second portion are coupled to beads or otherwise immobilized and a phage display library containing at least some of the ligands in the original mixture is contacted to the immobilized second portion. Phage that bind to the second portion are subsequently eluted and contacted to the immobilized phage described in the paragraph above. Phage-phage interactions are detected (e.g., using a monoclonal antibody specific for the ligand-expressing phage) and the resulting phage polynucleotides can be isolated.

[254] In some embodiments, the identity of an affinity agent-ligand pair is determined. For example, when both the affinity agent and the ligand are displayed on a phage or yeast, the DNA from the pair can be isolated and sequenced. In some embodiments, polynucleotides specific for the ligand and affinity agent are amplified. Amplification primers for each reaction can include 5' sequences that are complementary such that the resulting amplification products are fused, thereby forming a hybrid polynucleotide comprising a polynucleotide encoding at least a portion of the affinity agent and at least a portion of the ligand. The resulting hybrid can be used to probe affinity agent or ligand (e.g., cDNA-encoded) polynucleotide libraries to identify both affinity agent and ligand.

[255] The above-described methods can be readily combined with "walking" to simultaneously generate and identify multiple multimers, each of which bind to a ligand in a mixture of ligands. In these embodiments, a first library of affinity agents (monomer domains or multimers) are panned against multiple ligands and the eluted affinity agents are linked to the first or a second library of affinity agents to form a library of multimeric affinity agents (e.g., comprising 2, 3, 4, 5, 6, 7, 8, 9, or more monomer), which are subsequently panned against the multiple ligands. This method can be repeated to continue to generate larger multimeric affinity agents. Increasing the number of monomer domains may result in increased affinity and avidity for a particular target. For example, the inventors have found that trimers of monomer domains that bind CD28 have a higher affinity than dimmers, which in turn have a higher affinity than single CD28-binding monomer domains alone. Of course, at each stage, the panning is optionally repeated to enrich for significant binders. In some cases, walking will be facilitated by inserting recombination sites (e.g., lox sites) at the ends of monomers and recombining monomer libraries by a recombinase-mediated event.

[256] The selected multimers of the above methods can be further manipulated, e.g., by recombining or shuffling the selected multimers (recombination can occur between or within multimers or both), mutating the selected multimers, and the like. This results in altered multimers which then can be screened and selected for members that have an enhanced property compared to the selected multimer, thereby producing selected altered multimers.

[257] In view of the description herein, it is clear that the following process may be followed. Naturally or non-naturally occurring monomer domains may be recombined or variants may be formed. Optionally the domains initially or later are selected for those sequences that are less likely to be immunogenic in the host for which they are intended. Optionally, a phage library comprising the recombined domains is panned for a desired affinity. Monomer domains or multimers expressed by the phage may be screened for IC_{50} for a target. Hetero- or homo-meric multimers may be selected. The selected polypeptides may be selected for their affinity to any target, including, e.g., hetero- or homo-multimeric targets.

[258] Linkers, multimers or selected multimers produced by the methods indicated above and below are features of the present invention. Libraries comprising multimers, e.g, a library comprising about 100, 250, 500 or more members produced by the methods of the present invention or selected by the methods of the present invention are provided. In some embodiments, one or more cell comprising members of the libraries, are also included. Libraries of the recombinant polypeptides are also a feature of the present invention, e.g., a library comprising about 100, 250, 500 or more different recombinant polypetides.

[259] Compositions of the present invention can be bound to a matrix of an affinity material, e.g., the recombinant polypeptides. Examples of affinity material include, e.g., beads, a column, a solid support, and/or the like.

VII. THERAPEUTIC AND PROPHYLACTIC TREATMENT METHODS

[260] The present invention also includes methods of therapeutically or prophylactically treating a disease or disorder by administering *in vivo* or *ex vivo* one or more nucleic acids or polypeptides of the invention described above (or compositions comprising a pharmaceutically acceptable excipient and one or more such nucleic acids or polypeptides) to a subject, including, *e.g.,* a mammal, including a human, primate, mouse, pig, cow, goat, rabbit, rat, guinea pig, hamster, horse, sheep; or a non-mammalian vertebrate such as a bird (*e.g.*, a chicken or duck), fish, or invertebrate.

[261] c-MET antagonists, including c-MET-binding monomer domains or multimers of the invention, are useful in treatment of human cancers expressing c-MET. A compendium of human cancers known to express c-MET and/or its ligand HGF can be found in Table 1, p. 922 of Birchmeier, C., Birchmeier, W., Gherardi, E. & Vande Woude, G. F. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol* 4, 915-25 (2003). c-MET antagonists are of therapeutic value in all of these cancers. More particularly, c-MET antagonists are useful in meeting a significant unmet medical need in pancreatic cancer, mesothelioma, myeloma, head and neck cancer, lung (NSCLC) cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, glioblastoma and osteosarcoma. Other exemplary cancers include bladder, breast, cervical, colorectal, oesophageal, gastric, kidney, liver, lung, nasopharyngeal, gall bladder, prostate or thyroid cancer, osteosarcoma, synovial sarcoma, rhabdomosarcoma, MFH/fibrosarcoma, Kaposi's sarcoma, multiple myeloma, lymphomas, adult T-cell leukemia, glioblastomas, astrocytomas, melanoma, and Wilm's tumor.

[262] Individuals can be treated, for example, by once weekly intravenous injections of a soluble formulation of a c-MET antagonist composed of c-MET-binding monomer domains or multimers of the invention, optionally in combination with one or more additional therapeutic entities, for example either biologic or chemotherapeutic.

[263] In one aspect of the invention, in *ex vivo* methods, one or more cells or a population of cells of interest of the subject (*e.g.*, tumor cells, tumor tissue sample, organ cells, blood cells, cells of the skin, lung, heart, muscle, brain, mucosae, liver, intestine, spleen, stomach, lymphatic system, cervix, vagina, prostate, mouth, tongue, *etc.*) are obtained or removed from the subject and contacted with an amount of a selected monomer domain and/or multimer of the invention that is effective in prophylactically or therapeutically treating the disease, disorder, or other condition. The contacted cells are then returned or delivered to the subject to the site from which they were obtained or to another site (*e.g.*, including those defined above) of interest in the subject to be treated. If desired, the contacted cells can be grafted onto a tissue, organ, or system site (including all described above) of interest in the subject using standard and well-known grafting techniques or, *e.g.*, delivered to the blood or lymph system using standard delivery or transfusion techniques.

[264] The invention also provides *in vivo* methods in which one or more cells or a population of cells of interest of the subject are contacted directly or indirectly with an amount of a selected monomer domain and/or multimer of the invention effective in prophylactically or therapeutically treating the disease, disorder, or other condition. In direct contact/administration formats, the selected monomer domain and/or multimer is typically administered or transferred directly to the cells to be treated or to the tissue site of interest (*e.g.*, tumor cells, tumor tissue sample, organ cells, blood cells, cells of the skin, lung, heart, muscle, brain, mucosae, liver, intestine, spleen, stomach, lymphatic system, cervix, vagina, prostate, mouth, tongue, *etc.*) by any of a variety of formats, including topical administration, injection (*e.g.*, by using a needle or syringe), or vaccine or gene gun delivery, pushing into a tissue, organ, or skin site. The selected monomer domain and/or multimer can be delivered, for example, intramuscularly, intradermally, subdermally, subcutaneously, orally, intraperitoneally, intrathecally, intravenously, or placed within a cavity of the body (including, *e.g.*, during surgery), or by inhalation or vaginal or rectal administration.

[265] In *in vivo* indirect contact/administration formats, the selected monomer domain and/or multimer is typically administered or transferred indirectly to the cells to be treated or to the tissue site of interest, including those described above (such as, *e.g.*, skin cells, organ systems, lymphatic system, or blood cell system, *etc.*), by contacting or administering the polypeptide of the invention directly to one or more cells or population of cells from which treatment can be facilitated. For example, tumor cells within the body of the subject can be treated by contacting cells of the blood or lymphatic system, skin, or an organ with a sufficient amount of the selected monomer domain and/or multimer such that delivery of the selected monomer domain and/or multimer to the site of interest (*e.g.*, tissue, organ, or cells of interest or blood or lymphatic system within the body) occurs and effective prophylactic or therapeutic treatment results. Such contact, administration, or transfer is typically made by using one or more of the routes or modes of administration described above.

[266] In another aspect, the invention provides *ex vivo* methods in which one or more cells of interest or a population of cells of interest of the subject (*e.g.*, tumor cells, tumor tissue sample, organ cells, blood cells, cells of the skin, lung, heart, muscle, brain, mucosae, liver, intestine, spleen, stomach, lymphatic system, cervix, vagina, prostate, mouth, tongue, *etc.*) are obtained or removed from the subject and transformed by contacting said one or more cells or population of cells with a polynucleotide construct comprising a nucleic acid sequence of the invention that encodes a biologically active polypeptide of interest (*e.g.*, a selected monomer domain and/or multimer) that is effective in prophylactically or therapeutically treating the disease, disorder, or other condition. The one or more cells or population of cells is contacted with a sufficient amount of the polynucleotide construct and a promoter controlling expression of said nucleic acid sequence such that uptake of the polynucleotide construct (and promoter) into the cell(s) occurs and sufficient expression of the target nucleic acid sequence of the invention results to produce an amount of the biologically active polypeptide, encoding a selected monomer domain and/or multimer, effective to prophylactically or therapeutically treat the disease, disorder, or condition. The polynucleotide construct can include a promoter sequence (*e.g.*, CMV promoter sequence) that controls expression of the nucleic acid sequence of the invention and/or, if desired, one or more additional nucleotide sequences encoding at least one or more of another polypeptide of the invention, a cytokine, adjuvant, or co-stimulatory molecule, or other polypeptide of interest.

[267] Following transfection, the transformed cells are returned, delivered, or transferred to the subject to the tissue site or system from which they were obtained or to another site (*e.g.*, tumor cells, tumor tissue sample, organ cells, blood cells, cells of the skin, lung, heart, muscle, brain, mucosae, liver, intestine, spleen, stomach, lymphatic system, cervix, vagina, prostate, mouth, tongue, *etc.*) to be treated in the subject. If desired, the cells can be grafted onto a tissue, skin, organ, or body system of interest in the subject using standard and well-known grafting techniques or delivered to the blood or lymphatic system using standard delivery or transfusion techniques. Such delivery, administration, or transfer of transformed cells is typically made by using one or more of the routes or modes of administration described above. Expression of the target nucleic acid occurs naturally or can be induced (as described in greater detail below) and an amount of the encoded polypeptide is expressed sufficient and effective to treat the disease or condition at the site or tissue system.

[268] In another aspect, the invention provides *in vivo* methods in which one or more cells of interest or a population of cells of the subject (*e.g.*, including those cells and cells systems and subjects described above) are transformed in the body of the subject by contacting the cell(s) or population of cells with (or administering or transferring to the cell(s) or population of cells using one or more of the routes or modes of administration described above) a polynucleotide construct comprising a nucleic acid sequence of the invention that encodes a biologically active polypeptide of interest (*e.g.*, a selected monomer domain and/or multimer) that is effective in prophylactically or therapeutically treating the disease, disorder, or other condition.

[269] The polynucleotide construct can be directly administered or transferred to cell(s) suffering from the disease or disorder (*e.g.*, by direct contact using one or more of the routes or modes of administration described above). Alternatively, the polynucleotide construct can be indirectly administered or transferred to cell(s) suffering from the disease or disorder by first directly contacting non-diseased cell(s) or other diseased cells using one or more of the routes or modes of administration described above with a sufficient amount of the polynucleotide construct comprising the nucleic acid sequence encoding the biologically active polypeptide, and a promoter controlling expression of the nucleic acid sequence, such that uptake of the polynucleotide construct (and promoter) into the cell(s) occurs and sufficient expression of the nucleic acid sequence of the invention results to produce an amount of the biologically active polypeptide effective to prophylactically or therapeutically treat the disease or disorder, and whereby the polynucleotide construct or the resulting expressed polypeptide is transferred naturally or automatically from the initial delivery site, system, tissue or organ of the subject's body to the diseased site, tissue, organ or system of the subject's body (*e.g.*, via the blood or lymphatic system). Expression of the target nucleic acid occurs naturally or can be induced (as described in greater detail below) such that an amount of expressed polypeptide is sufficient and effective to treat the disease or condition at the site or tissue system. The polynucleotide construct can include a promoter sequence (*e.g.*, CMV promoter sequence) that controls expression of the nucleic acid sequence and/or, if desired, one or more additional nucleotide sequences encoding at least one or more of another polypeptide of the invention, a cytokine, adjuvant, or co-stimulatory molecule, or other polypeptide of interest.

[270] In each of the *in vivo* and *ex vivo* treatment methods as described above, a composition comprising an excipient and the polypeptide or nucleic acid of the invention can be administered or delivered. In one aspect, a composition comprising a pharmaceutically acceptable excipient and a polypeptide or nucleic acid of the invention is administered or delivered to the subject as described above in an amount effective to treat the disease or disorder.

[271] In another aspect, in each *in vivo* and *ex vivo* treatment method described above, the amount of polynucleotide administered to the cell(s) or subject can be an amount such that uptake of said polynucleotide into one or more cells of the subject occurs and sufficient expression of said nucleic acid sequence results to produce an amount of a biologically active polypeptide effective to enhance an immune response in the subject, including an immune response induced by an immunogen (*e.g.*, antigen). In another aspect, for each such method, the amount of polypeptide administered to cell(s) or subject can be an amount sufficient to enhance an immune response in the subject, including that induced by an immunogen (*e.g.*, antigen).

[272] In yet another aspect, in an *in vivo* or *ex vivo* treatment method in which a polynucleotide construct (or composition comprising a polynucleotide construct) is used to deliver a physiologically active polypeptide to a subject, the expression of the polynucleotide construct can be induced by using an inducible on- and off-gene expression system. Examples of such on- and off-gene expression systems include the Tet-On™ Gene Expression System and Tet-Off™ Gene Expression System (*see, e.g.*, Clontech Catalog 2000, pg. 110-111 for a detailed description of each such system), respectively. Other controllable or inducible on- and off-gene expression systems are known to those of ordinary skill in the art. With such system, expression of the target nucleic of the polynucleotide construct can be regulated in a precise, reversible, and quantitative manner. Gene expression of the target nucleic acid can be induced, for example, after the stable transfected cells containing the polynucleotide construct comprising the target nucleic acid are delivered or transferred to or made to contact the tissue site, organ or system of interest. Such systems are of particular benefit in treatment methods and formats in which it is advantageous to delay or precisely control expression of the target nucleic acid (*e.g.*, to allow time for completion of surgery and/or healing following surgery; to allow time for the polynucleotide construct comprising the target nucleic acid to reach the site, cells, system, or tissue to be treated; to allow time for the graft containing cells transformed with the construct to become incorporated into the tissue or organ onto or into which it has been spliced or attached, *etc.*).

VIII. ADDITIONAL MULTIMER USES

[273] The potential applications of multimers of the present invention are diverse and include any use where an affinity agent is desired.

[274] In some cases, a pair of monomers or multimers are selected to bind to the same target (i.e., for use in sandwich-based assays). To select a matched monomer or multimer pair, two different monomers or multimers typically are able to bind the target protein simultaneously. One approach to identify such pairs involves the following:

(1) immobilizing the phage or protein mixture that was previously selected to bind the target protein;

(2) contacting the target protein to the immobilized phage or protein and washing;

(3) contacting the phage or protein mixture to the bound target and washing; and

(4) eluting the bound phage or protein without eluting the immobilized phage or protein.

[275] One use of the multimers or monomer domains of the invention is use to replace antibodies or other affinity agents in detection or other affinity-based assays. Thus, in some embodiments, monomer domains or multimers are selected against the ability to bind components other than a target in a mixture. The general approach can include performing the affinity selection under conditions that closely resemble the conditions of the assay, including mimicking the composition of a sample during the assay. Thus, a step of selection could include contacting a monomer domain or multimer to a mixture not including the target ligand and selecting against any monomer domains or multimers that bind to the mixture. Thus, the mixtures (absent the target ligand, which could be depleted using an antibody, monomer domain or multimer) representing the sample in an assay (serum, blood, tissue, cells, urine, semen, etc) can be used as a blocking agent. Such subtraction is useful, e.g., to create pharmaceutical proteins that bind to their target but not to other serum proteins or non-target tissues.

[276] For example, the invention can be used in the application for creating antagonists, where the selected monomer domains or multimers block the interaction between two proteins, e.g., the α and β chains of Met and/or between Met and HGF. Optionally, the invention can generate agonists. For example, multimers binding two different proteins, e.g., enzyme and substrate, can enhance protein function, including, for example, enzymatic activity and/or substrate conversion.

[277] In some embodiments, the monomer domains are used for ligand inhibition, ligand clearance or ligand stimulation. Possible ligands in these methods, include, e.g., HGF.

[278] If inhibition of ligand binding to a receptor is desired, a monomer domain is selected that binds to the ligand (e.g., HGF) at a portion of the ligand that contacts the ligand's receptor, or that binds to the receptor at a portion of the receptor that binds contacts the ligand, thereby preventing the ligand-receptor interaction. The monomer domains can optionally be linked to a half-life extender, if desired.

[279] Ligand clearance refers to modulating the half-life of a soluble ligand in bodily fluid. For example, most monomer domains, absent a half-life extender, have a short half-life. Thus, binding of a monomer domain to the ligand will reduce the half-life of the ligand, thereby reducing ligand concentration by clearing the ligand through the kidney so long as the complex is no larger than the maximum size able to pass through the kidney (less than about 50 or 40 kD). The portion of the ligand (e.g., HGF) bound by the monomer domain will generally not matter, though it may be beneficial to bind the ligand at the portion of the ligand that binds to its receptor (e.g., Met), thereby further inhibiting the ligand's effect. This method is useful for reducing the concentration of any molecule in the bloodstream.

[280] Alternatively, a multimer comprising a first monomer domain that binds to a half-life extender and a second monomer domain that binds to a portion of the ligand that does not bind to the ligand's receptor can be used to increase the half-life of the ligand.

[281] In another embodiment, a multimer comprising a first monomer domain that binds to the ligand and a second monomer domain that binds to the receptor can be used to increase the effective affinity of the ligand for the receptor.

[282] In another embodiment, multimers comprising at least two monomers that bind to receptors are used to bring two receptors into proximity by both binding the multimer, thereby activating the receptors.

[283] Further examples of potential uses of the invention include monomer domains, and multimers thereof, that are capable of drug binding (e.g., binding radionucleotides for targeting, pharmaceutical binding for half-life extension of drugs, controlled substance binding for overdose treatment and addiction therapy), immune function modulating (e.g., immunogenicity blocking by binding such receptors as CTLA-4, immunogenicity enhancing by binding such receptors as CD80,or complement activation by Fc type binding), and specialized delivery (e.g., slow release by linker cleavage, electrotransport domains, dimerization domains, or specific binding to: cell entry domains, clearance receptors such as FcR, oral delivery receptors such as plgR for trans-mucosal transport, and blood-brain transfer receptors such as transferrinR).

[284] In further embodiments, monomers or multimers can be linked to a detectable label (e.g., Cy3, Cy5, etc.) or linked to a reporter gene product (e.g., CAT, luciferase, horseradish peroxidase, alkaline phosphotase, GFP, etc.).

[285] Monomers or multimers of the invention that bind to Met may also be used in diagnostic and predictive applications in which is is useful to detect Met. For example, detection of Met can be used to predict prognosis of breast cancer, wherein higher abundance of Met than in a normal tissue indicates a poor prognosis. *See, e.g.*, U.S. Patent No. 6,673,559.

IX. FURTHER MANIPULATING MONOMER DOMAINS AND/OR MULTIMER NUCLEIC ACIDS AND POLYPEPTIDES

[286] As mentioned above, the polypeptide of the present invention can be altered. Descriptions of a variety of diversity generating procedures for generating modified or altered nucleic acid sequences encoding these polypeptides are described herein and the references cited therein.

[287] Another aspect of the present invention includes the cloning and expression of monomer domains, selected monomer domains, multimers and/or selected multimers coding nucleic acids. Thus, multimer domains can be synthesized as a single protein using expression systems well known in the art. General texts which describe molecular biological techniques useful herein, including the use of vectors, promoters and many other topics relevant to expressing nucleic acids such as monomer domains, selected monomer domains, multimers and/or selected multimers, include Berger and Kimmel, <u>Guide to Molecular Cloning Techniques, Methods in Enzymology</u> volume 152 Academic Press, Inc., San Diego, CA (Berger); Sambrook et al., <u>Molecular Cloning - A Laboratory Manual</u> (2nd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989 ("Sambrook") and <u>Current Protocols in Molecular Biology</u>, F.M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (supplemented through 1999) ("Ausubel")). Examples of techniques sufficient to direct persons of skill through *in vitro* amplification methods, useful in identifying, isolating and cloning monomer domains and multimers coding nucleic acids, including the polymerase chain reaction (PCR) the ligase chain reaction (LCR), Q-replicase amplification and other RNA polymerase mediated techniques (*e.g.,* NASBA), are found in Berger, Sambrook, and Ausubel, as well as Mullis *et al.*, (1987) U.S. Patent No. 4,683,202; *PCR Protocols A Guide to Methods and Applications* (Innis *et al.* eds) Academic Press Inc. San Diego, CA (1990) (Innis); Arnheim & Levinson (October 1, 1990) *C&EN* 36-47; *The Journal Of NIH Research* (1991) 3, 81-94; (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86, 1173; Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87, 1874; Lomell *et al.* (1989) *J. Clin. Chem* 35, 1826; Landegren *et al.*, (1988) *Science* 241, 1077-1080; Van Brunt (1990) *Biotechnology* 8, 291-294; Wu and Wallace, (1989) *Gene* 4, 560; Barringer *et al.* (1990) *Gene* 89, 117, and Sooknanan and Malek (1995) *Biotechnology* 13: 563-564. Improved methods of cloning *in vitro* amplified nucleic acids are described in Wallace *et al.*, U.S. Pat. No. 5,426,039. Improved methods of amplifying large nucleic acids by PCR are summarized in Cheng *et al.*

(1994) *Nature* 369: 684-685 and the references therein, in which PCR amplicons of up to 40kb are generated. One of skill will appreciate that essentially any RNA can be converted into a double stranded DNA suitable for restriction digestion, PCR expansion and sequencing using reverse transcriptase and a polymerase. *See*, Ausubel, Sambrook and Berger, *all supra.*

[288] The present invention also relates to the introduction of vectors of the invention into host cells, and the production of monomer domains, selected monomer domains, multimers and/or selected multimers of the invention by recombinant techniques. Host cells are genetically engineered (i.e., transduced, transformed or transfected) with the vectors of this invention, which can be, for example, a cloning vector or an expression vector. The vector can be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants, or amplifying the monomer domain, selected monomer domain, multimer and/or selected multimer gene(s) of interest. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to those skilled in the art and in the references cited herein, including, e.g., Freshney (1994) *Culture of Animal Cells, a Manual of Basic Technique*, third edition, Wiley- Liss, New York and the references cited therein.

[289] As mentioned above, the polypeptides of the invention can also be produced in non-animal cells such as plants, yeast, fungi, bacteria and the like. Indeed, as noted throughout, phage display is an especially relevant technique for producing such polypeptides. In addition to Sambrook, Berger and Ausubel, details regarding cell culture can be found in Payne *et al.* (1992) *Plant Cell and Tissue Culture in Liquid Systems* John Wiley & Sons, Inc. New York, NY; Gamborg and Phillips (eds) (1995) *Plant Cell, Tissue and Organ Culture*; Fundamental Methods Springer Lab Manual, Springer-Verlag (Berlin Heidelberg New York) and Atlas and Parks (eds) *The Handbook of Microbiological Media* (1993) CRC Press, Boca Raton, FL.

[290] The present invention also includes alterations of monomer domains, immuno-domains and/or multimers to improve pharmacological properties, to reduce immunogenicity, or to facilitate the transport of the multimer and/or monomer domain into a cell or tissue (e.g., through the blood-brain barrier, or through the skin). These types of alterations include a variety of modifications (e.g., the addition of sugar-groups or glycosylation), the addition of PEG, the addition of protein domains that bind a certain protein (e.g., HSA or other serum protein), the addition of proteins fragments or sequences that signal movement or transport into, out of and through a cell. Additional components can also be added to a multimer and/or monomer domain to manipulate the properties of the multimer and/or monomer domain. A variety of components can also be added including, e.g., a domain that binds a known receptor (e.g., a Fc-region protein domain that binds a Fc receptor), a toxin(s) or part of a toxin, a prodomain that can be optionally cleaved off to activate the multimer or monomer domain, a reporter molecule (e.g., green fluorescent protein), a component that bind a reporter molecule (such as a radionuclide for radiotherapy, biotin or avidin) or a combination of modifications.

X. ANIMAL MODELS

[291] Another aspect of the invention is the development of specific non-human animal models in which to test the immunogenicity of the monomer or multimer domains. The method of producing such non-human animal model comprises: introducing into at least some cells of a recipient non-human animal, vectors comprising genes encoding a plurality of human proteins from the same family of proteins, wherein the genes are each operably linked to a promoter that is functional in at least some of the cells into which the vectors are introduced such that a genetically modified non-human animal is obtained that can express the plurality of human proteins from the same family of proteins.

[292] Suitable non-human animals employed in the practice of the present invention include all vertebrate animals, except humans (e.g., mouse, rat, rabbit, sheep, and the like). Typically, the plurality of members of a family of proteins includes at least two members of that family, and usually at least ten family members. In some embodiments, the plurality includes all known members of the family of proteins. Exemplary genes that can be used include those encoding monomer domains, such as, for example, members of the LDL receptor class A-domain family, the EGF-like domain family, as well as the other domain families described herein.

[293] The non-human animal models of the present invention can be used to screen for immunogenicity of a monomer or multimer domain that is derived from the same family of proteins expressed by the non-human animal model. The present invention includes the non-human animal model made in accordance with the method described above, as well as transgenic non-human animals whose somatic and germ cells contain and express DNA molecules encoding a plurality of human proteins from the same family of proteins (such as the monomer domains described herein), wherein the DNA molecules have been introduced into the transgenic non-human animal at an embryonic stage, and wherein the

DNA molecules are each operably linked to a promoter in at least some of the cells in which the DNA molecules have been introduced.

[294] An example of a mouse model useful for screening LDL receptor class A-domain derived binding proteins is described as follows. Gene clusters encoding the wild type human LDL receptor class A-domain monomers are amplified from human cells using PCR. Almost all of the 200 different A-domains can be amplified with only three separate PCR amplification reactions of about 7kb each. These fragments are then used to generate transgenic mice according to the method described above. The transgenic mice will recognize the human A-domains as “self", thus mimicking the “selfness” of a human with regard to A-domains. Individual A-domain-derived monomers or multimers are tested in these mice by injecting the A-domain-derived monomers or multimers into the mice, then analyzing the immune response (or lack of response) generated. The mice are tested to determine if they have developed a mouse anti-human response (MAHR). Monomers and multimers that do not result in the generation of a MAHR are likely to be non-immunogenic when administered to humans.

[295] Historically, MAHR test in transgenic mice is used to test individual proteins in mice that are transgenic for that single protein. In contrast, the above described method provides a non-human animal model that recognizes an entire family of human proteins as "self," and that can be used to evaluate a huge number of variant proteins that each are capable of vastly varied binding activities and uses.

XI. *KITS*

[296] Kits comprising the components needed in the methods (typically in an unmixed form) and kit components (packaging materials, instructions for using the components and/or the methods, one or more containers (reaction tubes, columns, etc.)) for holding the components are a feature of the present invention. Kits of the present invention may contain a multimer library, or a single type of monomer or multimer. Kits can also include reagents suitable for promoting target molecule binding, such as buffers or reagents that facilitate detection, including detectably-labeled molecules. Standards for calibrating a ligand binding to a monomer domain or the like, can also be included in the kits of the invention.

[297] The present invention also provides commercially valuable binding assays and kits to practice the assays. In some of the assays of the invention, one or more ligand is employed to detect binding of a monomer domain, immuno-domains and/or multimer. Such assays are based on any known method in the art, e.g., flow cytometry, fluorescent microscopy, plasmon resonance, and the like, to detect binding of a ligand(s) to the monomer domain and/or multimer.

[298] Kits based on the assay are also provided. The kits typically include a container, and one or more ligand. The kits optionally comprise directions for performing the assays, additional detection reagents, buffers, or instructions for the use of any of these components, or the like. Alternatively, kits can include cells, vectors, (e.g., expression vectors, secretion vectors comprising a polypeptide of the invention), for the expression of a monomer domain and/or a multimer of the invention.

[299] In a further aspect, the present invention provides for the use of any composition, monomer domain, immuno-domain, multimer, cell, cell culture, apparatus, apparatus component or kit herein, for the practice of any method or assay herein, and/or for the use of any apparatus or kit to practice any assay or method herein and/or for the use of cells, cell cultures, compositions or other features herein as a therapeutic formulation. The manufacture of all components herein as therapeutic formulations for the treatments described herein is also provided.

XII. INTEGRATED SYSTEMS

[300] The present invention provides computers, computer readable media and integrated systems comprising character strings corresponding to monomer domains, selected monomer domains, multimers and/or selected multimers and nucleic acids encoding such polypeptides. These sequences can be manipulated by in silico recombination methods, or by standard sequence alignment or word processing software.

[301] For example, different types of similarity and considerations of various stringency and character string length can be detected and recognized in the integrated systems herein. For example, many homology determination methods have been designed for comparative analysis of sequences of biopolymers, for spell checking in word processing, and for data retrieval from various databases. With an understanding of double-helix pair-wise complement interactions among 4 principal nucleobases in natural polynucleotides, models that simulate annealing of complementary homologous polynucleotide strings can also be used as a foundation of sequence alignment or other operations typically performed on the character strings corresponding to the sequences herein (*e.g.*, word-processing manipulations, construction of figures comprising sequence or subsequence character strings, output tables, etc.). An example of a software package with GOs for calculating sequence similarity is BLAST, which can be adapted to the present invention by inputting character strings corresponding to the sequences herein.

[302] BLAST is described in Altschul *et al.*, (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (available on the World Wide Web at ncbi.nlm.nih.gov). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff (1989) Proc. Natl. Acad. Sci. USA 89:10915).

[303] An additional example of a useful sequence alignment algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins & Sharp, (1989) CABIOS 5:151-153. The program can align, e.g., up to 300 sequences of a maximum length of 5,000 letters. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster can then be aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences can be aligned by a simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by a series of progressive, pairwise alignments. The program can also be used to plot a dendogram or tree representation of clustering relationships. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison. For example, in order to determine conserved amino acids in a monomer domain family or to compare the sequences of monomer domains in a family, the sequence of the invention, or coding nucleic acids, are aligned to provide structure-function information.

[304] In one aspect, the computer system is used to perform "in silico" sequence recombination or shuffling of character strings corresponding to the monomer domains. A variety of such methods are set forth in "Methods For Making Character Strings, Polynucleotides & Polypeptides Having Desired Characteristics" by Selifonov and Stemmer, filed February 5, 1999 (USSN 60/118854) and "Methods For Making Character Strings, Polynucleotides & Polypeptides Having Desired Characteristics" by Selifonov and Stemmer, filed October 12, 1999 (USSN 09/416,375). In brief, genetic operators are used in genetic algorithms to change given sequences, e.g., by mimicking genetic events such as mutation, recombination, death and the like. Multi-dimensional analysis to optimize sequences can be also be performed in the computer system, e.g., as described in the '375 application.

[305] A digital system can also instruct an oligonucleotide synthesizer to synthesize oligonucleotides, e.g., used for gene reconstruction or recombination, or to order oligonucleotides from commercial sources (e.g., by printing appropriate order forms or by linking to an order form on the Internet).

[306] The digital system can also include output elements for controlling nucleic acid synthesis (*e.g.*, based upon a sequence or an alignment of a recombinant, e.g., recombined, monomer domain as herein), i.e., an integrated system of the invention optionally includes an oligonucleotide synthesizer or an oligonucleotide synthesis controller. The system can include other operations that occur downstream from an alignment or other operation performed using a character string corresponding to a sequence herein, e.g., as noted above with reference to assays.

EXAMPLES

[307] The following example is offered to illustrate, but not to limit the claimed invention.

Example 1

[308] This example describes selection of monomer domains and the creation of multimers.

[309] Starting materials for identifying monomer domains and creating multimers from the selected monomer domains and procedures can be derived from any of a variety of human and/or non-human sequences. For example, to produce a selected monomer domain with specific binding for a desired ligand or mixture of ligands, one or more monomer domain gene(s) are selected from a family of monomer domains that bind to a certain ligand. The nucleic acid sequences encoding the one or more monomer domain gene can be obtained by PCR amplification of genomic DNA or cDNA, or optionally, can be produced synthetically using overlapping oligonucleotides.

[310] Most commonly, these sequences are then cloned into a cell surface display format (*i.e.*, bacterial, yeast, or mammalian (COS) cell surface display; phage display) for expression and screening. The recombinant sequences are transfected (transduced or transformed) into the appropriate host cell where they are expressed and displayed on the cell surface. For example, the cells can be stained with a labeled (e.g., fluorescently labeled), desired ligand. The stained cells are sorted by flow cytometry, and the selected monomer domains encoding genes are recovered (e.g., by plasmid isolation, PCR or expansion and cloning) from the positive cells. The process of staining and sorting can be repeated multiple times (e.g., using progressively decreasing concentrations of the desired ligand until a desired level of enrichment is obtained). Alternatively, any screening or detection method known in the art that can be used to identify cells that bind the desired ligand or mixture of ligands can be employed.

[311] The selected monomer domain encoding genes recovered from the desired ligand or mixture of ligands binding cells can be optionally recombined according to any of the methods described herein or in the cited references. The recombinant sequences produced in this round of diversification are then screened by the same or a different method to identify recombinant genes with improved affinity for the desired or target ligand. The diversification and selection process is optionally repeated until a desired affinity is obtained.

[312] The selected monomer domain nucleic acids selected by the methods can be joined together via a linker sequence to create multimers, e.g., by the combinatorial assembly of nucleic acid sequences encoding selected monomer domains by DNA ligation, or optionally, PCR-based, self-priming overlap reactions. The nucleic acid sequences encoding the multimers are then cloned into a cell surface display format (*i.e.*, bacterial, yeast, or mammalian (COS) cell surface display; phage display) for expression and screening. The recombinant sequences are transfected (transduced or transformed) into the appropriate host cell where they are expressed and displayed on the cell surface. For example, the cells can be stained with a labeled, e.g., fluorescently labeled, desired ligand or mixture of ligands. The stained cells are sorted by flow cytometry, and the selected multimers encoding genes are recovered (e.g., by PCR or expansion and cloning) from the positive cells. Positive cells include multimers with an improved avidity or affinity or altered specificity to the desired ligand or mixture of ligands compared to the selected monomer domain(s). The process of staining and sorting can be repeated multiple times (e.g., using progressively decreasing concentrations of the desired ligand or mixture of ligands until a desired level of enrichment is obtained). Alternatively, any screening or detection method known in the art that can be used to identify cells that bind the desired ligand or mixture of ligands can be employed.

[313] The selected multimer encoding genes recovered from the desired ligand or mixture of ligands binding cells can be optionally recombined according to any of the methods described herein or in the cited references. The recombinant sequences produced in this round of diversification are then screened by the same or a different method to identify recombinant genes with improved avidity or affinity or altered specificity for the desired or target ligand. The diversification and selection process is optionally repeated until a desired avidity or affinity or altered specificity is obtained.

Example 2

[314] This example describes *in vivo* intra-protein recombination to generate libraries of greater diversity.

[315] A monomer-encoding plasmid vector (pCK-derived vector; see below), flanked by orthologous *loxP* sites, was recombined in a Cre-dependent manner with a phage vector via its compatible *loxP* sites. The recombinant phage vectors were detected by PCR using primers specific for the recombinant construct. DNA sequencing indicated that the correct recombinant product was generated.

Reagents and experimental procedures

[316] pCK-*cre*-lox-Monomer-loxP. This vector has two particularly relevant features. First, it carries the *cre* gene, encoding the site-specific DNA recombinase Cre, under the control of P_{lac}. *Cre* was PCR-amplified from p705-*cre* (from *GeneBridges*) with *cre*-specific primers that incorporated *Xba*I (5') and *Sfi*I (3') at the ends of the PCR product. This product was digested with *Xba*I and *Sfi*I and cloned into the identical sites of pCK, a *bla*$^-$, Cm^R derivative of pCK110919-HC-Bla (pACYC ori), yielding pCK-*cre*.

[317] The second feature is the naïve A domain library flanked by two orthologous *loxP* sites, *loxP*(wild-type) and *loxP*(FAS), which are required for the site-specific DNA recombination catalyzed by Cre. *See, e.g.*, Siegel, R.W., *et al.*. FEBS Letters 505:467-473 (2001). These sites rarely recombine with another. *loxP* sites were built into pCK-*cre* sequentially. 5'-phosphorylated oligonucleotides loxP(K) and loxP(K_rc), carrying loxP(WT) and *EcoR*I and *Hin*DIII-compatible overhangs to allow ligation to digested *EcoR*I and *Hin*DIII-digested pCK, were hybridized together and ligated to pCK-*cre* in a standard ligation reaction (T4 ligase; overnight at 16C).

[318] The resulting plasmid was digested with *EcoR*I and *Sph*I and ligated to the hybridized, 5'-phosphorylated oligos loxP(L) and loxP (L_rc), which carry *loxP*(FAS) and *EcoR*I and *Sph*I-compatible overhangs. To prepare for library construction, a large-scale purification (Qiagen MAXI prep) of pCK-*cre*-lox-P(wt)-loxP(FAS) was performed according to Qiagen's protocol. The Qiagen-purified plasmid was subjected to CsCl gradient centrifugation for further purification. This construct was then digested with *Sph*I and *Bgl*II and ligated to digested naïve A domain library insert, which was obtained via a PCR-amplification of a preexisting A domain library pool. By design, the *loxP* sites andmonomer are in-frame, which generates monomers with *loxP*-encoded linkers. This library was utilized in the *in vivo* recombination procedure as detailed below.

[319] fUSE5HA-Monomer-lox-lox vector. The vector is a derivative of fUSE5 from George Smith's laboratory (University of Missouri). It was subsequently modified to carry an HA tag for immunodetection assays. *loxP* sites were built into fUSE5HA sequentially. 5'phosphorylated oligonucleotides loxP(I) *and* loxP(I)_rc, carrying loxP(WT), a string of stop codons and *Xma*I and *Sfi*I-compatible overhangs, were hybridized together and ligated to *Xma*I- and *Sfi*I-digested fUSE5HA in a standard ligation reaction (New England Biolabs T4 ligase; overnight at 16C).

[320] The resulting phage vector was next digested with *Xma*I and *Sph*I and ligated to the hybridized oligos loxP(J) and loxP(J)_rc, which carry *loxP*(FAS) and overhangs compatible with *Xma*I and *Sph*I. This construct was digested with *Xma*I/*Sfi*I and then ligated to pre-cut (*Xma*I/*Sfi*I) naïve A domain library insert (PCR product). The stop codons are located between the *loxP* sites, preventing expression of *gIII* and consequently, the production of infectious phage.

[321] The ligated vector/library was subsequently transformed into an *E. coli* host bearing a *gIII*-expressing *plasmid* that allows the rescue of the fUSE5HA-Monomer-lox-lox phage, as detailed below.

[322] **pCK-*gIII*.** This plasmid carries *gIII* under the control of its native promoter. It was constructed by PCR-amplifying *gIII* and its promoter from VCSM13 helper phage (Stratagene) with primers gIIIPromoter_EcoRI and gIIIPromoter_HinDIII. This product was digested with *Eco*RI and *Hin*DIII and cloned into the same sites of pCK110919-HC-Bla. As *gIII* is under the control of its own promoter, *gIII* expression is presumably constitutive. pCK-*gIII* was transformed into *E. coli* EC100 (Epicentre).

[323] ***In vivo* recombination procedure.** In summary, the procedure involves the following key steps: a) Production of infective (i.e. rescue) of fUSE5HA-Monomer-lox-lox library with an *E. coli* host expressing *gIII* from a plasmid; b) Cloning of 2nd library (pCK) and transformation into F^+ TG1 *E. coli*; c) Infection of the culture carrying the 2nd library with the rescued fUSE5HA-Monomer-lox-lox phage library.

[324] *a. Rescue of phage vector.* Electrocompetent cells carrying pCK-*gIII* were prepared by a standard protocol. These cells had a transformation frequency of 4 x 10^8/μg DNA and were electroporated with large-scale ligations (~5 μg vector DNA) of fUSE5HA-lox-lox vector and the naïve A domain library insert. After individual electroporations (100 ng DNA/electroporation) with ~ 70 μL cells/cuvette, 930 μL warm SOC media were added, and the cells were allowed to recover with shaking at 37C for 1 hour. Next, tetracycline was added to a final concentration of 0.2 μg/mL, and the cells were shaken for ~ 45 minutes at 37C. An aliquot of this culture was removed, 10-fold serially diluted and plated to determine the resulting library size (1.8 x 10^7). The remaining culture was diluted into 2 x 500 mL 2xYT (with 20 μg/mL chloramphenicol and 20 μg/mL tetracycline to select for pCK-*gIII* and the fUSE5HA-based vector, respectively) and grown overnight at 30°C.

[325] Rescued phage were harvested using a standard PEG/NaCl precipitation protocol. The titer was approximately 1 x 10^{12} transducing units/mL.

[326] *b. Cloning of the 2^{nd} library and transformation* into *an E. coli host*. The ligated pCK/ naïve A domain library is electroporated into a bacterial F^+ host, with an expected library size of approximately 10^8. After an hour-long recovery period at 37°C with shaking, the electroporated cells are diluted to OD_{600}~ 0.05 in 2xYT (plus 20 µg/mL chloramphenicol) and grown to mid-log phase at 37°C before infection by fUSEHA-Monomer-lox-lox.

[327] *c. Infection of the culture carrying the 2^{nd} library with the rescued fUSE5HA-Monomer-lox-lox phage library.* To maximize the generation of recombinants, a high infection rate (> 50%) of *E.coli* within a culture is desirable. The infectivity of *E. coli* depends on a number of factors, including the expression of the F pilus and growth conditions. *E. coli* backgrounds TG1 (carrying an F') and K91 (an Hfr strain) were hosts for the recombination system.

<u>Oligonucleotides</u>

loxP(K)
[P-5' agcttataacttcgtatagaaaggtatatacgaagttatagatctcgtgctgcatgcggtgcg]
(SEQ ID NO: 62)

loxP(K_rc)
[P-5' aattcgcaccgcatgcagcacgagatctataacttcgtatatacctttctatacgaagttataagct]
(SEQ ID NO: 63)

loxP(L)
[P-5' ataacttcgtatagcatacattatacgaagttatcgag] (SEQ ID NO: 64)

loxP (L_rc)
[P-5' ctcgataacttcgtataatgtatgctatacgaagttatg] (SEQ ID NO: 65)

loxP(I)
[P5'ccgggagcagggcatgctaagtgagtaataagtgagtaaataacttcgtatatacctttctatacgaagttatcg tctg] (SEQ ID NO: 66)

loxP(I)_rc

[P-5’ acgataacttcgtatagaaaggtatatacgaagttatttactcacttattactcacttagcatgccctgctc] (SEQ ID NO: 67)

loxP(J)

[5’ ccgggaccagtggcctctggggccataacttcgtatagcatacattatacgaagttatg] (SEQ ID NO: 68)

loxP(J)_rc

[5’ cataacttcgtataatgtatgctatacgaagttatggccccagaggccactggtc] (SEQ ID NO: 69)

gIIIPromoter_EcoRI

[5’ atggcgaattctcattgtcggcgcaactat (SEQ ID NO: 70)

gIIIPromoter_HinDIII

[5’ gataagctttcattaagactccttattacgcag] (SEQ ID NO: 71)

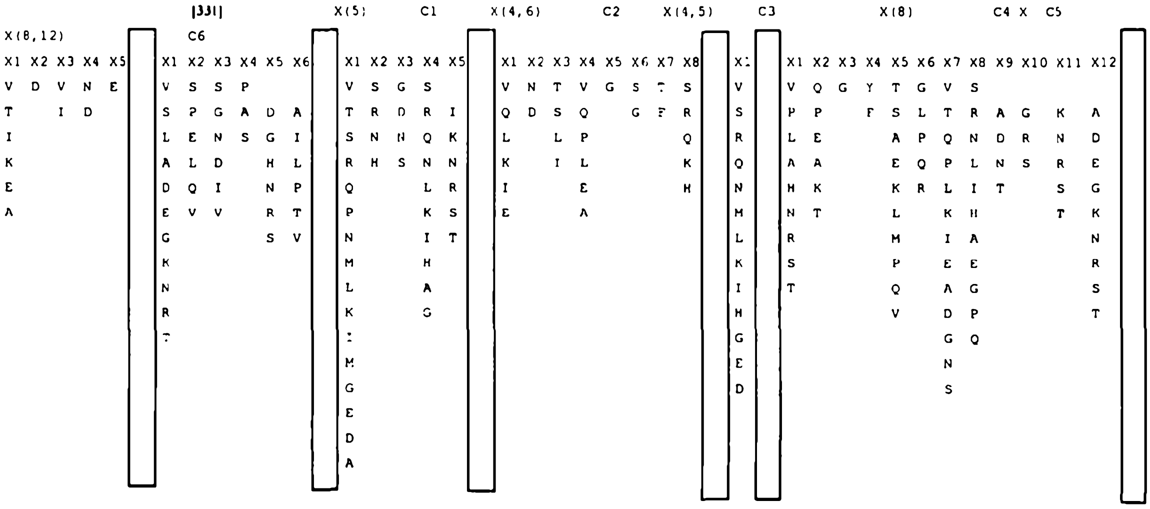
Example 6

[328] This example describes construction of an EGF-based monomer library.

[329] The CaEGF domain library, E3, encodes a protein domain of 36-43 amino acids having the following pattern:

X(5)C1-X(4/6)-C2-X(4,5)-C3-X(8)-C4-X(1)-C5-X(8/12)-C6 (SEQ ID NO: 72)

[330] The table below describes for each position which amino acids are encoded in the library based upon the natural diversity of human calcium binding EGF domains: Table discloses SEQ ID NOS 72 and 73.



[331] The library of DNA sequences, E3, encoding monomeric calcium binding EGF domains, was created by assembly PCR as described in Stemmer et al., Gene 164:49-53 (1995). The oligonucleotides used in this PCR reaction are in two groups, 1 and 2. They are:

Group 1:

1. 5'-AAAAGGCCTCGAGGGCCTGGGTGGCAATGGT-3' (SEQ ID NO: 74)
2. 5'-CCTGAACCACCACAKHKACCGYKSNBGCACGGAYYCGRCRMACATTC ATYAAYATCTDYACCATTGCCACCC-3' (SEQ ID NO: 75)
3. 5'-CCTGAACCACCACAKNTGSCGYYGYKMHSGCACGGAYYCGRCRMACAT TCATYAAYATCTDYACCATTGCCACCC-3' (SEQ ID NO: 76)
4. 5'-CCTGAACCACCACAKHKACCGYKSNBGCAARBAYBCGVAHYCWSKBYA CATTCATYAAYATCTDYACCATTGCCACCC-3' (SEQ ID NO: 77)
5. 5'-CCTGAACCACCACAKNTGSCGYYGYKMHSGCAARBAYBCGVAHYCWS KBYACATTCATYAAYATCTDYACCATTGCCACCC-3' (SEQ ID NO: 78)
6. 5'-TGAATTTTCTGTATGAGGTTTTGCTAAACAACTTTCAACAGTTTCGGCCC CAGAGGCCCTGGAGCCACCTGAACCACCACA-3' (SEQ ID NO: 79)

Group 2:

1. 5'-ACGGTGCCTACCCGTATGATGTTCCGGATTATGCCCCG

GGTGGCAATGGT-3’ (SEQ ID NO: 80)

2. 5’-CCTGAACCACCACAGHKTDBACCGGHAWAGCCTKSCRSGCAS
HBACAKYKAWAGCYACCCDSTRWATYTWBACCATTGCCACCC-3’
(SEQ ID NO: 81)

3. 5’-CCTGAACCACCACAKBYKBTKCYGKYCBSABYCNGCDBAWAGCCTK
BGBKGCASHBACAKYKAWAGCYACCCDSTRWATYTWBACCATTGCCACCC-3’
(SEQ ID NO: 82)

4. 5’-AAAAGGCCCCAGAGGCCCCTGAACCACCACA-3’ (SEQ ID NO: 83)

where R=A/G, Y=C/T, M=A/C, K=G/T, S=C/G, W=A/T, B=C/G/T, D=A/G/T, H=A/C/T, V=A/C/G, and N=A/C/G/T.

[332] Following the separate PCRs of the Group 1 and 2 oligonucleotides, the Group 1 PCR fragments were digested with BpmI and group 2 PCR fragments were digested with BsrDI. Digestion products were purified using Qiagen Qiaquick columns and then ligated together. The ligated DNA was then amplified in a PCR using two primers. These are:

5’-AAAAGGCCTCGAGGGCCTGGGTGGCAATGGT-3’ (SEQ ID NO: 84)
5’-AAAAGGCCCCAGAGGCCCCTGAACCACCACA-3’ (SEQ ID NO: 85)

[333] The PCR products were purified with Qiagen Qiaquick columns and digested with SfiI. The digested product was purified with Qiagen Qiaquick columns. The DNA fragments were ligated into the SfiI restriction sites of phage display vector fuse5-HA(G4S)4, a derivative of fuse5 carrying an in-frame HA-epitope and a glycine, serine flexible linker. The ligation mixture was electroporated into TransforMax™ EC100™ electrocompetent E. coli cells. Transformed *E. coli* cells were grown overnight at 37°C in 2xYT medium containing 20 µg/ml tetracycline. The resulting library contained $2X10^{9}$ independent clones. Phage particles were purified from the culture medium by PEG-precipitation. The titer of the phage was $1.3X10^{12}$/ml. The sequences of 24 individual clones were determined and these were consistent with the library design.

Example 3

[334] This example describes construction of an EGF-based monomer library.

[335] Recombination can be used for intradomain optimization. FOr example a PCR overlap reaction can be used that recombines two or more segments of a single domain relative to each other. One can use two, three, four, five or more fragment overlap reactions in the same way as illustrated. This recombination process has many applications. One application is to recombine a large pool of hundreds of previously selected clones without sequence information. All that is needed for each overlap to work is one known region of (relatively) constant sequence that exists in the same location in each of the clones (fixed site approach). For A domains, typically these clones would have been derived from a library in which 20-25 amino acids distributed over all five inter-cysteine segments were randomized. The intra-domain recombination method can also be performed on a pool of sequence-related monomer domains by standard DNA recombination (*e.g.*, Stemmer, *Nature* 370:389-391 (1994)) based on random fragmentation and reassembly based on DNA sequence homology, which does not require a fixed overlap site in all of the clones that are to be recombined.

[336] Another application of this process is to create multiple separate, naïve (meaning unpanned) libraries in each of which only one of the intercysteine loops is randomized, to randomize a different loop in each library. After panning of these libraries separately against the target, the selected clones are then recombined. From each panned library only the randomized segment is amplified by PCR and multiple randomized segments are then combined into a single domain, creating a shuffled library which is panned and/or screened for increased potency. This process can also be used to shuffle a small number of clones of known sequence.

[337] Any common sequence may be used as cross-over points. For A domains or other cysteine-containing monomers, the cysteine residues are logical places for the crossover. However, there are other ways to determine optimal crossover sites, such as computer modeling. Alternatively, residues with highest entropy, or the least number of intramolecular contacts, may also be good sites for crossovers.

[338] An exemplary method of generating libraries comprised of proteins with randomized inter-cysteine loops is presented below. In this example, in contrast to the separate loop, separate library approach described above, multiple intercysteine loops are randomized simultaneously in the same library.

[339] An A domain NNK library encoding a protein domain of 39-45 amino acids having the following pattern was constructed:
C1-X(4,6)-E1-F-R1-C2-A-X(2,4)-G1-R2-C3-I-P-S1-S2-W-V-C4-D1-G2-E2-D2-D3-C5-G3-D4-G4-S3-D5-E3-X(4,6)-C6; (SEQ ID NO: 86)
where,
C1-C6: cysteines;
X(n): sequence of n amino acids with any residue at each position;
E1-E3: glutamine;
F: phenylalanine;
R1-R2: arginine;
A: alanine;
G1-G4: glycine;
I: isoleucine;
P: proline;
S1-S3: serine;
W: tryptophan;
V: valine;
D1-D5: aspartic acid; and
C1-C3, C2-C5 & C4-C6 form disulfides.

[340] The library was constructed by creating a library of DNA sequences, containing tyrosine codons (TAT) or variable non-conserved codons (NNK), by assembly PCR as described in Stemmer *et al.*, *Gene* 164:49-53 (1995). Compared to the native A-domain scaffold and the design that was used to construct library A1 (described previously) this approach: 1) keeps more of the existing residues in place instead of randomizing these potentially critical residues, and 2) inserts a string of amino acids of variable length of all 20 amino acids (NNK codon), such that the average number of inter-cysteine residues is extended beyond that of the natural A domain or the A1 library. The rate of tyrosine residues was increased by including tyrosine codons in the oligonucleotides, because tyrosines were found to be overrepresented in antibody binding sites, presumably because of the large number of different contacts that tyrosine can make. The oligonucleotides used in this PCR reaction are:

1. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKNNKNNKGAATTCCGA- 3′
(SEQ ID NO: 87)

2. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKNNKNNKNNKGAATTCCGA- 3′ (SEQ ID NO: 88)

3. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKNNKNNKNNKNNKGAATTCCGA- 3′(SEQ ID NO: 89)

4. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTTATNNKNNKNNKGAATTCCGA- 3′ (SEQ ID NO: 90)

5. 5′-ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKTATNNKNNKNNKGAATTCCGA-3′ (SEQ ID NO: 91)

6. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKTATNNKNNKGAATTCCGA- 3′ (SEQ ID NO: 92)

7. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKTATNNKGAATTCCGA- 3′ (SEQ ID NO: 93)

8. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKNNKTATGAATTCCGA- 3′ (SEQ ID NO: 94)

9. 5′ -ATATCCCGGGTCTGGAGGCGTCTGGTGGTTCGTGTNNKNNKNNKTATNNKGAATTCCGA- 3′ (SEQ ID NO: 95)

10. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 96)

11. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNMNNMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 97)

12. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNMNNMNNMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 98)

13. 5′ -ATACCCAAGAAGACGGTATACATCGTCCATAMNNMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 99)

14. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNATAMNNMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 100)

15. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNATAMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 101)

16. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNMNNATATGCACATCGGAATTC- 3′ (SEQ ID NO: 102)

17. 5′ -ATACCCAAGAAGACGGTATACATCGTCCMNNMNNATAMNNTGCACATCGGAATTC- 3′ (SEQ ID NO: 103)

18. 5′ -ACCGTCTTCTTGGGTATGTGACGGGGAGGACGATTGTGGTGACGGATCTGACGAG- 3′ (SEQ ID NO: 104)

19. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 105)

20. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNMNNMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 106)
21. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNMNNMNNMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 107)
22. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAATAMNNMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 108)
23. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNATAMNNMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 109)
24. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNATAMNNMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 110)
25. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNATAMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 111)
26. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNMNNATACTCGTCAGATCCGT- 3′ (SEQ ID NO: 112)
27. 5′ -ATATGGCCCCAGAGGCCTGCAATGATCCACCGCCCCCACAMNNMNNMNNATAMNNCTCGTCAGATCCGT- 3′ (SEQ ID NO: 113)

where R=A/G, Y=C/T, M=A/C, K=G/T, S=C/G, W=A/T, B=C/G/T, D=A/G/T, H=A/C/T, V=A/C/G, and N=A/C/G/T

[341] The library was constructed though an initial round of 10 cycles of PCR amplification using a mixture of 4 pools of oligonucleotides, each pool containing 400pmols of DNA. Pool 1 contained oligonucleotides 1-9, pool 2 contained 10-17, pool 3 contained only 18 and pool 4 contained 19-27. The fully assembled library was obtained through an additional 8 cycles of PCR using pool 1 and 4. The library fragments were digested with XmaI and SfiI. The DNA fragments were ligated into the corresponding restriction sites of phage display vector fuse5-HA, a derivative of fuse5 carrying an in-frame HA-epitope. The ligation mixture was electroporated into TransforMax™ EC100™ electrocompetent *E. coli* cells resulting in a library of 2X10^{9} individual clones. Transformed *E. coli* cells were grown overnight at 37°C in 2xYT medium containing 20 μg/ml tetracycline. Phage particles were purified from the culture medium by PEG-precipitation and a titer of 1.1X10^{13}/ml was determined. Sequences of 24 clones were determined and were consistent with the expectations of the library design.

Example 4

[342] This example describes optimization of multimers by optimizing monomers and/or linkers for binding to a target.

[343] One approach for optimizing multimer binding to targets involves optimization of monomers, multimers and linkers. First a library of monomers is panned for binding to the target (e.g., Met). However, some of the monomers may bind at locations on the target that are far away from each other, such that the domains that bind to these sites cannot be connected by a linker peptide. It is therefore useful to create and screen a large library of homo- or heterotrimers from these monomers before optimization of the monomers. These trimer libraries can be screened, e.g., on phage (typical for heterotrimers created from a large pool of monomers) or made and assayed separately (e.g., for homotrimers). By this method, the best trimer is identified. The assays may include binding assays to a target or agonist or antagonist potency determination of the multimer in functional protein- or cell-based assays.

[344] The monomeric domain(s) of the single best trimer are then optimized as a second step. Homomultimers are easiest to optimize, since only one domain sequence exists, though heteromultimers may also be synthesized. For homomultimers, an increase in binding by the multimer compared to the monomer is an avidity effect.

[345] After optimization of the domain sequence itself (e.g., by recombining or NNK randomization) and phage panning, the improved monomers are used to construct a dimer with a linker library. Linker libraries may be formed, e.g., from linkers with an NNK composition and/or variable sequence length.

[346] After panning of this linker library, the best clones (e.g., determined by potency in the inhibition or other functional assay) are converted into multimers composed of multiple (e.g., two, three, four, five, six, seven, eight, etc.) sequence-optimized domains and length- and sequence-optimized linkers.

Example 5

[347] This example describes a structural analysis of A domains.

[348] As with virtually all proteins, only a small fraction of the total surface of an A-domain participates in binding a single target. Based on the solution structure of the domain, adjacent residue positions can be identified which are likely to be able to cooperate in binding to a given target. Herein, such groups of adjacent residues are referred to as structural categories. As an example, four such categories have been identified through examination of the A-domain structure, designated Top, Bottom, Loop 1, and Loop 2. By designing libraries which only allow diversity within a given category, the theoretical sequence space allowed by a library can be significantly reduced, allowing for better coverage of the theoretical space by the physical library. Further, in the case of non-overlapping categories such as the Top and Bottom categories, half-domain sequences selected against different targets can be combined into a single sequence which would be able

to bind simultaneously or alternatively to the selected targets. In either case, creating binding sites that occupy only half a domain allows for the creation of molecules that are half as large and would have half the number of immunogenic epitopes, reducing the risk of immunogenicity.

Structural Classification of A-domain Positions

A canonical A-domain sequence (SEQ ID NO: 114) is shown below with high-diversity positions represented as an X. Positions that belong to either the Top, Bottom, Loop 1, or Loop 2 categories are designated with a star.

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	C	X	X	X	X	F	X	C	X	X	X	X	C	I	X	X	X	W	X
Top	•	✪	•	•	✪	•	•	•	•	•	•	✪	•	✪	✪	•	✪	✪	•
Bottom	•	•	•	•	•	✪	✪	•	✪	•	•	•	•	•	•	✪	•	•	✪
Loop 1	•	✪	✪	✪	✪	•	•	•	•	•	•	•	•	•	✪	✪	✪	•	•
Loop 2	•	•	•	•	•	•	•	•	✪	✪	✪	✪	•	•	•	•	•	•	•

	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
	C	D	G	X	X	D	C	X	D	X	S	D	E	X	X	C
Top	•	✪	✪	✪	✪	✪	•	✪	•	✪	•	•	•	•	•	•
Bottom	•	•	•	•	•	•	•	•	✪	•	✪	•	•	✪	✪	•
Loop 1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Loop 2	•	•	•	•	•	•	•	✪	✪	✪	•	•	•	•	•	•

Example 6

[349] This example describes screening for monomers or multimers that bind c-MET (also known as HGFR).

[350] Phage libraries were panned through several rounds either on solid support (e.g. Nunc Maxisorp plates) or in solution (e.g. Dynal Streptavidin or Protein A beads). Output phage pools with (a) the highest frequency of individual phage clones that bind to c-MET and (b) high sequence diversity among the binding-positive phage clones were chosen for protein screening.

I. Round 1 (Maxisorp plates or Dynal Beads)

1. Coating Target

[351] A. ***Coating plates:*** Six wells/library were directly coated with c-MET extracellular domain (ECD)/Fc chimera (0.5 μg/well) using 100 μL/well of 5 μg/mL c-MET-ECD diluted in TBS[pH 7.5]/2 mM $CaCl_2$. When using c-MET-ECD/Fc fusion (R & D Systems; carrier free) as the target, the plates were pre-coated with Protein A for 1 hr at room temperature with shaking. When using a biotinylated form of c-MET ECD/Fc, plates were pre-coated with streptavidin for 1 hr at room temperature with shaking. In addition, one negative control well/library was coated with TBS[pH 7.5]/2 mM $CaCl_2$ only. After pre-coating was complete, c-MET-Fc (+/- biotin) was added and the plates were incubated for 1.5 hr at room temperature with shaking.

[352] **B.** ***Coating beads*****:** 20 µL Dynal streptavidin (M-280; Dynal ASA) or Dynal Protein A beads (Dynal ASA) were incubated with 5 µg biotinylated c-MET/Fc or non-biotinylated c-MET/Fc, respectively, in 500 µL TBS[pH 7.5]/2 mM $CaCl_2$ and rotated at room temperature for 1 hr in Eppendorf tubes. As a negative control, 20 µL Dynal streptavidin or Protein A beads without target were incubated in 500 µL of TBS[pH 7.5]/2 mM $CaCl_2$ and rotated at room temperature for 1 hr. Note that Dynal beads were washed at least twice with TBS [pH 7.5]/2 mM $CaCl_2$ before adding target, and beads were coated in bulk.

2. Blocking

[353] **A.** ***Blocking Plates*****:** Coating solution was removed and wells were washed one time with 200 µL/well of TBS[pH 7.5]/2 mM $CaCl_2$. 250 µl/well of 1% BSA (protease-free) in TBS[pH 7.5]/2 mM $CaCl_2$ was added and incubated for 1 hr. at room temperature with shaking. Alternative reagents (e.g. casein or milk) can be used for blocking.

[354] **B.** ***Blocking Beads*****:** Coating solution was removed and beads were washed twice with TBS [pH 7.5]/2 mM $CaCl_2$. 500 µl 1% BSA (protease-free) was added in TBS[pH 7.5]/2 mM $CaCl_2$ and rotated for 1 hr at room temperature. As noted above, alternative blocking reagents can be used.

3. Washes

[355] **A.** ***Wash Plates*****:** Wells were washed three times with 200 µL/well of TBS[pH 7.5]/2 mM $CaCl_2$ to remove excess target.

[356] **B.** ***Wash Beads*****:** Beads were washed three times with 1000 µL of TBS[pH 7.5]/2 mM $CaCl_2$ to remove excess target. Beads were allowed to collect on a magnet for a few min after each wash to avoid bead loss.

4. Phage addition

[357] A. ***<u>Phage addition to Plates</u>*:** About 1000 library equivalents (A1 domain naïve phage library) were added in phage addition buffer (1% nonfat dry milk/ 0.2% BSA (protease-free), or other appropriate blocking agent, in TBS [pH 7.5]/2 mM $CaCl_2$) and incubated at room temperature for 2 hr with shaking. In rounds 2-3, 100 μL total of harvested phage was added to 7 wells (6 target + 1 negative control) diluted in phage addition buffer.

[358] B. ***<u>Phage addition to Beads</u>*:** About 1000 library equivalents (A1 domain naïve phage library) were added in 500 μl 1% non-fat dry milk + 100 μl 1% BSA (protease-free) in TBS [pH 7.5]/2 mM $CaCl_2$ and incubated with rotation at room temperature for 2 hr. In rounds 2-3, 100 μL total of harvested phage were added to beads.

5. Washes

[359] A. ***<u>Washing Plates:</u>*** The plates were washed eight to twelve times with 200 μl/well of TBS [pH 7.5]/2 mM $CaCl_2$/0.1 % Tween-20 over a period of 10 min.

[360] B. ***<u>Washing Beads</u>*:** The beads were washed 8-12 times with 800 μl of TBS [pH 7.5]/2 mM $CaCl_2$/0.1 % Tween-20 over a period of 30 - 45 min. Bead resuspension was facilitated by dispensing wash buffer directly onto collected beads or by pipetting up and down (not by vortexing). Alternatively, a KingFisher apparatus (Thermo LabSystems) or equivalent can be used for bead washing.

Conditions for Stringent washes (options)

[361] a. 800 μl of TBS [pH 7.5]/2 mM $CaCl_2$/0.1 % Tween-20 at 37°C;

[362] b. 800 μl of TBS [*450 mM NaCl*, pH 7.5]/2 mM $CaCl_2$/0.1 % Tween-20 at room temperature;

[363] c. Beads were washed normally 6-8 times, then 1 μg of unlabeled c-MET-ECD was added for 1 hr at room temperature or 37°C. Phage that remained bound after this wash were retained for elution/infection;

[364] d. 1% milk/0.2% BSA/with or without 1 M urea/ 37°C (high stringency).

6. Competition (optional):

[365] **A.** ***Competition on Plates:*** Phage were incubated with 100 μL/well of 50 μg/mL (5 μg/well) of HGF (the c-MET ligand)) in TBS [pH 7.5]/ 2mM $CaCl_2$ for 1 hr at room temperature with shaking. HGF eluates were retained for infection of BlueKan K91 *E. coli.*

[366] **B.** ***Competition on Beads*:** Phage were incubated with 10 μg HGF in 500 μL TBS [pH 7.5]/ 2mM $CaCl_2$ for 1 hr at room temperature with shaking. HGF eluates were retained for infection of BlueKan K91 *E. coli.*

7. Phage Elution

[367] **A.** ***Elution off of Plates:*** 100 μL/well of 10 mg/mL trypsin in TBS [pH 7.5]/ 2mM $CaCl_2$ was added, and the plates were incubated at 37°C for 30 min with shaking.

[368] **B.** ***Elution off of Beads*:** 100 μL 10 mg/ml trypsin TBS [pH 7.5]/ 2mM $CaCl_2$ was added to beads, which were then incubated at 37°C (in an Eppendorf rack) for 30 min with shaking.

[369] **C.** ***Alternative elution/infection:*** 200 μL of log-phase BlueKan K91 *E. coli* cells at OD_{600} ~ 0.5 were added to each well (for plates) or to aspirated beads. The infection was allowed to proceed for 30 min at 37°C without shaking. Next, the 200 μL volumes were pooled and added to ~ 3 mL of 2xYT/0.2 μg/mL tetracycline and shaken for 15 min at 37°C.

8. Infection: (same for Plate and Bead Protocol)

[370] An appropriate volume of log-phase BlueKan K91 *E. coli* (in 2xYT/40 μg/mL kanamycin) was grown to OD_{600} ~ 0.5 - 0.6. When the culture reached OD_{600}, it was placed on ice prior to use, although the time on ice was generally minimized.

[371] **A.** In a 50 mL sterile conical tube, eluted phage were mixed with 5 mL log-phase BlueKan K91 *E. coli* culture and incubated at 37°C for 25 min without shaking. The sterile conical tubes were covered with AirPore tape (Qiagen) to facilitate aeration.

[372] B. Tetracycline was added to a final concentration of 0.2 μg/mL and shaken for 15 min at 37°C.

[373] C. A 10 μL aliquot was sampled for titering and serially diluted 10-fold (10^{-1} to 10^{-6}) in 2xYT, plated in 8 μL/dilution spots on 2xYT/20 μg/ml tetracycline plates and incubated overnight at 30°C or 37°C. The remaining volume of the 10^{-2} – 10^{-4} dilutions was plated to obtain single colonies for subsequent phage ELISAs.

[374] D. Infected 5 mL cultures were diluted ~10-fold into 50 mL 2xYT/ 20 μg/mL tetracycline and incubated with shaking at 30°C overnight to saturation.

9. Titering input phage was used in the current round of panning (same for Plate and Bead Protocol)

[375] A. 100-fold serial dilutions (10^{-4} to 10^{-10}) of harvested phage were made in 2xYT.

[376] B. 100 μL/well of a log-phase BlueKan K91 *E. coli* culture at OD_{600} 0.5-0.6 was added to 6 wells of a 96-well polypropylene plate.

[377] C. 10 μL of diluted phage was added to the wells containing 100 μL of BlueKan K91 *E. coli.*

[378] D. Phage/cell mixtures were incubated at 37°C for 25 min without shaking, and the plates were covered with AirPore tape (Qiagen) to allow for aeration.

[379] E. Tetracycline was added to a final concentration of 0.2 μg/mL and the plate was shaken for 15 min at 37°C.

[380] F. 8 μL of each dilution (10^{-4} to 10^{-10}) was plated onto a dry 2xYT agar/ 20 μg/mL tetracycline plate.

[381] G. Plates were incubated at 30°C or 37°C overnight.

10. *Harvesting phage* (same for Plate and Bead Protocols)

[382] A. Overnight cultures were centrifuged at 7000 rpm in disposable 50 mL tubes for 25 min to pellet cells.

[383] B. A standard PEG/NaCl phage-precipitation procedure was performed by adding 1/5 volume of a 20% PEG/15% NaCl stock to culture supernatant. It was mixed well by repeatedly inverting and incubating on ice for 45 min to 1 hr.

[384] C. The culture was centrifuged at 7000 rpm for 40 min to pellet phage and the supernatant was discarded.

[385] D. The phage pellet was resuspended in 1 mL TBS [pH 7.5]/ 2 mM $CaCl_2$, transferred to an Eppendorf tube and centrifuged at 13K rpm for at least 2 min to pellet insoluble material.

[386] E. Supernatant was transferred to a fresh tube and 1/5 volume of PEG/NaCl was added, mixed and incubated on ice for ~ 5 min.

[387] F. The mixture was then centrifuged at 13000 rpm for at least 2 min, and the supernatant was removed. The pelleted, purified phage were resuspended in up to 1 mL TBS [pH 7.5]/ 2mM $CaCl_2$ and stored at 4°C.

II. Round 2 and round 3 panning

[388] The 2nd and 3rd round panning conditions were generally the same as in Round 1 described above, except the coated target (i.e. c-MET-ECD) amount was decreased 2- to 4-fold for each subsequent round, and the plates (or beads) were washed 2 - 4 additional times in each subsequent round of panning.

III. Optional intra-domain recombination

[389] Monomer sequences in phage display-selected phage pools were recombined in the following procedure. This process generated hybrid monomers derived from mixed halves of the starting monomer collection in a given pool(s). For A1-domain-based phage libraries, the primer pairs SHF1 (ATTATGCCCCGGGTCTGGAGGCGTC) (SEQ ID NO: 115)/ SHBoverlap (CGCCGTCGCAA) (SEQ ID NO: 116) and SHFoverlap (TTGCGACGGCG) (SEQ ID

NO: 117)/B3 (TCGGCCCCAGAGGCCTGCAATG) (SEQ ID NO: 118) were used to PCR-amplify the two halves of the monomers. The 2 halves were fused together with LA Taq polymerase (Takara). Next, the fused hybrid coding sequences were amplified by primers SHF2 (CCGGATTATGCCCCGGGTCTGGA) (SEQ ID NO: 119) and SHB4 (AACAGTTTCGGCCCCAGAGGCCTGC) (SEQ ID NO: 120). Purified PCR products were digested by SfiI (NEB) and ligated with the SfiI-digested fUSE5HA phage vector to generate recombined monomer libraries. Recombined libraries were panned at least two more rounds against c-MET ECD/Fc and screened as described below. Data from characterization of recombined monomers is in Tables 1 and 2.

IV. Analysis of panning output (same for plate and bead protocols)

[390] ***Phage ELISAs:*** For each output "phage pool" to be analyzed (typically Rounds 2, 3 and 4, if applicable), independent clones were inoculated into 1 mL (2xYT/ 20 µg/mL tetracycline) cultures grown in Costar 96-well polypropylene deep-well plates. Inoculating tips were left in, and plates were shaken overnight at 37°C. Cells were pelleted by centrifugation at 3600 rpm for 15 min. Culture supernatants were retained and ELISAs were performed as described below.

[391] Non-biotinylated c-MET ECD/Fc (0.1 µg/well) was directly coated onto Nunc Maxisorp plates. However, biotinylated c-MET ECD/Fc, 96-well Nunc Maxisorp plates should first be coated with 50 µL/well of 50 µg/mL (2.5 µg/well) of streptavidin, diluted in TBS [pH 7.5]/ 2 mM $CaCl_2$. The plate was incubated at 37°C for 1 hr with shaking. Plates were washed three times with 200 µL/well of TBS [pH 7.5]/ 2 mM $CaCl_2$. Wells were blocked with 200 µL/well of 1% BSA (fraction V) and the covered plate was incubated at RT for 1 hr with shaking. The plate was washed three times with TBS [pH 7.5]/2 mM $CaCl_2$. Next, the 96-well Maxisorp plate was coated with 100 µL/well of 1 µg/mL (0.1 µg/well) biotinylated c-MET-ECD diluted in TBS [pH 7.5]/2 mM $CaCl_2$ or 100 µL/well buffer only (negative control). The plate was incubated at RT for 1 hr with shaking. Plates were washed three times with TBS [pH 7.5]/2 mM $CaCl_2$. Next, 30 µL of each phage supernatant is added to wells in the presence of 70 µL of 1% Milk/0.2% BSA/[pH 7.5]/2 mM $CaCl_2$/0.02% Tween-20. Covered plates were incubated at RT for 1.5 hr with shaking.

[392] Plates were washed four times with TBS [pH 7.5]/2 mM $CaCl_2$/0.02% Tween-20. Next, 100 μL/well of α-M13-HRP monoclonal antibody (Amersham Pharmacia), diluted 1:5000 in TBS [pH 7.5]/2 mM $CaCl_2$ + 0.02% Tween-20, was added. Plates were incubated at 4°C for 1 hr with shaking. Plates were washed three times with cold TBS [pH 7.5]/2 mM $CaCl_2$/0.02% Tween-20. 100 μL/well of TMB/H_2O_2 mixture (Pierce), diluted 1:1, was added for ELISA development.

[393] The reactions were allowed to turn blue until the strongest OD_{650} signals reached ~ 1.0. The reaction was stopped with 100 μL/well 2N H_2SO_4, and positive wells changed in color from blue to yellow. Once the reaction was stopped, it was read at OD_{450} on an ELISA plate reader using SoftMaxPro software.

[394] Phage ELISA-positive phage pools were chosen for subcloning into an expression vector if they had (a) a high frequency of individual phage clones that bound to c-Met ECD/Fc and (b) high sequence diversity among the binding-positive phage clones. Pools meeting these criteria were chosen for protein screening in the process outlined below. To subclone the monomer or multimer sequences from a given phage pool into the expression vector, pEve, approximately 10^8-10^{10} phage were amplified by 25 cycles of PCR as follows:

PCR recipe

0.5 – 1 μL purified phage
5 μL 10X Buffer
8 μL 2.5mM dNTPs
5 μL 10uM VS-For primer (5'-ATCATCTGGCCGGTCCGGCCTACCCGTATGATGTTCCGGA-3') (SEQ ID NO: 121)
5 μL 10uM EveNut primer (5'-AAAAGGCCCCAGAGGCCTTCTGCAATGAC-3') (SEQ ID NO: 122)
26 μL H_2O
0.5 μL LA Taq polymerase (1 unit) (Takara)

Cycles: 25 X [94°C/10sec.-45°C/30sec.-72°C/30sec.]

[395] PCR products were run on a 3% agarose gel for analysis. The monomer or multimer product (approximately 200 bp) was purified with a QIAquick spin column (Qiagen), digested with Sfi I (NEB), purified again with a QIAquick column and then ligated using T4 DNA Ligase (NEB) to the Sfi I digested vector, pEve. The ligation was transformed into electrocompetent BL21 (DE3) *E. coli* and plated onto 2xYT plates containing kanamycin at 40 μg /mL. Following overnight growth, approximately 6000 individual clones were inoculated into 2xYT/kanamycin and grown overnight. Positive and negative controls were also included on the plates.

V. Screening of thousands of monomer proteins in 1 mL cell lysates

[396] Protein Production of 1 mL heated lysates (Day 1): Individual clones were inoculated into wells of a 96-well Costar deep-well plate containing 400 μL/well of

2xYT/ 40 μg /mL kanamycin. Cultures were grown overnight (which left inoculating tips in wells) while shaken at 300 rpm at 37°C. This process allowed screening of thousands of individual, partially-purified monomers at the cell-lysate level.

[397] (Day 2) 100 μL of overnight culture was inoculated into new 96-well Costar deep-well plate containing 1 mL/well of 2xYT/ 40 μg/mL kanamycin + 1 mM $CaCl_2$. (The remaining overnight culture was archived by the addition of 25% final glycerol concentration and then stored at -80°C for later use.) Plates were covered with AirPore Tape (Qiagen) and cultures were grown with shaking at 375 rpm at 37°C until an OD_{600} of ~ 0.8 to 1.0 was reached. Once the desired OD_{600} was reached, cultures were induced with 1 mM IPTG for 3 hr while shaking at 375 rpm at 37°C. Plates containing induced cultures were then centrifuged for 15 min at 3600 rpm at 4°C to pellet cells. Supernatant was removed and discarded, and the remaining cell pellet was resuspended in 100 μL of TBS [pH 7.5]/1 mM $CaCl_2$. Resuspended cells were transferred from the 96-well deep-well plate to a 96-well polypropylene PCR plate and heated for 5 min at 65°C in a PCR machine. Heated/lysed cells were then centrifuged for 15 min at 3600 rpm at 4°C. After centrifugation, protein production was complete, and heated lysates were ready for characterization in a primary screen via binding ELISA and/or competition AlphaScreen assays.

[398] <u>C-Met ECD/Fc Protein ELISA</u>: 96-well Maxisorp plates were coated with 100 μL/well of 1 μg /mL (0.1 μg/well) c-MET ECD/Fc (R&D systems) diluted in TBS[pH 7.5]/ 1 mM $CaCl_2$, and the plate was incubated at 4°C overnight or room temperature (RT) for 1.5 hr with shaking. Wells were emptied and then blocked with 200 μL/well of 1% BSA (fraction V)/TBS[pH7.5]/1 mM $CaCl_2$. The covered plate was incubated at RT for 1 hr with shaking. The plate was washed three times with TBS [pH 7.5]/1 mM $CaCl_2$. 100 μL/well of monomer protein was added to the plate diluted in TBS [pH 7.5]/1 mM $CaCl_2$/ 0.1% BSA/ 0.02% Tween-20. Protein from 1 mL heated lysate preparations was added to the wells as a single point concentration diluted 1:10. Covered plates were incubated at RT for 1.5 hr with shaking. The plate was washed three times with TBS [pH 7.5]/1 mM $CaCl_2$/ 0.02% Tween-20. 100 μL /well of anti-HA-HRP detection antibody (Roche) diluted 1:2000 in TBS [pH 7.5]/1 mM $CaCl_2$/ 0.1% BSA/ 0.02% Tween-20 was added. Covered plates were incubated at RT for 1 hr with shaking. The plate was washed three times with TBS [pH 7.5]/ 1 mM $CaCl_2$/ 0.02% Tween-20. 100 μL /well of TMB/ H_2SO_4 mixture diluted 1:1 was added. Color was allowed to turn blue until OD_{650} of the strongest signals reached ~ 1.0. The reaction was stopped with 100 µL/well of 2N H_2SO_4. Once stopped, the plate was read on ELISA plate reader at OD_{450}.

[399] AlphaScreen c-Met/Fc-biotinylated (bn) HGF homogeneous competition assay: All assay components were diluted in AlphaScreen Buffer: 40 mM HEPES [pH 7.4] w/ NaOH,1 mM $CaCl_2$, 0.1 % BSA (w/v), 0.05 % Tween-20, 100 mM NaCl. Three additions were made to a white, 384-well, reduced-volume, Greiner microtiter assay plate with no incubation time in between additions. First, monomers or unlabeled recombinant human HGF (rhHGF) (as positive control) were added to the plate at 2 µL/well. Monomers from 1 mL heated lysate preparations were added to the wells at a single concentration (either undiluted [i.e. 1:4 final assay dilution] or up to a 1:100 dilution [1:400 final assay dilution]). As a positive control, instead of monomer protein, 2 µL/well of unlabeled rhHGF (PeproTech) was added to the plate as a twelve-point concentration curve starting with 400 nM (i.e. 100 nM final assay concentration) and then 1:4 serial dilutions thereafter with the last point as buffer only. Secondly, 4 µL/well of c-MET ECD/Fc at 0.6 nM (i.e. 0.3 nM final assay concentration) was added to the plate. Note that the remainder of the assay was done in subdued or green-filtered light as AlphaScreen beads are light sensitive. Thirdly, 2 µL/well of a mixture of bn-HGF at 1 nM (i.e. 0.25 nM final assay concentration) and AlphaScreen Streptavidin "donor beads" and Protein A "acceptor beads" (PerkinElmer) both diluted to 40 µg/mL (i.e., 10 µg/mL final assay concentration) was added to the plate. The assay plate was then covered with topseal and spun down for ~ 30 sec at 800 rpm. The plate was then incubated overnight in the dark at room temperature and read the next day on the Fusion Plate reader (PerkinElmer).

VI. Multimerization and recombination of phage display-selected monomers

[400] Monomers that have been subcloned into pEve (pEve/monomer) were multimerized in the following manner. pEve/monomer plasmids (individually or in pools) were digested with either BsrDI or BpmI (NEB). The ~1.1 kb BsrDI and ~2.9 BpmI fragments were isolated from 1% agarose gels and purified with Qiagen QIAquick spin columns. Pools of each of the two fragments were ligated using T4 DNA ligase (NEB); subsequently, the ligation was purified with a Qiagen QIAquick spin column. Using the primers VS-For and EveNut described in the phage subcloning section above, the multimer coding sequences were PCR-amplified from the ligation. The PCR products were purified and digested with SfiI (NEB), followed by ligation with pEve and transformation of BL21 (DE3) *E. coli*. This method created dimers comprised of different combinations of the starting monomers. This method can also be used to generate other multimers, such as trimers. When making trimers, pools of pEve/dimers (e.g. in above example) and pEve/monomers (the starting collection) are the starting materials. They are processed as above. A molecular biology procedure similar to that described below for making "walking libraries" was also used to generate multimers. In all cases, proteins were expressed, purified and screened as above.

[401] Additional libraries, referred to as "walking libraries," were generated by ligating phage display-selected monomers (i.e. selected monomers) with the full representation of a naïve monomer library. These libraries were constructed in the following manner. PCR was used to amplify in two separate reactions: a) the coding sequences of the selected monomers with pETF (ACCCGTATGATGTTCCGGATTA) (SEQ ID NO: 123) /pETB2r (GATGTATTCGGCCCCAGA GGCCTGCAATGAC) (SEQ ID NO: 124); and b) the coding sequences of naïve monomers in a monomer library with 21new1 (GAAATTCACCTCGAAAGCAA) (SEQ ID NO: 125)/23 (ATGGGTTCCTATTGGGCT) (SEQ ID NO: 126). The ~200 bp products were isolated from a 3% agarose gel and purified with Qiagen QIAquick spin columns. Each product from (a) and (b) above was digested with either BsrDI or BpmI (NEB) in separate reactions. BpmI-digested monomers have an overhang which can be ligated to BsrDI-digested monomers. The purified digestion products were ligated to one another using T4 DNA ligase (NEB). Ligation of BsrDI-cut naïve monomers with BpmI-cut selected monomers generates a walking dimer library comprised of N-terminal naïve monomers fused to C-terminal selected monomers. Ligation of BpmI-cut naïve monomers with BsrDI-cut selected monomers generates a walking dimer library comprised of C-terminal naïve monomers fused to N-terminal selected monomers. Primers pETF/pETB2r were used to PCR-amplify the ligated dimer coding sequences from the ligation, and the purified products were digested with SfiI followed by XmaI. The digested products were ligated to the phage vector fUSE5HA for the generation of a phage display dimer "walking library", typically with 10^8-10^9 unique members. A trimer (or larger multimer) "walking library" can be generated in a similar fashion, except that the starting materials are dimers (or larger) and naïve monomers. Walking libraries were panned against c-MET ECD/Fc and screened as described above.

VII. Characterization of purified monomers in binding and competition assays

[402] Once proteins were characterized at the heated protein lysate level, the best monomers were chosen for further characterization. Larger-scale cultures of individual clones were prepared and the monomers, which bear a 6His tag (SEQ ID NO: 967), were purified via Ni-NTA resin. These nickel-purified monomers were assayed in binding ELISAs and the AlphaScreen competition assay. Protein sequence data and biochemical data from characterization of purified monomers are in Tables 1 and 2.

[403] Protein Purification 500 mL Cultures for NiNTA: (Day 1) In a 15 mL culture tube containing 3 mL of 2xYT + 40 μg /mL kanamycin, the appropriate "primary hit well" archived glycerol stock was inoculated. Culture was shaken overnight at 300 rpm at 37°C.

[404] (Day 2) 2 mL of overnight culture was inoculated into 1 L Erlenmeyer shake flask containing 500 mL of 2xYT + 40 μg/mL kanamycin. Cultures were grown with shaking at 375 rpm at 37°C until an OD_{600} of about 0.8-1.0 was reached. Once desired OD_{600} was reached, cultures were induced with 1 mM final concentration of IPTG for 3 hr while shaking at 375 rpm. After 3 hr induction, the 500 mL culture was transferred to clean/autoclaved Sorvall tube and centrifuged for 8 min at 8000 rpm at 4°C to pellet cells.

[405] Once cells were pelleted, supernatant was removed and discarded, and 20 mL of sonication buffer (10% sucrose/20 mM Tris [pH 7.5]/150 mM NaCl/0.2 mM $CaCl_2$) was added to each tube. The pellet was resuspended in sonication buffer with 10 mL serological pipet until there were no visible clumps, and then the resuspended cells (~ 30 mL) were transferred into 35 mL Oakridge Tubes and sonicated for 8 min at ~ 16 power output. After sonication, the warm Oakridge Tubes containing sonicated cells were placed on ice/water bath for ~ 10 min to cool. Once cooled, tubes were centrifuged for 30 min at 18,000 rpm at 4°C to pellet lysed cells.

[406] While tubes containing lysed cells were being centrifuged, NiNTA resin (Qiagen) was washed with Milli-Q water to remove ethanol. 3 mL of 1:1 diluted NiNTA resin/protein was used (i.e. actually 1.5 mL of resin/protein was used). 3 mL of resin/water mix each was added to appropriately labeled (with protein ID) clean 50 mL screw cap tube. After sonicated cells were pelleted, protein supernatant was removed and added to 50 mL tube containing the 1.5 mL of washed NiNTA resin.

Protein was allowed bind to NiNTA resin by rocking gently for 0.5 hr. @ RT. After incubation with NiNTA resin, centrifuge 50 mL tubes with NiNTA were bound to protein for 10 min at ~1500 rpm. Supernatant was gently poured out and discarded.

[407] NiNTA resin + bound protein was transferred to appropriately labeled 15 mL Clontech columns by adding 1 mL of NiNTA Wash Buffer (20 mM Tris [pH 7.5], 200 mM NaCl, 0.1 mM $CaCl_2$, 20 mM imidazole) to 50 mL tube containing resin, swirling to resuspend, then pipetting the mixture into a column which has been mounted on a vacuum manifold. NiNTA resin + bound protein was washed with at least 10 column volumes (15 mL) of NiNTA wash buffer. 15 mL columns containing NiNTA resin + bound and washed protein was transferred to clean 15 mL screw cap collection tubes. 4 mL of Ni Elution buffer (20 mM Tris [pH 7.5], 200 mM NaCl, 0.1 mM $CaCl_2$, 200 mM imidazole) was added to each column to elute off protein into the 15 mL collection tube. It was then allowed to elute by gravity.

[408] Eluted protein was transferred to slide-A-lyzer cassette (appropriate MW cutoff—for monomers used 3.5 kDa cutoff and for dimers and trimers used 10 kDa cutoff) using 18.5 gauge needle and 5 mL syringe to load cassette. Slide-A-lyzers containing eluted proteins were placed into overnight dialysis buffer containing redox reagents (20 mM Tris [pH 7.5], 100 mM NaCl, 1 mM $CaCl_2$, 1 mM 2-mercaptoethanol, 0.25 mM 2-hydroxyethyldisulfide).

[409] (Day 3) Slide-A-lyzer cassettes containing overnight dialyzed proteins were transferred into dialysis buffer without redox (20 mM Tris [pH 7.5], 100 mM NaCl, 1 mM $CaCl_2$). After 3 hr dialysis, slide-A-lyzer cassettes were transferred into fresh TBS/ $CaCl_2$ without redox for another 3 hr. After 2nd dialysis change, proteins were removed from slide-A-lyzer cassettes using 18.5 gauge needle and 5 mL syringe, and protein was transferred by filtering using 0.2 micron syringe filter into appropriately labeled 15 mL polypropylene tube.

[410] The anti-c-MET NiNTA purified proteins, which were selected as the "best inhibitors" in AlphaScreen competition assays, were further purified by Q-Sepharose anion exchange to remove contaminants. Q-Sepharose Purification: 1 mL of Q-Sepharose Fast-Flow Resin (Amersham Biosciences) was added to 15 mL Clontech column. Resin with 15 column volumes (or 15 mL) of 20 mM Tris [pH 7.5], 50 mM NaCl, 1 mM $CaCl_2$ was equilibrated. 2 mL (~ 5 mg) of filtered NiNTA-purified protein was added to resin and protein was allowed to bind to resin by gravity. Flow-through into first column of 96-well plate was collected. Columns loaded with protein were transferred to 15 mL collection tube and resin/bound protein were washed with 10 column volumes (or 10 mL) of 20 mM Tris [pH 7.5], 50 mM NaCl, 1 mM $CaCl_2$. Once washed, NaCl gradient elution of protein was started. NaCl concentration was varied in gradient as follows: 100 mM, 150 mM, 200 mM, 250 mM, 300 mM, 350 mM, 400 mM, 500 mM, and finally 1 M NaCl, to a base of 20 mM Tris [pH 7.5], 1 mM $CaCl_2$. Fractions were collected in 96-well deep-well polypropylene plate—2 mL/fraction, in 1 mL increments. Fractions containing protein were tested by Bradford and analyzed by SDS PAGE. Fractions were tested in binding ELISAs and competition assays as described above with the following change. Protein from 500 mL NiNTA purified preparations or NiNTA + Q-sepharose purified preparations was added to the plate as a twelve-point concentration curve starting with a 1:5 to 1:100 first dilution and then 1:4 serial dilutions thereafter with the last point as buffer only. Protein sequence data and biochemical data from characterization of purified monomers are in Tables 1 and 2.

Table 1. Anti-c-MET Avimer (M) and Recombined (Rec) Monomer Sequences. Note that some proteins isolated from the recombined monomer library are dimers. Table discloses SEQ ID NOS 127-180, respectively, in order of appearance.

Protein ID	Construct	Sequence
M01	C128	CPSDEFKCHSTGRCLPVEWLCDGVNDCEDGSDEASCSAPASEPPGSLSLQ
M02	C129	CQSNEFTCQSTNRCLPLPWVCDGDNDCEDSSDEANCGQRTSLQ
M03	C130	CEANEFRCKSTGRCISQTWRCDGDDDCEDSSDEANCKPPTSLQ
M04	C131	CLSNEFRCSSTGRCLPRPWVCDGDNDCEDGSDEAPAICGRPGPGATSAPAASLQ
M05	C132	CNTTQFSCRSTNRCIPLDWQCDGVTDCEDNSDEASCSAPASEPPGSLSLQ
M06	C133	CPPDEFTCRSTERCIPLAWVCDGDNDCEDSSDEAGCTTPEPTSLQ
M07	C134	CXATQFRCPRTRLCIPPTWLCDGDNDCEDGSDEANCTASESKPLGSLQ
M08	C135	CQSSEFTCKSTERCIPLTWVCDGDNDCEDGSDEENCSQDPEFHKVSLQ
M09	C136	CLASEFTCHSTGRCIPETWVCDGVNDCEDSSDEADCGRPGPGATSAPAASLQ
M10	C137	CQPDEFTCNSTGRCIPPDWVCDGVDDCEDGSDETGCSQDPEFHKVSLQ
M11	C237	CLASEFTCHSTGRCIPETWVCDGVNDCEDSSDEDNAHCGRPGPGATSAPAASLQ
M12	C238	CESSQFTCNSTKRCIPLAWVCDGDDDCEDGSDEKSCEAPAHTSLQ
M13	C239	CLADEFQCHSTKRCVPRHWLCDGVNDCEDGSDEKSCSQDPEFHKVSLQ
M14	C240	CAPNEFTCSSTGRCLPRAWVCDGVDDCEDGSDETSCGATVHTSLQ
M15	C241	CAPDEFPCRSTGRCVPLTWLCDGDNDCEDGSDEASATCGRPGPGATSAPAASLQ
M16	C377	CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPTSLQ
M17	C378	CRANEFQCHSTGRCIPQTWLCDGDNDCEDGSDEAGCAASGPTSLQ
M18	C379	CESNEFQCQSTSRCIPLTWRCDGVNDCEDGSDEANCTAAVHTSLQ
M19	C380	CESSEFRCRSTGRCIPGGWLCDGDNDCEDSSDETDCSAPASEPPGSLSLQ
M20	C381	CEADEFRCRSTGRCISVDWRCDGVSDCEDSSDEESCESTAPTSLQ
M21	C382	CVSNEFTCRSTKRCVPQEWVCDGVNDCEDGSDETGCPKHTSLQ
M22	C383	CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTSLQ
M23	C384	CAANEFQCHSTGRCIPLSWVCDGVNDCEDSSDETNCRAPTSEPKGSVSLQ
M24	C385	CPPDEFRCHSTGRCIPRAWLCHGDNDCEDSSDEKDCKPHTSLQ
M25	C386	CESGEFQCHSTGRCIPASWLCDGDNDCEDGSDESQLCTAHTSLQ
M26	C387	CQSFTEFECHSTGRCIPASWLCDGDNDCEDSSDESPANCATPAHTSLQ
M27	C388	CVASEFTCRSTGRCIPESWRCDGDNDCEDSSDESPDLCSAPASEPPGSLQ
M28	C389	CGSSEFQCHSTGRCIPENWVCDGDDDCEDSSDEKSCTSAAPTSLQ
M29	C390	CQAGQFECRSTNRCIPQDWVCDGVNDCEDSSDEESCTSPARTSLQ
M30	C391	CQAGQFECRNTNRCIPQDWVCDGVNDCEDSSDEESCTSPARTSLQ
M31	C392	CLPSEFQCKSTNRCIPQAWLYDGVNDCEDGSDETNCSAPASEPPGSLSLQ
M32	C393	CQPNEFQCHSTGRCIPASWLCDGDNDCEDGSDESQLCTAHTSLQ
M33	C394	CAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDEAGCATSGPTSLQ
M34	C395	CPSSQFTCHSTRRCIPQTWVCDGDNDCEDGSDETDCPPHTSLQKASSGGS CLANEFRCNSTGRCIPRAWLCDGDNDCEDSSDEKDCKQHTSLQ
M35	C396	CSSDEFQCSSTSRCIPREWVCDGVNDCEDGSDEALAPCTSTAHTSLQ
M36	C397	CESNEFQCHSTSRCIPLTWRCDRVNDCEDGSDEANCTAAVHTSLQ
M37	C398	CGANEFTCQSTNRCIPQSWVCDGVNDCEDGSDESPVLCATTVHTSLQ
M38	C399	CVSNEFTCRSTKRCVPQEWVCDGVNDCEDGSDETGCPKHTSLQ
M39	C400	CVSNEFPCQSTDRCIPRSWRCDGDNDCEDGSDEKDCSAPASEPPGSLSLQ
M40	C401	CLPSEFQCKSTNRCIPQAWLYDGVNDCEDGSDETSCSAPASEPPGSLSLQ
RecM01 (dimer)	C409	CPAGQFTCRSTNRCIPLQWVCDGDNDCEDSSDESPAICATTGPTSLQKASAAYPYDVPDYAPGLEASGGS CESNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEKNCKAPTSLQ
RecM02	C410	CESNEFQCQSTSRCIPLQWVCDGDNDCEDSSDEASCGCPGPGATSAPAASLQ
RecM03 (dimer)	C411	CHAPTQFECRSTGRCIPLTWVCDGDNDCEDGSDEKDCGDSHILPFSTPGPSTSLQKASAAYPYDVPDYAPGLEASG CDPIAEFKCHSTGRCIPLDWLCDGVNDCEDSSDESPAHCSAPASEPPGSLSLQ
RecM04	C412	CEASEFTCRSTNRCIPVDWVCDGVNDCEDSSDESSDICSAPASEPPGSLSLQ
RecM05	C413	CHPTAEFECHSTGRCIPVDWLCDGDNDCEDSSDEKNCKAHTSLQ
RecM06 (dimer)	C414	CQASDQFECKSTGRCIPLAWRCDGDNDCEDGSDESPAICGRPGLEASGGS CRANEFQCHSTGRCIPASWLCDGDNDCEDGSDEASCGRPGPGGTSAPAASLQ
RecM07	C415	CAADEFQCNSTGRCIPVNWLCDGDNDCEDSSDEENCSAPASEPPCSLSLQ
RecM08	C416	CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDESPAICSAPASEPPGSLSLQ
RecM09	C417	CESNEFQCRSTGRCIPVSWVCDGDNDCEDSSDEASCGDSHILPFGTPGPSTSLQ
RecM10 (dimer)	C418	CRANEFQCHSTGRCIPASWLCDGDNDCEDSSDEAPDLCASAAPTSLQASGLEASGGS CHAPTQFECRSTGRCIPAAWVCDGDNDCEDGSDESPAICGRPGLGATSAPAASLQ
RecM11 (dimer)	C419	CLANEFTCRSTGRCIPLQWVCDGDNDCEDSSDEKGCGDSHILPGLEASGGS CPASQFPCRSTGRCIPAEWVCDGDNDCEDSSDEASRGDSHILPFSTPGPSTSLQ
RecM12 (dimer)	C420	CESNEFQCQSTSRCIPLTWRCDGDNDCEDSSDEKSCSAPASEPPGLEASGGS CPASEFTCRSTGRCISQGWVCDGDNDCEDSSDESPAICATTGPTSLQ
RecM13 (dimer)	C421	CASSEFRCRSTGRCIPQRWVCDGDNDCEDGSDETNCGDSHILPFSTPGLEASGGS CQTGEFRCRSTDRCIPAEWVCDGDSDCEDGSDETNCGDSHILPFSTPGPSTSLQ
RecM14	C422	CEPDEFQCRSTGRCIPLEWLCDGDNDCEDSSDETGCAKPTSLQ

Table 2. Anti-c-MET Monomer and Recombined Monomer Binding Kd and Biochemical IC50 data. Note that some proteins isolated from the recombined monomer library are dimers (noted in Table 1). Blank entries indicate data not available.

Protein ID	Construct #	AlphaScreen IC50 NiNTA-pure (nM)	Binding ELISA Kd NiNTA-pure (nM)	AlphaScreen IC50 Q-pure (nM)	Binding ELISA Kd Q-pure (nM)
M01	C128	120	105		
M02	C129	196	172		
M03	C130	129	58	328	
M04	C131	197	251		
M05	C132	392	69		
M06	C133	27	40	19	
M07	C134	161	121		
M08	C135	80	130		
M09	C136	81	185		
M10	C137	256	439		
M11	C237	41	NA	386	
M12	C238	79	NA		
M13	C239	247	NA		
M14	C240	293	NA		
M15	C241	81	NA		
M16	C377	15	46	27	
M17	C378	36	79	165	
M18	C379	58	113		
M19	C380	35	82	111	
M20	C381	22	158	186	
M21	C382	83	116		
M22	C383	34	66	57	
M23	C384	43	138		
M24	C385	57	77		
M25	C386	11	74	29	
M26	C387	13	100	16	5.8
M27	C388	42	93	105	
M28	C389	30	31	152	
M29	C390	23	43	162	
M30	C391	34	73	161	
M31	C392	19	99	145	
M32	C393	20	232	69	
M33	C394	42	157	185	
M34 (dimer)	C395	3	556	2	
M35	C396	28	93	290	
M36	C397	52	79	213	
M37	C398	28	85	232	
M38	C399	50	95	881	
M39	C400	35	86	85	
M40	C401	21	240	97	
RecM01	C409	2	2.4	1	0.3
RecM02	C410	2	20.3	2	344.3
RecM03	C411	2	2.7	3	0.2
RecM04	C412	24	16.4	94	126.2
RecM05	C413	15	9.7	23	2.0
RecM06	C414	1	0.4	2	0.7
RecM07	C415	1	3.5	13	5.4
RecM08	C416	8	39.3	16	24.6
RecM09	C417	19	42.2	52	51.6
RecM10	C418	1	2.0	2	3.9
RecM11	C419	1	1.1	1	0.3
RecM12	C420	1	3.8	0.33	0.3
RecM13	C421	3	2.5	2	0.2
RecM14	C422	11	7.9	15	44.6
Control	rhHGF (R&D)	0.152			

Example 7

[411] This example describes experiments demonstrating inhibition of HGF-induced cell proliferation by c-MET-binding monomers.

[412] HGF is a potent stimulator of epithelial cell proliferation. The use of A549 human lung adenocarcinoma cells in assays of HGF-induced proliferation for determining efficacy of HGF and/or c-MET inhibitors is well established in the art. For the purposes of these experiments a single cell clone of the A549 cell line, termed A549-SC, was derived by limiting dilution. The A549-SC clone was selected on the basis of its strong cell scattering response in the presence of HGF.

[413] A549-SC cells were plated on collagen-coated 96 well plates ($1x10^4$ cells/well) in 100 μl serum-free F-12 medium per well, then incubated for 48 hr at 37°C in 5% CO_2. After 48 hr, medium was removed from the wells and replaced with dilutions of monomer, in a volume of 50 μl per well serum-free F-12 medium. After 1 hr incubation at 37°C in 5% CO_2, 50 μl serum-free F-12 medium supplemented with 40 ng/ml recombinant human HGF was added, to give a final concentration of 20 ng/ml HGF, the EC50 for HGF. The plates were incubated for a further 48 hr at 37°C in 5% CO_2, then pulsed with 2 μCi tritiated methylthymidine per well for a further 15 hr. After pulsing, medium was removed and replaced with 200 μl 0.05% trypsin per well, and the plates were incubated at 37°C for 5 min. The labeled cells were then harvested to a glass fiber filter using a Tomtec Harvester 96. Incorporated label was then measured by scintillation counting.

[414] A recombinant fusion of the extracellular domain of human c-MET with immunoglobulin Fc domain (c-METFc) was used as a positive control on these experiments (R&D Systems). A titration of c-METFc was mixed with recombinant human HGF to a final concentration of 20 ng/ml HGF and incubated at 37°C for 1 hour. This mixture of c-METFc and HGF was then added to serum-starved A549-SC cells in a 96 well plate. These cells were then processed in the same fashion as those treated with the monomers or multimers.

[415] Figure 9 shows a comparison between c-METFc, a c-MET-specific monomer (M26) and a c-MET-specific dimer (RM12; RecM12) with regards to their relative abilities to block HGF-induced proliferation of serum-starved A549-SC human lung adenocarcinoma cells.

[416] The IC50 for dimer RM12 is 0.32nM. The IC50 for c-METFc is 1.73nM. (n=3 for all data points.) Monomer M26 showed little detectable inhibitory activity in this cell-based assay.

[417] This assay provides a means to screen monomers or multimers for anti-c-MET activity in an in vitro bioassay using human cells. By determining IC50 values for tested multimers or monomers, optimal molecules can be identified and ranked on the basis of their biological activity.

Example 8

[418] This example describes experiments demonstrating monomer binding to a c-MET-expressing human cell line.

[419] Monomers were constructed to include an influenza hemagluttinin (HA) epitope tag. This enables the monomer to be used as a primary flow cytometry detection agent, with a fluorescent-tagged anti-HA secondary antibody being used as the secondary detection agent.

[420] 15 monomers selected by panning against c-MET were tested for the ability to bind A549 human lung adenocarcinoma cells, a c-MET-expressing cell line. Jurkat T cells were used as a c-MET-negative control cell line.

[421] The adherent A549 cells were harvested from tissue culture plates using 10 mM EDTA in phosphate buffered saline (pH 7.4). Jurkat T cells were removed from culture medium by centrifugation. To determine monomer binding, 2.5 X 10^5 cells were stained with 10 μM c-MET monomer in 100 μl flow cytometry staining buffer ("FACS buffer:" PBS pH 7.4, 5% fetal calf serum, 0.01% sodium azide) on ice for 30 min. Cells were washed once with 4 ml ice-cold FACS buffer, then resuspended in 100 μl FACS buffer plus 0.2 μg FITC-conjugated anti-HA monoclonal antibody (Santa Cruz Biotechnology) and incubated on ice for 30 min. Cells were washed once with 4 ml ice-cold FACS buffer, then resuspended in 200 μl FACS buffer and analyzed using a FACSCalibur Flow Cytometer (BD Biosciences). Data were collected and analyzed using CellQuest Pro (BD Biosciences). The geometric mean fluorescence was determined for both A549 and Jurkat T cells, and normalized against the geometric mean fluorescence for that cell line stained with FITC-conjugated anti-HA monoclonal antibody alone.

[422] The following illustrates the preferential binding of c-MET-specific monomerss to the c-MET positive A549 cells rather than to the c-MET negative Jurkat T cells.

Monomer #	Geometric Mean Fluorescence (Fluorescein Channel) vs. Secondary Antibody Alone **A549**	 **Jurkat**
Secondary Antibody Alone	1	1
1	1.19	0.97
2	1.69	1.01
3	1.60	1.05
4	1.77	1.05
5	1.72	1.11
6	1.72	1.09
7	1.70	1.11
8	1.46	1.05
9	1.48	1.05
10	1.56	1.04
11	2.03	1.07
12	2.42	1.12
13	2.41	1.10
14	2.80	1.13
15	2.22	1.12

[423] These data show that anti-c-MET monomers bind to A549 human lung adenocarcinoma, a c-MET positive cell line, but not to Jurkat T cells, a c-MET negative cell line. This flow cytometry based method has utility in confirming specific monomer binding to target in the context of other cell surface proteins. In addition to demonstrating that monomers bind to native c-MET, this method also shows that monomers exhibit little or no non-specific binding to cells.

Example 9

[424] This example describes experiments designed to show monomer inhibition of HGF-induced cell scattering.

[425] HGF was identified as 'scatter factor', inducing a motile phenotype in epithelial cells. On addition of HGF, epithelial cell clusters break apart, and the cells migrate away from each other, or scatter.

[426] A single cell clone of A549 human lung adenocarcinoma (termed A549-SC) was isolated by limiting dilution on the basis of forming tight clusters which scatter over the course of 24 hr after addition of recombinant human HGF. This clone was used in all subsequent experiments.

[427] A549-SC was plated at 25 cells/well in a 96 well plate in F-12 medium supplemented with 10% FBS. Cells were cultured until clusters of 20 to 30 cells were visible, approximately 4 days.

[428] After 4 days, medium was removed from the cells, and replaced with monomer dilutions in a volume of 50 μl/well of serum-free F-12 medium. In addition, a recombinant fusion protein of the extracellular domain of human c-MET with immunoglobulin Fc domain (c-METFc) was used as a positive control on these experiments (R&D Systems). After 1 hr incubation at 37°C in 5% CO_2, 50 μl per well 40 ng/ml recombinant HGF in serum free F-12 medium was added, to give a final concentration of 20 ng/ml HGF. Control wells lacking HGF were also included. The plates were then incubated for 24 hr at 37°C in 5% CO_2. After 24 hr medium was removed from the plates, and the cells were fixed with 100% methanol for 15 min at room temperature, and then stained for 1 hr at room temperature with 0.2% crystal violet in 30% ethanol. Stained cells were washed with phosphate-buffered saline, and then photographed.

[429] Twenty ng/ml (approximately EC50) of the c-MET ligand induces a cell scattering response in A549-SC cells; a monomer of irrelevant specificity (negative control) as expected did not inhibit this scattering response. In contrast, both 0.5 μM c-MET-Fc (positive control) and 1 μM of an anti-c-MET monomer Avimer partially reversed the HGF-induced scattering response. These data illustrate that a anti-c-MET monomer can inhibit the scattering response to at least a similar extent as a comparable concentration of a positive control inhibitor c-MET-Fc.

c-MET binding monomers & dimers

[430] The following provides a summary of the c-MET monomers identified, grouped by sequence homology. There are 10 families, wherein members of the same family have related sequences.

[431] The information can be summarized as follows. Sequences in brackets ("[]") inidicate alternate amino acids at a single position.

Motif for all 10 families:

Family consensus sequences (periods (".") indicate any amino acid; spacing is merely for alignment purposes. One row includes one contiguous polypeptide): (SEQ ID NOS 181-190, respectively, in order or appearance)

Fam 1	c...	[eq]f.c.	st.r	c[iv] ...	w.cdgdndced.sde.
Fam 2	c....	[eq]fec.	st.r	c[iv] ...	w.cdg.ndced.sde.
Fam 3	c....	[eq]f.c.	st.r	c[ilv]p..	w.cdg..dced.sde..
Fam 4	c...	[eq]fqc.	st.r	c[iv] p..	w.cdg.ndcedssde..c
Fam 5	c....	[eq]f.c.	....	c[ilv]...	.......dc.d.sde.
Fam 6	c...	[eq]f.c.	stgr	c. p..	w.c.g.ndced.sde.
Fam 7	c....	[eq]f.c.	st.r	c[ilv]...	w.c....dc.d.sd.....c.
Fam 8	c...	[eq]f.c.	....	c[ilv]...	w.cdg.ndc.d.s.e....c
Fam 9	c....	[eq]f.c.	st.r	c[ilv]p..	w.c.g..dc.d.sde.
Fam 10	c....	[eq]f.c.	....	c[ilv]...	w.cdg..dc.d.sde.

Natural A-domains: (SEQ ID NO 191)

```
     c(.)...    . f.c.   ...(.)  c[ilv]...   ..cd...dc.d.sde.(.......)c
```

A1 library: (SEQ ID NOS 192-195, respectively, in order of appearance)

```
     c..(.).  .   f.c.   .....  c  .   ...   ..cdg..dc.d.sde..(..)c
       a      e                    I   p     ll   dp
       p      q                    l   s     wr   en
       s      k                    v          v   vd
```

[432] Based on family 10 alignments, the invention provides polypeptides comprising non-naturally occurring monomer domains that bind c-MET and that have the sequence GR or KR immediately preceding the third cysteine in an A domain scaffold.

[433] Details of each c-MET-binding family follows. Dashes ("-") are inserted for alignment purposes and do not represent positions in the proteins

Fam1 (SEQ ID NOS 196-215, respectively, in order of appearance)

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

```
CAPSQFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCAIAAPT
CLANEFTCRSTGRCIPQTWVCDGDNDCEDSSDEAPDLCASAAPT
CESNEFQCRSTNRCIPLQWVCDGDNDCEDSSDEAPDLCASAAPT
CESNEFQCSSTGRCIPQAWVCDGDNDCEDSSDEAPDLCASAAPT
CRANEFQCHSTGRCIPASWLCDGDNDCEDSSDEAPDLCASAAPT
CEPNEFQCRSTGRCISLAWVCDGDNDCEDSSDEAPALCKASVPT
CPASEFTCRSTGRCISQGWVCDGDNDCEDSSDESPAICATTGPT
CPAGQFTCRSTNRCIPLQWVCDGDNDCEDSSDESPAICATTGPT
CPASQFTCRSTDRCIPLAWVCDGDNDCEDSSDESPEICSAPASEPPG
CQASQFTCRSTGRCIPLDWVCDGDDDCEDGSDESPEICAAPAPT
CESNEFQCRSTGRCVPLSWVCDGDNDCEDGSDESPAICKTPGHT
CESNEFQCHSTGRCIPQAWLCDGDNDCEDSSDEAPAICKTPGHT
CRSNEFTCRSTERCIPLGWVCDGDNDCEDSSEEAPXIRKTPGHT
CPANEFKCHSTGRCISLAWVCDGDNDCEDSSDEKS--CRGPGHT
```

Fam2 (SEQ ID NOS 216-239, respectively, in order of appearance)

```
CQSFTEFECHSTGRCIPLQWVCDGDNDCEDSSDESP-------ATCATPGHT
CQSFTEFECHSTGRCIPASWLCDGDNDCEDSSDESP-------ANCATPAHT
CQSFTEFECHSTGRCIPVEWLCDGDNDCEDSSDEAP-------AICKTPGHT
CQSFTEFECHSTGRCIPASWLCDGDNDCEDSSDE---------EGCEAAAPT
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDE---------KDCKQ--HT
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDE---------KDCKQ--HT
CQSFTEFECHSTGRCIPRTWLCDGDNDCEDSSDE---------KDCKQ--HT
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDGSDE---------KSCPA--HT
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDE---------KNCQP--PT
CHPTAEFECHSTGRCIPVDWLCDGDNDCEDSSDE---------KNCKA--HT
CHPIAEFECHSTSRCIPRTWLCDGDNDCEDSSDE---------ANCQP--PT
CHPTAEFECNSTGRCVSADWLCDGDNDCEDGSDESP-------ALCK--APT
CHPTAEFECNSTGRCVSADWLCDGDNDCEDGSDESP-------ALCK--APT
CHPTAEFECNSTGRCVSADWLCDGDNDCEDGSDESS-------APCETTGPT
CHPTSEFECRSTARCIPLTWVCDGDNDCEDSSDEK---------HCQPP--T
CHPTSEFECRSTARCIPLTWVCDGDNDCEDSSDEAP-------AICKTPGHT
CHAPTQFECRSTNRCIPLQWVCDGDNDCEDSSDE---------TGCAK--PT
CHTPTQFECRSTGRCIPLEWLCDGDNDCEDSSDE---------TGCAK--PT
CHAPTQFECRSTGRCIPLQWVCDGDNDCEDSSDES-------LATCQQ--HT
CNAPNQFECRSTSRCIPLGWVCDGVNDCEDSSDE---------TDCQE--PT
CHAPTQFECRSTGRCIPRDWVCDGDNDCEDSSDEA-------SCGAPG--PT
CQASDQFECKSTGRCIPLAWRCDGDNDCEDGSDESPAICGRPGLEASG--GS
```

```
CQASDQFECKSTGRCIPLAWRCDGVNDCEDGSDE-------AGCAASG--PT
CQASDQFECKSTGRCIPLDWLCDGVNDCEDSSDE--------ALENCA-QHT
```

Fam3 (SEQ ID NOS 240-285, respectively, in order of appearance)

```
CG-SSEFQCHSTGRCIPENWVCDGDDDCEDSSDEK--SCTSAAPT----------
CG-SSEFQCHSTGRCIPENWVCDGDDDCEDSSDEK--SCTSAAPT----------
CG-SSEFQCHSTGRCIPENWVCDGDDDCDDSSDEK--SCTSAAPT----------
CE-SNEFQCQSTGRCIPRTWVCDGDNDCEDSSDEK--SCTTPAPT----------
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDET--GCKAPT------------
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDET--GCAKPT------------
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEK--NCKAHT------------
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEK--NCKAPT------------
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEK--DCSAPASEPPGSL-----
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEA--NCGDSHILPFSTPGPST-
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEK--DCGDSHILPFSTPGPST-
CE-SNEFQCRSTGRCIPVSWVCDGDNDCEDSSDEA--SCGDSHILPFGTPGPST-
CE-SNEFQCRSTGRCVPVAWVCDGDNDCEDSSDEA--SCG--------APGPT--
CE-ASEFTCRSTNRCIPVDWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CE-ASEFTCRSTNRCIPVDWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CE-ASEFTCRSTNRCIPQDWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CE-ASEFTCRSTNRCIPLQWVCDGDNDCEDSSDEA--NCGDSHILPFSTPGPST-
CP-AGQFTCRSTNRCIPLQWVCDGDNDCEDSSDEA--NCGDSHILPFSTPGPST-
CE-ASEFTCRSTNRCIPANWVCDGDNDCEDSSDEA--NCGDSHILPFSTPGPSX-
CE-PSQFTCRSTSRCIPRTWLCDGDNDCEDSSDEAPALCGDSHILPFSTLGPST-
CL-SSEFTCKSTNRCIPRAWVCDGDNDCEDSSDEAPALCGDSHILPFSTPGPST-
CX-XSQFXCRSTGRCIPAEWVCDGDNDCEDSSDEA--SRGDSHILPFSTPGPST-
CQ-ADQFQCRSTSRCIPAPWVCDGVNDCEDGSDET--SCGDSHILPFSTPGPST-
CR-ADQFQCRSTNRCLPGPWVCDGVNDCEDGSDET--GCGDSHILPFSTPGPST-
CQ-TGEFRCRSTDRCIPAEWVCDGDSDCEDGSDET--NCGDSHILPFSTPGPST-
CA-SNEFRCRSTGRCIPQRWVCDGDNDCEDGSDET--NCGDSHILPFNTPGPIT-
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CQSFTEFECHSTGRCIPAEWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CHPTAEFECHSTGRCIPVDWLCDGDNDCEDSSDEK--GCGDSHILPFSTPGPST-
CHAPTQFECRSTGRCIPLTWVCDGDNDCEDGSDEK--DCGDSHILPFSTPGPST-
CX-PSEFTCKSTGRCIPLDWVCDGDNDCEDSSDEK--GCGDPHILPFSTPGPST-
CA-ADEFQCNSTGRCIPVSWVCDGDNDCEDSSDEK--GCGDPHILPFSTPGPST-
CL-ANEFTCRSTGRCIPLQWVCDGDNDCEDSSDEK--GCGDSHILP----GLEAS
CE-ASEFTCRSTNRCIPLQWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGLEAS
CA-SSEFRCRSTGRCIPQRWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGLEAS
```

```
CA-SSEFRCRSTGRCIPQRWVCDGDNDCEDGSDET-NCGDSHILPFSTPGLEAS
CR-SNEFTCRSTGRCIPRTWVCDGDNDCEDGSDESPAICGDSHILPFSTPGLEAS
CE-SNEFQCQSTSRCIPLTWRCDGDNDCEDSSDER--SCKPPT-----------
CE-SNEFQCQSTSRCIPLTWRCDGDNDCEDSSDEK--SCSAPASEPPGLEAS---
CE-SNEFQCQSTSRCIPLDWVCDGDNDCEDSSDEA--SCGAPGPT---------
CE-SNEFQCQSTSRCIPLTWRCDGDNDCEDSSDEA--SCGAPGPT---------
CG-SDEFQCKSTSRCIPLTWRCDGDSDCEDSSDEA--NCGRPGLEASGGS-----
CQ-SNEFTCQSTNRCLPLPWVCDGDNDCEDSSDEA--NCGQRT-----------
CA-ADEFQCNSTGRCIPAAWVCDGDNDCEDSSDEA--SCGAPGPT---------
CE-ADEFTCRSTNRCIPLQWVCDGDNDCEDSSDEA--SCGAPGPT---------
CA-ADEFQCRSTNRCIPLQWVCDGDNDCEDSSDEA--NC-TP-PT---------
```

Fam4 (SEQ ID NOS 286-296, respectively, in order of appearance)

```
CAPNEFQCSSTSRCIPQRWLCDGDNDCEDSSDEANCAK--HT
CAPNEFQCSSTSRCIPQRWLCDGDNDCEDSSDEANCAK--HT
CVSSEFQCHSTGRCIPRTWLCDGDNDCEDSSDEANCAK--HT
CAPSEFQCQSTKRCIPEGWLCDGVNDCEDSSDEKGCEAPVRT
CAPSEFQCQSTKRCIPEGWLCDGVNDCEDSSDEKGCEAPVRT
CVPSEFQCQSTGRCIPRTWLCDGDNDCEDSSDEADCKAPGHT
CPSDQFQCSSTNRCIPRSWLCDGVNDCEDSSDEADCAA--PT
CPSDQFQCSSTNRCIPRSWLCDGVNDCEDSSDEADCAA--PT
CESNQFQCHSTGRCVPQSWRCDGVNDCEDSSDETDCAP--PT
CLSNQFQCNSTNRCIPQHWLCDGDNDCEDSSDEKGCAATGHT
CGADQFQCQSTNRCVPQRWVCDGDNDCEDSSDEKDCKATART
```

Fam5 (SEQ ID NOS 297-357, respectively, in order of appearance)

```
CPX-NEFRCG-NGRCLPLRLRCXXENDCGDXSDE--E-------NCSAPASEPPG
CPA-GEFQCK-NGRCLPPAWLCDGDNDCGDNSDE--T-------GCSAPASEPPG
CQA-DQFPCS-NGHCVPQTLVXDGVPDCQDDSDE--T-------NCSAPASEPPG
CLA-DEFPCHSTGRCIPAAWLCDGDNDCEDGSDE--T-------NCSAPASEPPG
CAA-DEFQCQSTGRCIPVRWLCDGDNDCEDGSDE--T-------SCSAPASEPPG
CLA-NQFQCRSTGRCISRDWVCDGVNDCEDGSDE--T-------SCSAPASEPPG
CAA-DQFQCRSTGRCIPRTWLCDGVNDCEDGSDEPLA-------LCSAPASEPPG
CNT-TQFSCRSTNRCIPLDWQCDGVTDCEDNSDE--A-------SCSAPASEPPG
CLP-SEFQCKSTNRCIPQAWLYDGVNDCEDGSDE--T-------NCSAPASEPPG
CLP-SEFQCKSTNRCIPQAWLYDGVNDCEDGSDE--T-------SCSAPASEPPG
CLP-SQFQCNSTNRCIPLAWLYDGVNDCEDSSDE--X-------SCSAPASEPPG
```

```
CXP-SQFTCHSTDRCIPLEWLCDGDNDCEDNSDE--T-------GCSAPASEPPG
CEP-NQFTCHSTSRCIPQPWRCDGVNDCEDGSDEALA-------TCSAPASEPPG
CEP-NQFTCHSTSRCIPQPWRCDGVNDCEDGSDEALA-------TCSAPASEPPG
CES-NEFQCQSTSRCIPASWLCDGVNDCEDGSDE--T-------NCSAPASEPPG
CGS-DEFQCKSTRRCIPLNWLCDGVNDCEDSSDEPPA-------TCSAPASEPPG
CGS-DEFQCKSTRRCIPLNWLCDGVNDCEDSSDEPPA-------TCSAPASEPPG
CGS-DEFQCKSTRRCIPLNWLCDGVPDCEDSSDEPPA-------TCSAPASEPPG
CPS-DEFQCNSTGRCISLTWLCDGVNDCEDGSDE--K-------SCSAPASEPPG
CPS-DEFQCNSTGRCISLTWLCDGVNDCEDGSDE--K-------SCSAPASEPPG
CPS-DEFQCNSTGRCISLTWLCDGVNDCEDRSDE--K-------SCSAPASEPPG
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDESPA-------ICSAPASEPPG
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDESPA-------ICSAPASEPPG
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDSSDESSA-------HCSAPASEPPG
CHPTAEFECHSTGRCIPVAWLCDGDNDCEDSSDESSA-------HCSAPASEPPG
CDPIAEFKCHSTGRCIPLDWLCDGVNDCEDSSDESPA-------HCSAPASEPPG
CPS-DEFKCHSTGRCLPVEWLCDGVNDCEDGSDE--A-------SCSAPASEPPG
CPP-NEFQCHSTGRCISRDWLCDGVNDCEDSSDEAPD-------LCGAPASEPPG
CVA-SEFTCRSTGRCIPESWRCDGDNDCEDSSDESPD-------LCSAPASEPPG
CGA-SEFQCRSTGRCLPQHWRCDGDNDCEDSSDEED---------CSAPASESPG
CQA-SEFTCHSTGRCLPRAWLCDGDNDCEDGSDEED---------CSAPASEPPG
CES-SEFRCRSTGRCIPGGWLCDGDNDCEDSSDETD---------CSAPASEPPG
CAA-DEFQCNSTGRCIPVSWVCDGDNDCEDSSDESPD-------LCSAPASEPPG
CAA-DEFQCNSTGRCIPVSWVCDGDNDCEDSSDESSA-------HCSAPASEPPG
CAA-DEFQCNSTGRCIPVSWVCDGDNDCEDSSDEKD---------CSAPASEPPG
CSS-DEFQCSSTSRCIPREWVCDGDNDCEDSSDEKD---------CGAPASEPPG
CLA-NEFTCRSTERCIPLGWVXXGDNDCEDSSDE--E-------NCSASASEPPC
CLX-NEFTCRSTNRCIPLQWVCXGXNDCEDSSDE--K-------NCSAPASEPPG
CLA-NEFTCRSTNRCIPLQWVCDGDNDCEDSSDE--A-------GCSAPASEPPG
CLS-NEFTCRSTKRCLPRQWVCDGDNDCEDSSDE--E-------DCSAPASEPPG
CGS-NQFTCRSTKRCITATWVCDGDNDCEDSSDE--T-------DCSAPASEPPG
CQA-NEFTCRSTSRCIPATWVCDGDNDCEDSSDE--K-------DCSAPASEPPG
CES-NEFQCQSTGRCISRDWVCDGDNDCEDSSDE--E-------DCSAPASEPPG
CES-NEFQCQSTSRCIPLTWRCDGDNDCEDSSDEAPE-------HCSAPASEPPG
CES-NEFQCQSTSRCIPREWVCDGDNDCEDSSDESSA-------HCSAPASEPPG
CES-NEFQCHSTGRCIPASWLCDGDNDCEDSSDESSA-------HCSAPASEPPG
CRS-NEFTCRSTERCIPLGWVCDGDNDCEDSSDESSA-------HCSAPASEPPG
CXSFTEFECRSTGXCIPLTWVCDGDNDCEDSSDE--E-------XCSAPASEPPG
CEA-SEFTCRSTNRCIPLDWVCDGDNDCEDSSDEKS---------CSAPASEPPG
CEA-SEFTCRSTNRCIPVDWVCDGVNDCEDSSDESSD-------ICSAPASEPPG
CVP-SEFQCRSTNRCIPLDWVCDGDNDCEDSSDEKS---------CSAPASEPPG
CVS-GEFTCRSTNRCIPVDWVCDGDNDCEDSSDEKD---------CGAPASEPPG
```

```
CEP-SQFTCRSTNRCIPQEWVCDGDNDCEDGSDE--K-------SCSAPAPEPPG
CEP-SQFPCHSTNRCLPLAWVCDGDNDCEDSSDE--K-------NCSAPASEPSG
CES-SQFTCNSTKRCIPLAWVCDGDDDCEDGSDE--K-------SCEAPAHT---
CQP-SQFTCHSTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAHT-----
CQP-SQFTCHSTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAHT-----
CLP-SQFTCHSTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAHT-----
CQP-DQFTCHSTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAHT-----
CPP-NQFTCHSTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAHT-----
CQP-SQFTCXRTDRCIPLEWLCDGDNDCEDSSDE--K-------NCKAXT-----
```

Fam6 (SEQ ID NOS 358-394, respectively, in order of appearance)

```
CAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDEAGC-ATSGPT--
CAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDEAGC-ATSGPT--
CAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDEAGC-ATSGPT--
CAADQFQCHSTGRCIPVSWVCDGVNDCEDSSDEAGC-ATSGPT--
CAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDETDC-APH--T--
CAADEFQCNSTGRCIPVSWVCDGDNDCEDGSDESPA-LCKAPT--
CAADEFQCNSTGRCIPQEWVCDGVNDCEDSSDESPA-LCKAPT--
CAADEFQCNSTGRCIPVSWVCDGDNDCEDSSDEES---CETPT--
CAASEFQCRSTGRCIPVEWXCDGDNDCEDSSDETG---CKXPT--
CESDEFQCHSTGRCIPLDWVCDGDNDCEDSSDE--K-DCKQHT--
CESDEFQCHSTGRCIPLDWVCDGDNDCEDSSDE--K-DCKQHT--
CESNEFQCHSTGRCIPLQWVCDGDNDCEDSSDE--K-DCKXXT--
CVS-NEFQCHSTGRCIPREWRCDGDNDCEDSSDE-K-DCKQHT--
CESNEFQCHSTGRCIPASWLCDGDNDCEDSSDE--K-DCKQHT--
CRANEFQCHSTGRCIPASWLCDGDNDCEDSSDE--K-DCKQHT--
CLANEFTCRSTGRCIPASWLCDGDNDCEDSSDE--K-DCKQHT--
CEASEFQCNSTGRCIPRQWLCDGDNDCEDSSDE--K-DCKQHT--
CAASEFQCNSTGRCIPASWLCDGDNDCEDSSDESLA-TCQQHT--
CPPDEFRCNSTGRCIPRAWLCDGDNDCEDSSDE--K-DCKQHT--
CPPDEFRCNSTGRCIPRAWLCDGDNDCEDSSDE--K-DCKQHT--
CPPDEFRCNSTGRCIPRAWLCHGDNDCEDSSDE--K-DCKQHT--
CPPDEFRCNSTGRCIPRAWLCDGDNDCEDSSDE--K-DCKKHT--
CPPDEFRCHSTGRCIPRAWLCHGDNDCEDSSDE--K-DCKPHT--
CLANEFRCNSTGRCIPRAWLCDGDNDCEDSSDE--K-DCKQHT--
CQTGEFRCRSTGRCIPRAWVCDGDNDCEDSSDE--K-DCKQHT--
CRADEFQCRSTGRCIPGAWRCDGDNDCEDSSDE--K-DCKQHT--
CAADEFQCNSTGRCIPVSWVCDGDNDCEDSSDE--K-DCKQHT--
CAADEFQCNSTGRCIPLQWVCDGDNDCEDSSDE--K-DCKQHT--
```

```
CAADEFQCNSTGRCIPVSWVCDGDNDCEDSSDE--K-NCKAHT--
CAADEFQCNSTGRCXPAEWVCDGDNDCEDSSDE--K-NCKAHT--
CAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDE--K-DCKQHT--
CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPA-NCATPTHT
CVPNEFQCNSTGRCIPQAWVCDGVNDCEDSSDESSA-LCSEPT--
CEPDEFQCRSTGRCIPLEWLCDGDNDCEDSSDET---GCAKPT--
CPPDEFRCNSTGRCIPLAWLCDGDNDCEDSSDET---NCQPPT--
CAAGEFQCNSTGRCIPAAWLCDGDNDCEDSSDEEGC-GAAEPT--
CQLDQFRCRSTGRCIPQAWLCDGDNDCEDSSDEEGC-GAAEPT--
```

Fam7 (SEQ ID NOS 395-455, respectively, in order of appearance)

```
CP-ADQFTCRSTDRCIPGDWVCDAVNDCEDGSDEK--NCLER------T---
CP-ADQFTCRSTDRCIPGDWVCDAVNDCEDGSDEK--NCLER------T---
CG-SDQFQCRSTDRCIPRTWVCDGDNDCEDGSDEK--DCTRS------VPT-
CQ-SGQFQCXSTGRCIPRTWVCDGDNDCEDSSDEK--NCQPP------T---
CQ-SGQFQCXSTGRCIPRTWVCDGDNDCEDSSDEK--NCQPP------T---
CA-SDQFQCRSTGRCIPQHWLCDGDNDCEDGSDEK--NCGPPGPSAISTAAG
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CR-ANEFQCHSTGRCLPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CL-ANQFPCHSTGRCIPASWVCDGDNDCEDGSDE-SHLCTA------HT---
CR-ANEFPCHSTGRCIPASWLCDGDNDCEDGSDE-SHLCTA------HT---
CL-SNEFPCRSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CE-SGEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CE-SGEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CE-SGEFQCHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CEPSGQFECHSTGRCIPASWLCDGDNDCEDGSDE-SQLCTA------HT---
CL-ADEFQCHSTGRCIPQAWRCDGDNDCEDGSDE-SQLCTA------HT---
CE-ASEFTCRSTDRCIPVHWVCDGVNDCEDGSDE-AQVCTE------HT---
CL-ADEFRCSSTNRCIPLDWVCDGVNDCEDGSDE-AQVCTE------HT---
CP-AGQFTCRSTNRCIPLQWVCDGVNDCEDSSDE-SQHCPP------HT---
```

```
CP-AGQFTCRSTNRCIPLQWVCHGVNDCEDSSDE-SQHCPP------HT---
CA-SDEFTCHSTRRCIPQTWVCDGDNDCEDGSDE-TD-CPP------HT---
CP-SSQFTCHSTRRCIPQTWVCDGDNDCEDGSDE-TD-CPP------HT---
CV-SNEFTCRSTKRCVPQEWVCDGVNDCEDGSDE-TG-CPK------HT---
CV-SNEFTCRSTKRCVPQEWVCDGVNDCEDGSDE-TG-CPK------HT---
CV-SNEFTCRSTKRCVPQEWVCDGVNDCEDGSDE-TG-CPK------HT---
CV-SNEFTCRSTKRCVPQEWVCDGVNDCEDGSDE-TG-CPK------HT---
CQ-ANQFKCRSTSRCIPLAWVCDGDNDCEDGSDE-EG-CKP------HT---
CA-SGQFQCRSTGRCLPLPWVCDGDNDCEDGSDEAPAICEK------H--T-
CA-SSEFQCKSTERCLPLEWVCDGVNDCEDGSDEAPAICTT------PGPT-
CP-PSQFQCRSTGRCIPLHWRCDGVNDCEDGSDEPPEPCTA------TVPT-
CQ-PNQFQCHSTGRCLPLDWVCDGVNDCEDGSDESSAPCET------TGPT-
CE-SSQFQCRSTGRCLPPDWVCDGVNDCEDGSDEAG--CQP------HR---
CE-ASEFQCRSTKRCLPRHWVCDGDNDCEDGSDEKS--CPA------HT---
CE-ASEFQCRSTKRCLPRHWVCDGDNDCEDGSDEKS--CPA------HT---
CE-ASEFQCRSTKRCLPRHWVCDGDNDCXDGSDEKS--CPL------H----
CR-SGQFQCRSTNRCISRTWVCDGDNDCEDGSDEASAICES------SEHT-
CP-PDEFRCNSTNRCISRTWVCDGDNDCEDGSDEASAICES------SEHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCXSTSRCIPLTWRCDGVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCHSTSRCIPLTWRCDRVNDCEDGSDE--ANCTA------AVHT-
CE-SNEFQCQSTSRCIPLTWRCDGVXDCEDGSDE--AXCTA------AVHT-
CE-PSQFTCRSTSRCIPRTWLCDGDNDCEDGSDE--ANCTA------AVHT-
CS-SDEFQCSSTSRCIPREWVCDGVNDCEDGSDEALAPCTS------TAHT-
CS-SXEFQCSSTSRCIPREWVCDGVNDCEDGSDXALAXCTS------TAHT-
CV-SGEFQCRSTGRCIPRDWLCDGVNDCEDGSDEPSAPCTT------AAHT-
```

Fam8 (SEQ ID NOS 456-498, respectively, in order of appearance)

```
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
```

```
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRXTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEX--SCTP-PT----
CPPGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPXTWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPKTWLCDGDNDCEDGSDEE--SCTP-PT----
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEE--SCTX-XT----
CPSGEFRCRXTXRCIPXTWLCDGDNDCEDGSXEE--SCTP-PT----
CPSSQFQCPSTNRCIPETWLCDGDNDCEDGSDEK--SCTP-PT----
CQASQFTCGSGN-CVPPPWGCDGDDDCEDGSDEE--SCTP-PT----
CPANQFQCRSTNRCVPGTWVCDGDNDCEDGSDEE--SCAT-PT----
CVAGQFMCRSTGRCVSATWVCDGVNDCEDGSDEK--SCTA-PT----
CLSDEFRCRSTGRCFPVNWLCDGDNDCEDGSDEE--SCPQ-PT----
CQSDEFTCX-NGQCIPQDWVCDGEDDCGDSSDEAPAHCSQDPEFHKV
CQPDEFTCNSTGRCIPPDWVCDGVDDCEDGSDET--GCSQDPEFHKV
CVSSQFTCRSTGRCIPRAWVCDGDDDCEDGSDEK--GCSQDPEFHKV
CQSSEFTCKSTERCIPLTWVCDGDNDCEDGSDEE--NCSQDPEFHKV
CESDEFTCKSTSRCIPEAWVCDGDNDCEDGSDET--NCSQDPEFHKV
CLADEFQCHSTKRCVPRHWLCDGVNDCEDGSDEK--SCSQDPEFHKV
CPADQFQCRSTGRCIPEHWLCDGVNDCEDSSDEK--GCSQDPEFHKV
```

Fam9 (SEQ ID NOS 499-536, respectively, in order of appearance)

```
CPP-DEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CT--------TPEPT-
CPP-DEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CT--------TPEPT-
CPP-DEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CT--------TPEPT-
CPP-DEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CT--------TPEPT-
CPP-DEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CT--------TPEPT-
CPP-DEFTCRSTERCIPLAWVCHGDNDCEDSSDEAG--CT--------TPEPT-
CAP-SEFTCRSTGRCIPRTWLCDGDNDCEDSSDEAPALCT--------TPVPA-
CPA-SEFQCHSTGRCIPASWLCDGDNDCEDSSDEAG--CT--------TPEPT-
CES-GEFQCHSTGRCIPASWLCDGDNDCEDSSDEAG--CT--------TPEPT-
CAS-XEFKC-SSGRCLPPSWLCDGXXDCEDGSDEAN--CT--------XPVPT-
CPS-GEFQCRSTNRCIPETWLCDGEDDCGDSSDESLALCGRPG--PGATSAPAA
CVS-GEFTCRSTNRCIPVDWVCDGDNDCEDGSDEPPALCGRPG--PGATSAPAA
CES-SEFQCRSTDRCLPVTWVCDGDNDCEDSSDES--NCGRPG--PGATSAXAA
CHAPTQFECRSTGRCIPAAWVCDGDNDCEDGSDESPAICGRPG--LGXTSAPAA
CHAPTQFECRSTGRCIPVSWVCDGVNDCEDGSDESPAICGRPG--LGATSAPAA
CRA-NQFQCHSTGRCIPXSWLCDGVNDCEDGSDESPAICGRPG--LGATSAPAA
CEA-SEFTCRSTDRCLPVSWVCDGVNDCEDGSDESPAICGRPG--LGATSAPA-
CLS-NEFRCSSTGRCLPRPWVCDGDNDCEDGSDEAPAICGRPG--PGATSAPAA
CLA-SEFTCHSTGRCIPETWVCDGVNDCEDSSDE--ADCGRPG--PGATSAPAA
CLA-SEFTCHSTGRCIPETWVCDGVNDCEDSSDEDNAHCGRPG--PGATSAPAA
CPP-NEFTCQSTDRCLPADWVCDGVNDCEDSSDE-ADCGRPG--PGATSAPAA
CDPIAEFKCHSTGRCIPLDWLCDGDNDCEDGSDEAS--CGRPG--PGGTSAPAA
CQSFTEFECHSTGRCIPVDWLCDGDNDCEDGSDEAS--CGRPG--PGGTSAPAA
CR-ANEFQCHSTGRCIPASWLCDGDNDCEDGSDEAS--CGRPG--PGGTSAPAA
CA-PDEFPCRSTGRCVPLTWLCDGDNDCEDGSDEASATCGRPG--PGATSAPAA
CRA-NEFQCHSTGRCIPETWLCDGDNDCEDGSDE--ESC----------TPPT-
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDGSDESLEIC----------PQPT-
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDGSDE--KDC--------KTPGPT-
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDSSDE--KGCGDSHILPFXTPGPST
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDSSDE--TGC----------AKPT-
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDSSDE--TGC----------AKPT-
CRA-NEFQCHSTGRCIPASWLCDGDNDCEDSSDE--TGC----------AKPX-
CRA-NEFQCHSTGRCIPQTWLCDGDNDCEDGSDE--AGC--------AASGPT-
CEA-NEFQCQSTGRCIPLNWLCDGDNDCEDGSDE--TNCG--------TPGPT-
CEA-SEFTCRSTDRCIPLEWLCDGDNDCEDGSDEAN--CG--------AAART-
CQS-SEFTCKSTNRCIPLAWLCDGVNDCEDGSDEAN--CT--------SPERT-
CRS-SEFTCRSTSRCIPENWLCDGVNDCEDGSDETG--CG--------TSAPT-
CRS-SEFTCRSTSRCIPENWLCDGVNDCEDGSDETG--CG--------TSAPT-
```

Fam10 (SEQ ID NOS 537-603, respectively, in order of appearance)

```
-CQA-GQFECRSTNRCIPQDWVCDGVNDCEDSSDEE----SCTSPART
-CQA-GQFECRSTNRCIPQDWVCDGVNDCEDSSDEE----SCTSPART
-CQA-GQFECRSTNRCIPQDWVCDGVNDCEDSSDEE----SCTSPART
-CQA-GQFECRSTNRCIPQDWVCDGVNDCEDSSDEE----SCTSPART
-CQA-GQFQCRSTNRCIPQDWVCDGVXDCEDSSDEE----RCTSPART
-CPA-GQFQCRSTNRCIPQDWVCDGVNDCEDSSDEE----SCTSPART
-CEA-NQFRCKSTSRCIPQNWLCDGVNDCEDSSDEE----NCTRTAPT
-CEA-DEFRCRSTGRCISVDWRCDGVSDCEDSSDEE----SCESTAPT
-CEA-GEFRCKSTDRCIPLAWRCDGVNDCEDSSDEA----SCKSSAHT
-CLA-NEFTCRSTGRCIPRTWRCDGVNDCEDGSDEA----NCKKPT--
-CLA-NEFTCRSTGRCIPRTWRCDGVNDCEDGSDEA----NCKKPT--
-CEA-NEFRCKSTGRCISQTWRCDGDDDCEDSSDEA----NCKPPT--
-CLP-SEFPCS-NGRCVPRPWVCDGDDDCEDNSDEA----GCPKPT--
-CEP-GEFPCSSTGRCVPVAWHCDGVNDCEDGSDET----GCQKRT--
-CQP-DEFRCRNTDICIPQRWVCDGDNDCEDSSDEA----DCQQPT--
-CQA-DEFRCGN-GRCIPQRWVCDGDDDCGDGSDXX----DCXTPT--
-CLA-DEFRCXSNNRCLPLDWVCDGDNDCEDSSDEK----DCAXPT--
-CPP-DQFPC-DNGDCLPQPWVCDGEXDCPDDSDE----ASCTTSVHT
-CAA-DQFKC-DNGRCVPQNWRCDGEXDCGDNSDE----ENCTTPT--
SQPI-GQFKC-GNGNCVPRTWRCDGVNDCPDNSDE----TDCPTPT--
-CEA-GQFRC-NNGNCXPQHWLCXGEXDCEDNSDE----AXCEKPT--
-CAP-DXFXC-XNGKCLPLDWVCDGEDDCGDNSDE----TXCQ-----
-CAS-NQFTC-NNGHCLPQHWRCDGEDDCGDNSDE----ASCQPPT--
-CQA-DEFKC-GNGRCLPEAWVCDGEDDCGDNSDE----ADCQAPT--
-CQA-DEFRC-GNGRCISPTWVCDGEXDCGDDSDE----ANCATTERT
-CQP-GEFRC-RNGKCIPQTWLXXGXDDCGDNSDE----ADCATTAPT
-CPP-DEFKC-GNGHCISQTWLCDGEXDCGDNSDE----ESCA--APT
-CPS-GEFRC-SNGSCIPQEWGCDGXNDCGDDSDE----KNCAAAGPT
-CPS-GEFRCQSSNTCIPLNWLCDGEDDCGDDSDE----KNCEASVPT
-CLS-GEFRC-SNGNCLPADWLCDGEDDCGDNSDE----TSCAASEPT
-CQP-GEFTC-NNGNCLPLEWVCDGENDCGDSSDE----ENCGGSEHT
-CQS-DQFRC-SNGRCIPVEWVCDGEDDCLDGSDEP---QVCGTTAPT
-CPP-DEFRC-SNGRCLPQPWVCDGEDDCGDGSDE----TSCATTAPT
-CAS-NQFRC-RNGRCIPLPWVCDGEDDCQDNSDE----ASCAAPAPT
-CAS-NQFRC-RNGRCIPLPWVCDGEDDCQDNSDE----ASCAAPAPT
-CVA-DEFPCGN-GNCIPLPWRCDGDDDCGDNSDE----TDCESSXPT
-CPP-DEFPCSNSGICIPRSWRCDGEDDCGDNSDE----EDCTSAGHT
-CAP-NEFPCGN-GRCIPATWLCDGDNDCGDNSDE----EGCGGSART
```

```
-CPP-SEFPCGN-GSCVPQAWVCDGDPDCPDNSDE----EGCTGTGPT
-CPP-DEFRCNN-GKCIPLSWRCDGDDDCQDSSDE----AGCT--ERT
-CXP-GEFQC-NNGRCIPATWLCDGDDDCGDNSDE----TGCTEHT--
-CXP-GEFQC-NNGRCIPATWLCDGDDDCGDNSDE----TGCTEHT--
-CQS-NEFQC-NNGRCISVTWLCDGDDDCGDSSDE----TDCTSAVPT
-CPS-SEFQCRNNKTCIPRNWLCDGEDDCGDSSDE----TDCTTHT--
-CVP-GEFRCHDSGTCVPLAXLCXGDNDCGDNSDE----ASCESSEPT
-CAP-GQFRCKN-GRCVPLSWVCDGDDDCEDDSDE----ANCESPEPT
-CAA-DQFRCSS-GRCVPLTWLCDGDDDCADDSDE----KDCESTAHT
-CAA-DEFQCNSTGRCIPVSWVCDGEDDCRDDSDE----ENCRSSEPT
-CLA-GEFRCNS-GRCIPEHWRCDGEDDCLDSSDE----KDCTTSEPT
-CX-AXQFTC-DNGQCLPQNWVCDGENDCPDXSDE----KNCAPHT--
-CX-SSXFRC-XNGXCLPLXWVCDGENDCGDXSDE----XXC------
-CV-ADQFRC-DNGRCLSREWVCDGVNDCQDGSDE----TNCQERT--
-CA-AGEFRCRDSGRCLPQHWLCDGENDCADGSDE----TNCTQHT--
-CX-PSEFTC-SSGQCIPEDWVCXGXNDCGDDSDE----TNCETRT--
-CV-ANEFKC-GSGKCIPETWVCDGDNDCGDGSDE----ASCAQPT--
-CG-ANEFKC-SSGSCIPQEWRCDGENDCGDNSDES--LAPCKEPT--
-CR-ADEFKC-GNGHCIPGQWLCDGENDCQDGSDE----KSCEQPT--
-CL-PNQFQCQSSGRCIPLNWLCDGDDDCGDDSDE----TSCKAPT--
-CP-ASEFQCGN-GRCISEHWLCDGDNDCGDNSDE----TSCKAPVPT
-CQ-ADEFQCRNTEKCLPLNWLCDGDNDCGDDSDE----TSCATPT--
-CVA-SEFTCKDTDRCIPLHWVCDGVDDCGDNSDEAD----CETSVHT
-CEA-NEFRCQSTDRCIPASWVCDGVDDCEDGSDEKS----CTTSGHT
-CEA-SEFTCNSTGRCLPLTWVCDGVNDCEDGSDEKS----CTTSVRT
-CAP-NEFTCSSTGRCLPRAWVCDGVDDCEDGSDETS----CGATVHT
-CGA-NEFTCQSTNRCIPQSWVCDGVNDCEDGSDESPV--LCATTVHT
-CQP-DEFRCRSTGRCLPQEWLCDGVNDCEDSSDEAD----CGTSAHT
-CAP-GEFPCRSTGRCIPQTWVCDGVNDCEDSSDEKS----CATAEHT
```

[434] Fam 10 monomer domains can be further divided into subfamilies (designated "10A", 10B", etc.). The following lists the consensus motifs for the various subfamilies:

10A CxxxEFQCNnGRCIPxxWLCDGDdDCGDxSDETxC
(SEQ ID NO: 604)

10B CPPxEFPCxNGxCIPxxWxCDGDxDCxDNSDEEGCT
(SEQ ID NO: 605)

10C CxAgEFrCxxGRCiPLxWxCDGdDDCgDxSDExdCESS
(SEQ ID NO: 606)

10D CpsGEFRCSNGxCIpqxWlCDGeDDCGDxSDExxCA
(SEQ ID NO: 607)

10E CxADEFKCGNGrCIpxxWvCDGexDCGDdSDExsC
(SEQ ID NO: 608)

[435] Several consensus sequences of all Fam 10 subfamilies were generated:

10A-E CpaxEFxCxNGrCIPxxWxCDGddDCGDxSDExxC (SEQ ID NO: 609)

10A-E CxxxEFxCxNGxCIPxxWxCDGxdDCGDxSDExxC (SEQ ID NO: 610)

[436] Thus, c-MET-binding monomer domains having an A domain scaffold and comprising the sequence:

EFXCXNGXCIPXXWXCDGXDDCGDXSDE (SEQ ID NO: 17)

are encompassed by the present invention.

[437] The following provides c-MET binding dimers, i.e., polypeptides comprising two monomer domains, each of which bind c-MET. Tables following each family of dimers represent consensus motifs based on alignment of the family members. Note that "Fam" designations below refer to dimer families, which are different than the monomer families listed above.

Fam 1 (SEQ ID NOS 611-620, respectively, in order of appearance)

CQASDQFECKSTGRCIPLAWRCDGDNDCEDGSDESPAICG--------RPGLEASGGSCRAN-
EFQCHSTGRCIPASWLCDGDNDCEDGSDE–AS-CGRPGPGGTS---APAA

CRAN-
EFQCHSTGRCIPASWLCDGDNDCEDSSDEAPDLCASAAPTSLQASGLEASGGSCHAPTQFECRSTGRCIPA
AWVCDGDNDCEDGSDESPAICGRPGLGXTSA--PAA

CESG-EFQCHSTGRCIPASWLCDGDNDCEDGSDES-QLCT---------------AHTCAPG-
EFQCHSTGRCIPASWLRDGDNDCEDGSDES-XLCTA-HX----------

CRSN-EFTCRSTGRCIPRTWVCDGDNDCEDGSDESPAICGDSHILPFSTPGLEASGGSCP-
AGQFTCRSTNRCIPLQWVCDGDNDCEDSSDEAN–-CGDSHILPFSTPGPST

CLAN-EFTCRSTGRCIPLQWVCDGDNDCEDSSDEK--GCGDSHILP----GLEASXGSCX-
XSQFXCRSTGRCIPAEWVCDGDNDCEDSSDEAS—CGDSHILPFSTPGPST

CASS-EFRCRSTGRCIPQRWVCDGDNDCEDGSDET--NCGDSHILPFSTPGLEASGGSCQ-
TGEFRCRSTDRCIPAEWVCDGDSDCEDGSDETN—CGDSHILPFSTPGPST

CASS-EFRCRSTGRCIPQRWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGLEASGGSCA-
ADQFQCRSTGRCIPRTWLCDGVNDCEDGSDEPLALCSAPASEP-----PGSL

CEAS-EFTCRSTNRCIPLQWVCDGDNDCEDSSDEK--GCGDSHILPFSTPGLEASGGSCG-
SNQFTCRSTKRCITATWVCDGDNDCEDSSDE—TD-CSAPASEP-----PGSL

CGSD-EFQCKSTSRCIPLTWRCDGDSDCEDSSDEA--NCGR--------PGLEASGGSCQ-
SGQFQCXSTGRCIPRTWVCDGDNDCEDSSDEK—N-CQ—P-----------PT

CESN-EFQCQSTSRCIPLTWRCDGDNDCEDSSDEK--SCSAPASEP---PGLEASGGSCP-
ASEFTCRSTGRCISQGWVCDGDNDCEDSSDESPAICATTG----------PT

[438] The consensus sequences below include question marks ("?"). These indicate positions that can be present or absent.

score	**matches**	**expected**	**motif**
1266	6	10^{-56}	c.[as]..?[eq]f.c.st.rcip..w.cdgd.dced.sde..?.?.c..?.?.?.?.?.?.?.?.?.?.?.?.?.?.?..[st]c..?..?[eq]f.c.st.rci...w[ilv].dgdndced.sde..?.?....?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 621)
1127	5	10^{-60}	c.[as]..?[eq]f.c.st.rcip..w.cdgd.dced.sde..?.?.c..?.?.?.?.?.?.?.?.?.?.?.?.?.?.?ggsc..?..?[eq]f.c.st.rci...w[ilv]cdgdndced.sde..?.?....?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 622)
953	4	10^{-64}	c.[as]..?[eq]f.c[kr]st.rcip..w.cdgd.dced.sde..?.?.cg.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?ggsc..?..?[eq]f.c.st.rci...w[ilv]cdgdndced.sde..?.?c...?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 623)

771	3	10^{-70}	c[ekqr][as]..?[eq]f[eq]c.stgrcip.[as]w.cdgdndced.sde[as].?.?[ilv]c..?.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?..[st]c..?..?[eq]f[eq]c.stgrcipa[as]w[ilv].dgdndcedgsde[as].?.?....?.?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 624)
1052	2	10^{-151}	c.s[dn].?ef.c[kr]st.rcip.tw.cdgd.dced.sde[as].?.?.cg.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?ggsc..?[as].?qf.c.st.rcip..wvcdgdndcedssde..?.?c...?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 625)
676	1	10^{-196}	cgsd.?efqckstsrcipltwrcdgdsdcedssdea.?.?ncg.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?.?ggscq.?s.?qfqc.stgrciprtwvcdgdndcedssdek.?.?cqp.?.?.?.?.?.?.?.?.?.?.?.?.?.? (SEQ ID NO: 626)

Fam 2 (SEQ ID NOS 627-641, respectively, in order of appearance)

CXAXQFTCD-NGQCLPQNWVCDGENDCPDXSDEKN--C--
APHTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CQPGEFTCN-NGNCLPLEWVCDGENDCGDSSDEEN--
CGGSEHTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CLAGEFRCN-SGRCIPEHWRCDGEDDCLDSSDEKD--
CTTSEPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CPSGEFRC-SNGSCIPQEWGCDGXNDCGDDSDEKN--
CAAAGPTCPSGEFQCRSTNRCIPKTWLCDGDNDCEDGSDEESCTPPT

CPSGEFRCQSSNTCIPLNWLCDGEDDCGDDSDEKN--
CEASVPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CASNQFRCR-NGRCIPLPWVCDGEDDCQDNSDEAS--
CAAPAPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CASNQFRCR-NGRCIPLPWVCDGEDDCQDNSDEAS--
CAAPAPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CASNQFTCN-NGHCLPQHWRCDGEDDCGDNSDEAS--CQP--
PTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTXXT

CQADEFRCG-NGRCISPTWVCDGEXDCGDDSDEAN--
CATTERTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CPPDEFKCG-NGHCISQTWLCDGEXDCGDNSDEES--CAAP--
TCPSGEFQCRXTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CPPDEFRCS-NGRCLPQPWVCDGEDDCGDGSDETS--
CATTAPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CVANEFKCG-SGKCIPETWVCDGDNDCGDGSDEAS--CAQPT--
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CGANEFKCS-SGSCIPQEWRCDGENDCGDNSDESLAPCKEPT--
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CRADEFKCG-NGHCIPGQWLCDGENDCQDGSDEKS--CEQPT--
CPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CVPGEFRCHDSGTCVPLAXLCXGDNDCGDNSDEAS--
CESSEPTCPSGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

score	**matches**	**expected**	**motif**
1215	15	10^{-17}	c...[eq]f.c.?.?...c[ilv].....c.g..dc.d.sde...?.?..?.?.?.?.?.?......................[dn][dn]..[de]...[de]e....... (SEQ ID NO: 642)
3282	14	10^{-63}	c...[eq]f.c.?.?...c[ilv].....c.g..dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcr.tnrcip[ekq]twlcdgdndcedgsdeesct..t (SEQ ID NO: 643)
3185	13	10^{-66}	c...[eq]f.c.?.?...c[ilv]...w.cdg..dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcr.tnrcip[ekq]twlcdgdndcedgsdeesct..t (SEQ ID NO: 644)

3045	12	10^{-69}	c...[eq]f.c.?.?...c[ilv]...w.cdg..dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcr.tnrcip[ekq]twlcdgdndcedgsdeesctppt (SEQ ID NO: 645)
2849	11	10^{-70}	c...[eq]f.c.?.?...c[ilv]...w.cdge.dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcr.tnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 646)
2653	10	10^{-72}	c...[eq]f.c.?.?...c[ilv]p..w.cdg.[dn]dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcrstnrcip[ekq]twlcdgdndcedgsdeesctppt (SEQ ID NO: 647)
2435	9	10^{-74}	c...[eq]f.c.?.?...c[ilv]p..w.cdge[dn]dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcrstnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 648)
2195	8	10^{-75}	c...[eq]f.c.?.?.g.c[ilv]p..w.cdge[dn]dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcrstnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 649)
1687	6	10^{-77}	c...[eq]f.c.?.?ng.c[ilv]p..w[ilv]cdge[dn]dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcrstnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 650)
1414	5	10^{-78}	c...[eq]f.c.?.?ng.c[ilv]p..wvcdge[dn]dc.d.sde...?.?c.?.?.?.?.?.?cpsgefqcrstnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 651)
1166	4	10^{-80}	c..[dn][eq]f[kr]c.?.?ng.c[ilv]p..w[ilv]cdge[dn]dc.d.sde.s.?.?c.?.?.?.?.?.?cpsgefqcrstnrcipetwlcdgdndcedgsdeesctppt (SEQ ID NO: 652)

Fam 3 (SEQ ID NOS 653-665, respectively, in order of appearance)

CPSG-EFQCRSTNRCIPETWLCDGE-DDCGDSSDESLALCGRPGPATSAPAACP-
SGEFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPT

CPSG-EFQCRSTNRCIPETWLCDGD--NDCEDGSDE--------ESCTPPTCP-
PGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CQSFTEFECHSTGRCIPASWLCDGD--NDCEDSSDEE------GCEAAAPTCP-
SGFRCRXTXRCIPXTWLCDGDNDCEDGSXEESCTPPTE

CRAN-EFQCHSTGRCIPASWLCDGD--NDCEDGSDE-------SQLCTAHTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEES-CTPPE

CXPG-EFQCNNGR-CIPATWLCDGD--DDCGDNSDET------GCT--EHTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CXPG-EFQCNNGR-CIPATWLCDGD--DDCGDNSDET------GCT--EHTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CQSN-EFQCNNGR-CISVTWLCDGD--DDCGDSSDET------DCTSAVPTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CPSS-EFQCRNNKTCIPRNWLCDGE--DDCGDSSDET------DCT--THTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CLPS-EFPC-SNGRCVPRPWVCDGD--DDCEDNSDEA------GCP--KPTCP-
SGFQCRSTNRCIPXTWLCDGDNDCEDGSDEESCTPPTE

CPPS-EFPC-GNGSCVPQAWVCDGD--PDCPDNSDEE------GCTGTGPTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CLPN-QFQCQSSGRCIPLNWLCDGD--DDCGDDSDET------SCK--APTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CQAD-EFQCRNTEKCLPLNWLCDGD--NDCGDDSDET------SCA--TPTCP-
SGFQCRSTNRCIPETWLCDGDNDCEDGSDEESCTPPTE

CQPD-EFRCRNTDICIPQRWVCDGD--NDCEDSSDEADCQQPTCR-
ANEFQCHSTGRCIPETWLCDGDNDCEDGSDEES-------CTPPT

score	**matches**	**expected**	**motif**
776	13	10^{-10}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.......[de]..?.?.?.?.?.?.?.?..?.?.?......?.?.....................[de]...?.?.?.?.?.?.?.?.....? (SEQ ID NO: 666)
1426	12	10^{-28}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.dc.d.sde.?.?.?.?.?.?.?.?..?.?.?...c..?.?g.....t..c.......dg.[dn][de]...?.?.?.?.?.?.?.?..p..? (SEQ ID NO: 667)
2132	11	10^{-51}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.dc.d.sde.?.?.?.?.?.?.?.?..?.?.?..tcp.?.?gf[kqr]cr.t.rcip.twlcdgdndce.?.?.?.?.?.?.?.?..p..? (SEQ ID NO: 668)
2065	10	10^{-55}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.dc.d.sde.?.?.?.?.?.?.?.?..?.?.?..tcp.?.?gf[kqr]cr.t.rcip.twlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 669)
1951	9	10^{-58}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.dc.d.sde.?.?.?.?.?.?.?.?..?.?.?..tcp.?.?gfqcrstnrcip.twlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 670)
1782	8	10^{-60}	🔍 c....?[eq]f.c.?....?c[ilv]...w[ilv]cdg[de].?.?.dc.d.sde.?.?.?.?.?.?.?.?c.?.?.?..tcp.?.?gfqcrstnrcip.twlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 671)
1610	7	10^{-62}	🔍 c....?[eq]fqc.?....?c[ilv]...wlcdg[de].?.?[dn]dc.d.sde.?.?.?.?.?.?.?.?..?.?.?..tcp.?.?gfqcrstnrcipetwlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 672)

1439	6	10^{-65}	c....?[eq]fqc.?....?c[ilv]...wlcdg[de].?.?[dn]dcgd.sde.?.?.?.?.?.?.?.?c.?.?.?..tcp.?.?gfqcrstnrcipetwlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 673)
1236	5	10^{-67}	c....?efqc.?n.[ekqr].?c[ilv]...wlcdg[de].?.?[dn]dcgd.sde.?.?.?.?.?.?.?.?c.?.?.?..tcp.?.?gfqcrstnrcipetwlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 674)
1006	4	10^{-68}	c....?efqc.?n.[ekqr].?c[ilv]p..wlcdg[de].?.?[dn]dcgd.sde.?.?.?.?.?.?.?.?c.?.?.?..tcp.?.?gfqcrstnrcipetwlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 675)
783	3	10^{-71}	c....?efqc.?ngr.?ci..twlcdgd.?.?ddcgd.sde.?.?.?.?.?.?.?.?c.?.?.?..tcp.?.?gfqcrstnrcipetwlcdgdndce.?.?.?.?.?.?.?.?tppt.? (SEQ ID NO: 676)

Fam 4 (SEQ ID NOS 677-685, respectively, in order of appearance)

CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHTCPASEFQCHSTGRCIPASWLCDGDNDC
EDSSDEAG--CTTPEPT

CAPGQFRCK-NGRCVPLSWVCDGDDDCEDDSDE--
ANCESPEPTCESGEFQCHSTGRCIPASWLCDGDNDCEDSSDEAG–CTTPEPT
CQSDQFRCSN-GRCIPVEWVCDGEDDCLDGSDEP-
QVCGTTAPTCAADEFQCNSTGRCIPVSWVCDGVNDCEDSSDEAG--CATSGPT

CQADEFKCGN-GRCLPEAWVCDGEDDCGDNSDE----
ADCQAPTCAADEFQCNSTGRCIPVSWVCDGXNDCEDSSDEAG--CATSGPT

CPPDEFPCSNSGICIPRSWRCDGEDDCGDNSDEE-D-
CTSAGHTCAPSEFTCNSTGRCIPQEWVCDGDNDCEDSSDEAPDLCASAAPT

CQPGEFRCRN-GKCIPQTWLXXGXDDCGDNSDE--
ADCATTAPTCPPDEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CTTPEPT

CLSGEFRCSN-GNCLPADWLCDGEDDCGDNSDE--
TSCAASEPTCPPDEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CTTPEPT

CGSSEFQCHSTGRCIPENWVCDGDDDCEDSSDE--
KSCTSAAPTCPPDEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CTTPEPT

CAADQFKCDN-GRCVPQNWRCDGEXDCGDNSDE--ENCTT--
PTCPPDEFTCRSTERCIPLAWVCDGDNDCEDSSDEAG--CTTPEPT

score	**matches**	**expected**	**motif**
1879	9	10^{-55}	🔍 c...[eq]f.c..?.?g.c[ilv]p..w...g..dc.d.sde.?.?.?.?....?.?.tc...ef.c.st.rcip..w[ilv]cdg.ndcedssdea..?.?c[ast][st]..pt (SEQ ID NO: 686)
1776	8	10^{-59}	🔍 c...[eq]f.c..?.?g.c[ilv]p..w.cdg[de].dc.d.sde.?.?.?.?....?.?.tc...ef.c.st.rcip..w[ilv]cdg.ndcedssdea..?.?c[ast][st]..pt (SEQ ID NO: 687)
1628	7	10^{-63}	🔍 c...[eq]f[kqr]c..?.?g.c[ilv]p..w.cdg[de].dc.d.sde.?.?.?.?....?.?.tc...ef.c.st.rcip.[as]w[ilv]cdg.ndcedssdeag.?.?c[ast]t..pt (SEQ ID NO: 688)
1451	6	10^{-65}	🔍 c...[eq]f[kqr]c..?.?g.c[ilv]p..w...g..dc.d.sde.?.?.?.?c.[ast].?.?.tc...ef.c.st.rcip.[as]w[ilv]cdgdndcedssdeag.?.?cttpept (SEQ ID NO: 689)
1276	5	10^{-69}	🔍 c...[eq]f[kqr]c..?.?g.c[ilv]p..w.cdg[de].dc.d.sde.?.?.?.?c.[ast].?.?.tc...ef.c.st.rcip.[as]w[ilv]cdgdndcedssdeag.?.?cttpept (SEQ ID NO: 690)
1120	4	10^{-77}	🔍 c...[eq]f[kqr]c..?.?g.c[ilv]p..w...g..dc.d.sde.?.?.?.?c[ast][ast].?.?ptcppdeftcrsterciplawvcdgdndcedssdeag.?.?cttpept (SEQ ID NO: 691)

898	3	10^{-83}	c.[as].[eq]f[kqr]c..?.?g.c[ilv]p.[dn]w.cdg[de].dc.d.sde.?.?.?.?c[ast][ast].?.?ptcppdeftcrsterciplawvcdgdndcedssdeag.?.?cttpept (SEQ ID NO: 692)
622	2	10^{-86}	c.[as].[eq]f[kqr]c..?.?grc[iv]p[eq]nw.cdg[de].dc.d.sde.?.?.?.?ct[st].?.?ptcppdeftcrsterciplawvcdgdndcedssdeag.?.?cttpept (SEQ ID NO: 693)

Example 11

[439] Monomers or multimers that bind human IgG and/or IgGs from other species, including cynomolgus monkey IgG (referred to collectively as IgG) were identified essentially by the methods described in Example 7.

[440] The following IgG-binding monomers were identified. Tables following each family of dimers represent consensus motifs based on alignment of the family members.

Fam1 (SEQ ID NOS 694-703, respectively, in order of appearance)

```
CASGQFQCRSTSICVPMWWRCDGVPDCPDNSDEK--SCEPP----T-------
CASGQFQCRSTSICVPMWWRCDGVPDCVDNSDET--SCTST----VHT-----
CASGQFQCRSTSICVPMWWRCDGVPDCADGSDEK--DCQQH----T-------
CASGQFQCRSTSICVPMWWRCDGVNDCGDGSDEA--DCGRPGPGATSAPAA--
CASGQFQCRSTSICVPMWWRCDGVPDCLDSSDEK--SCNAP----ASEPPGSL
CASGQFQCRSTSICVPMWWRCDGVPDCRDGSDEAPAHCSAP----ASEPPGSL
CASGQFQCRSTSICVPQWWVCDGVPDCRDGSDEP-EQCTPP----T-------
CLSSQFRCRDTGICVPQWWVCDGVPDCGDGSDEKG--CGRT----GHT-----
CLSSQFRCRDTGICVPQWWVCDGVPDCRDGSDEAAV-CGRP----GHT-----
CLSSQFRCRDTGICVPQWWVCDGVPDCRDGSDEAPAHCSAP----ASEPPGSL
```

score	matches	expected	motif
1175	10	10^{-28}	c.s.qf[kqr]cr.t.icvp.ww.cdgv.dc.d.sde..?.?.?c....?.?.?.?..?.?.?.?.?.?.? (SEQ ID NO: 704)
1096	9	10^{-29}	c.s.qf[kqr]cr.t.icvp.ww.cdgvpdc.d.

			sde..?.?.?c....?.?.?.?..?.?.?.?.?.?.? (SEQ ID NO: 705)
942	7	10^{-33}	casgqfqcrstsicvp.ww.cdgv.dc.d.sde..?.?.?c....?.?.?.?..?.?.?.?.?.?.? (SEQ ID NO: 706)
866	6	10^{-36}	casgqfqcrstsicvpmwwrcdgv.dc.d.sde..?.?.?c....?.?.?.?..?.?.?.?.?.?.? (SEQ ID NO: 707)

Fam2 (SEQ ID NOS 708-712, respectively, in order of appearance)

CGAS-EFTCRSSSRCIPQAWVCDGENDCRDNSDE--ADCSAPASEPPGSL
CRSN-EFTCRSSERCIPLAWVCDGDNDCRDDSDE--ANCSAPASEPPGSL
CVSN-EFQCRGTRRCIPRTWLCDGLPDCGDNSDEAPANCSAPASEPPGSL
CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDE--ENCSAPASEPPGSL
CQAG-EFQC-GNGRCISPAWVCDGENDCRDGSDE--ANCSAPASEPPGSL

score	matches	expected	motif
683	5	10^{-34}	c....?[eq]f.c.?...rc[iv]..[ast]w[ilv]cdg..dc.d.sde.?.?.[dn]csapaseppgsl (SEQ ID NO: 713)
584	4	10^{-36}	c....?[eq]f.c.?...rc[iv]..[ast]wvcdg[de]ndc.d.sde.?.?.[dn]csapaseppgsl (SEQ ID NO: 714)
480	3	10^{-41}	c.[as]..?ef.c.?...rci..awvcdg[de]ndcrd.sde.?.?a[dn]csapaseppgsl (SEQ ID NO: 715)

[441] A motif summarizing the Family 2 IgG binding A domain monomers follows:

[eq]fxcrx[st]xrc[iv]xxxw[ilv]cdgxxdcxd[dn]sde (SEQ ID NO: 716)

Fam3 (SEQ ID NOS 717-721, respectively, in order of appearance)

CPPSQFTCKSNDKCIPVHWLCDGDNDCGDSSDE--ANCGRPGPGATSAPAA

CPSGEFPCRSSGRCIPLAWLCDGDNDCRDNSDEPPALCGRPGPGATSAPAA
CAPSEFQCRSSGRCIPLPWVCDGEDDCRDGSDES-AVCGAPAP--T-----
CQASEFTCKSSGRCIPQEWLCDGEDDCRDSSDE--KNCQQPT---------
CLSSEFQCQSSGRCIPLAWVCDGDNDCRDDSDE--KSCKPRT---------

score	matches	expected	motif
526	5	10^{-24}	c...[eq]f.c[kqr]s..[kr]cip..w[ilv]cdg[de][dn]dc.d.sde.?.?..c.....?.?.?.?.?.?.?.?.? (SEQ ID NO: 722)
476	4	10^{-28}	c...ef.c[kqr]ssgrcip..w[ilv]cdg[de][dn]dcrd.sde.?.?..c.....?.?.?.?.?.?.?.?.? (SEQ ID NO: 723)
375	3	10^{-30}	c..sef.c[kqr]ssgrcip..w[ilv]cdg[de][dn]dcrd.sde.?.?..c...[ast].?.?.?.?.?.?.?.?.? (SEQ ID NO: 724)

[442] Two motifs summarizing the Family 3 IgG binding A domain monomers follow:

CXSSGRCIPXXWVCDGXXDCRDXSDE (SEQ ID NO: 2)
CXSSGRCIPXXWLCDGXXDCRDXSDE (SEQ ID NO: 3)

[443] Based on family 3 alignments, the invention provides polypeptides comprising non-naturally occurring monomer domains that bind IgG and that has the sequence SSGR immediately preceding the third cysteine in an A domain scaffold.

Fam4 (SEQ ID NOS 725-730, respectively, in order of appearance)

CPANEFQCSNGRCISPAWLCDGENDCVDGSDE--KGCTPRT
CPPSEFQCGNGRCISPAWLCDGDNDCVDGSDE--TNCTTSGPT
CPPGEFQCGNGRCISAGWVCDGENDCVDDSDE--KDCPART
CGSGEFQCSNGRCISLGWVCDGEDDCPDGSDE--TNCGDSHILPFSTPGPST
CPADEFTCGNGRCISPAWVCDGEPDCRDGSDE-AAVCETHT
CPSNEFTCGNGRCISLAWLCDGEPDCRDSSDESLAICSQDPEFHKV

score	matches	expected	motif
630	6	10^{-24}	c...ef.c.ngrcis..w[ilv]cdg[de].dc.d.sde.?.?..c.... (SEQ ID NO: 731)

546	5	10^{-25}	cp..ef.c.ngrcis..w[ilv]cdg[de].dc.d.sde.?.?..c.. .. (SEQ ID NO: 732)
452	4	10^{-27}	cp..ef.cgngrcis..w[ilv]cdg[de].dc.d.sde.?.?..c.. .. (SEQ ID NO: 733)
367	3	10^{-29}	cp..efqc.ngrcis..w[ilv]cdg[de]ndcvd.sde.?.?..c.. .. (SEQ ID NO: 734)

Example 10

[444] This example illustrates binding affinities of IgG-binding monomers for IgG from various animal species.

	IgG Affinity (nM) by Species			
Domain	Human	Cynomolgus macaque	Mouse	Rat
IgM02	10.7	8.7	23.8	47.7
Ig156	95.5	586	1326	1513
RM09	3900	8900	5300	5750
RM15	812	5630	6300	>10000
502	336	1850	>10000	>10000

Table: Affinity of IgG-binding domains by species

[445] 0.2 ug of whole IgG fraction from the indicated species was immobilized in duplicate wells of a 96-well Maxisorp plate (Nunc) and blocked with 1% BSA. Serial dilutions of purified domains were then added, and the amount of bound protein was quantitated via an HRP-conjugated, high-affinity anti-HA secondary antibody using standard ELISA methods. The data was fit to a 1:1 binding model using a non-linear best fit algorithm to determine the K_D (affinity).

Example 11

[446] This example describes an experiment designed to illustrate pharmacokinetic half-life conferred on a multimer by the presence of an IgG-binding Avimer domain, Ig-M02.

[447] Avimer construct C242 is a trimer of Avimer domains (~15 kDa). The N-terminal Avimer domain is Ig-M02. Three Cynomolgus macaques were injected with a single 1 mg/kg dose of Avimer C242 which had been trace-labeled with ^{125}I. Monkeys 1 and 2 received intravenous doses; monkey 3 received an intramuscular dose. Serum samples were obtained and assessed for ^{125}I cpm at the times indicated in Figure 10, out to 288 hr.

[448] The observed terminal serum half-life in this experiment is ~53 hr, which allometrically scales to a predicted ~106 hr half-life in humans. In a similar experiment in mice, a 7-9 hr terminal half-life was observed, consistent with the rodent's smaller size. Furthermore, as the plots for the i.m.-injected and i.v.-injected animals converge and become nearly identical from about 12 hr post-injection onward, we infer that the monomer exhibits high bioavailability *in vivo*.

[449] 53 hr is significantly longer than expected for a protein of this size. For example, the serum half-life of the 20 kDa cytokine interleukin-6 in marmosets is 4-6 hr (Ryffel, B. et al. *Blood* 83, 2093-102 (1994)). Thus the IgG-binding Ig-M02 domain confers a half-life sufficiently long to allow at least once weekly dosing in human subjects.

[450] While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be clear to one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention. For example, all the techniques, methods, compositions, apparatus and systems described above can be used in various combinations. All publications, patents, patent applications, or other documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application, or other document were individually indicated to be incorporated by reference for all purposes.

SEQUENCE LISTING

SEQ ID NO:1 - c-MET Amino acid sequence

```
   1 mkapavlapg ilvllftlvq rsngeckeal aksemnvnmk yqlpnftaet piqnvilheh
  61 hiflgatnyi yvlneedlqk vaeyktgpvl ehpdcfpcqd csskanlsgg vwkdninmal
 121 vvdtyyddql iscgsvnrgt cqrhvfphnh tadiqsevhc ifspqieeps qcpdcvvsal
 181 gakvlssvkd rfinffvgnt inssyfpdhp lhsisvrrlk etkdgfmflt dqsyidvlpe
 241 frdsypikyv hafesnnfiy fltvqretld aqtfhtriir fcsinsglhs ymemplecil
 301 tekrkkrstk kevfnilqaa yvskpgaqla rqigaslndd ilfgvfaqsk pdsaepmdrs
 361 amcafpikyv ndffnkivnk nnvrclqhfy gpnhehcfnr tllrnssgce arrdeyrtef
 421 ttalqrvdlf mgqfsevllt sistfikgdl tianlgtseg rfmqvvvsrs gpstphvnfl
 481 ldshpvspev ivehtlnqng ytlvitgkki tkiplnglgc rhfqscsqcl sappfvqcgw
 541 chdkcvrsee clsgtwtqqi clpaiykvfp nsapleggtr lticgwdfgf rrnnkfdlkk
 601 trvllgnesc tltlsestmn tlkctvgpam nkhfnmsiii snghgttqys tfsyvdpvit
 661 sispkygpma ggtlltltgn ylnsgnsrhi siggktctlk svsnsilecy tpaqtistef
 721 avklkidlan retsifsyre dpivyeihpt ksfisggsti tgvgknlnsv svprmvinvh
 781 eagrnftvac qhrsnseiic cttpslqqln lqlplktkaf fmldgilsky fdliyvhnpv
 841 fkpfekpvmi smgnenvlei kgndidpeav kgevlkvgnk scenihlhse avlctvpndl
 901 lklnselnie wkqaisstvl gkvivqpdqn ftgliagvvs istallllg fflwlkkrkq
 961 ikdlgselvr ydarvhtphl drlvsarsvs pttemvsnes vdyratfped qfpnssqngs
1021 crqvqypltd mspiltsgds disspllqnt vhidlsalnp elvqavqhvv igpsslivhf
1081 nevigrghfg cvyhgtlldn dgkkihcavk slnritdige vsqfltegii mkdfshpnvl
1141 sllgiclrse gsplvvlpym khgdlrnfir nethnptvkd ligfglqvak gmkylaskkf
1201 vhrdlaarnc mldekftvkv adfglardmy dkeyysvhnk tgaklpvkwm aleslqtqkf
1261 ttksdvwsfg vllwelmtrg appypdvntf ditvyllqgr rllqpeycpd plyevmlkcw
1321 hpkaemrpsf selvsrisai fstfigehyv hvnatyvnvk cvapypslls sednaddevd
1381 trpasfwets
```

CLAIMS

1. An isolated polypeptide comprising at least one monomer domain that binds to c-MET, wherein the at least one monomer domain comprises a sequence selected from the group consisting of (i) SEQ ID NO:7, (ii) SEQ ID NO:12, (iii) and at least amino acids 1-34 of SEQ ID NO:14 and (iv) a sequence that is at least 95% identical to a sequence defined by any of (i), (ii) or (iii), as defined herein:

Cxxx[EQ]FxCxSTxRC[IV]xxxWxCDGDNDCEDxSDEx (SEQ ID NO:7),
wherein the first x is an amino acid chosen from A, L, E, R, P, and Q,
the second x is an amino acid chosen from P, A, and S,
the third x is an amino acid chosen from S, N, and G,
the fourth x is an amino acid chosen from T, Q, and K,
the fifth x is an amino acid chosen from N, R, S, and H,
the sixth x is an amino acid chosen from G, N, D, and E,
the seventh x is an amino acid chosen from P and S,
the eighth x is an amino acid chosen from Q, L, and A,
the ninth x is an amino acid chosen from E, T, Q, A, S, G, and D
the tenth x is an amino acid chosen from V and L,
the eleventh x is an amino acid chosen from S and G,
the twelfth x is an amino acid chosen from A, S, and K,
and amino acids in brackets are alternative amino acids at a single position;
Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO:12),
wherein the first x is an amino acid chosen from A, E, V, R, L, P, and Q,
the second x is an amino acid chosen from A, S, P, T, and L,
the third x is an amino acid chosen from D, S, N, and G,
the fourth x is an amino acid chosen from Q, T, and R,
the fifth x is an amino acid chosen from N, H, and R,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from V, Q, L, R, A, and G,
the eighth x is an amino acid chosen from S, E, D, Q, and A,
the ninth x is any amino acid,

the tenth x is an amino acid chosen from D and H,
the eleventh x is an amino acid chosen from V and D,
the twelfth x is an amino acid chosen from S and G,
the thirteenth x is an amino acid chosen from A, T, S, and E,
and amino acids in brackets are alternative amino acids at a single position; and at least amino acids 1-34 of
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid,
the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position.

2. The polypeptide of claim 1 comprising at least two monomer domains that bind to c-MET, wherein each of the at least two monomer domains comprises a sequence selected from the group consisting of SEQ ID NO:7, a sequence that is at least 95% identical to SEQ ID NO:7, SEQ ID NO:12, a sequence that is at least 95% identical to SEQ ID NO:12, at least amino acids 1-34 of SEQ ID NO:14, and a sequence that is at least 95% identical to at least amino acids 1-34 of SEQ ID NO:14, as defined in claim 1.

3. The polypeptide of claim 1 comprising at least three monomer domains that bind to c-MET wherein each of the monomer domains comprises a sequence selected from the group consisting of SEQ ID NO:7, a sequence that is at least 95% identical to SEQ ID NO:7, SEQ ID NO:12, a sequence that is at least 95% identical to SEQ ID NO:12, at least amino acids 1-34 of SEQ ID NO:14, and a sequence that is at least 95% identical to at least amino acids 1-34 of SEQ ID NO:14, as defined in claim 1.

4. An isolated polypeptide comprising at least one monomer domain that binds to c-MET, wherein the at least one monomer domain comprises the amino acids of SEQ ID NO:14 as defined herein:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,

the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,
the twenty-first x is an amino acid chosen from S, H, G and N,
and amino acids in brackets are alternative amino acids at a single position

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein.

5. The polypeptide of claim 4 comprising at least two monomer domains that bind to c-MET wherein each of the at least two monomer domains comprises the amino acids of SEQ ID NO:14 or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined in claim 4.

6. The polypeptide of claim 4 comprising at least three monomer domains that bind to c-MET wherein each of the monomer domains comprises the amino acids of SEQ ID NO:14 or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined in claim 4.

7. The polypeptide of any one of claims 1 to 6, further comprising the following sequence:

CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHT (SEQ ID NO:389).

8. An isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein one monomer domain comprises a sequence selected from the group consisting of

(1) Cxxx[EQ]FxCxSTGRCxPxxWxCxGxNDCEDxSDEx (SEQ ID NO:12),
wherein the first x is an amino acid chosen from A, E, V, R, L, P, and Q,
the second x is an amino acid chosen from A, S, P, T, and L,
the third x is an amino acid chosen from D, S, N, and G,
the fourth x is an amino acid chosen from Q, T, and R,
the fifth x is an amino acid chosen from N, H, and R,
the sixth x is any amino acid, the seventh x is an amino acid chosen from V, Q, L, R, A, and G,
the eighth x is an amino acid chosen from S, E, D, Q, and A,
the ninth x is any amino acid,
the tenth x is an amino acid chosen from D and H,
the eleventh x is an amino acid chosen from V and D,
the twelfth x is an amino acid chosen from S and G,
the thirteenth x is an amino acid chosen from A, T, S, and E,
and amino acids in brackets are alternative amino acids at a single position, and
(ii) a sequence that is at least 95% identical to a sequence defined by (i);
another monomer domain comprises a sequence selected from the group consisting of
(iii) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,

the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid,
the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position, and
(iv) a sequence that is at least 95% identical to a sequence defined by (iii); and
yet another monomer domain comprises a sequence selected from the group consisting of
(v) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid, the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid,
the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position; and
(vi) a sequence that is at least 95% identical to a sequence defined by (v).

9. An isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein one monomer domain comprises at least amino acids 1-38 of: CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHT (SEQ ID NO:389); another monomer domain comprises a sequence selected from the group consisting of

(i) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E,
the second x is an amino acid chosen from A, S, and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T, and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G, and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A, and H,
the thirteenth x is an amino acid chosen from L, G, and V,
the fourteenth x is an amino acid chosen from D, V, and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is any amino acid, the twentieth x is any amino acid,
the twenty-first x is any amino acid,
and amino acids in brackets are alternative amino acids at a single position,
and (ii) a sequence that is at least 95% identical to a sequence defined by (i); and yet another monomer domain comprises a sequence selected from the group consisting of (iii) at least amino acids 1-34 of:
Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L, and E, the second x is an amino acid chosen from A, S, and P, the third x is an amino acid chosen from G, S, N, and D, the fourth x is an amino acid chosen from Q, R, T, and M, the fifth x is an amino acid chosen from any amino acid, the sixth x is any amino acid, the seventh x is an amino acid chosen from T, G, and N, the eighth x is any amino acid, the ninth x is an amino acid chosen from R and Q, the tenth x is an amino acid chosen from P and S, the eleventh x is any amino acid, the twelfth x is an amino acid chosen from T, P, N, D, A, and H, the thirteenth x is an amino acid chosen from L, G, and V, the fourteenth x is an amino acid chosen from D, V, and E, the fifteenth x is an amino acid chosen from E and G, the sixteenth x is an amino acid chosen from G and S, the seventeenth x is any amino acid, the eighteenth x is any amino acid, the nineteenth x is any amino acid, the twentieth x is any amino acid, the twenty-first x is any amino acid, and amino acids in brackets are alternative amino acids at a single position; and (iv) a sequence that is at least 95% identical to a sequence defined by (iii).

10. An isolated polypeptide comprising at least three monomer domains that bind to c-MET, wherein each of the at least three monomer domains comprises the amino acids of the following sequence

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,

the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,
the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,
the twenty-first x is an amino acid chosen from S, H, G and N,
and amino acids in brackets are alternative amino acids at a single position,

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein.

11. An isolated polypeptide comprising at least two monomer domains that bind to c-MET, wherein one monomer domain comprises the amino acids of the following sequence:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,

the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,
the tenth x is an amino acid chosen from P and S,
the eleventh x is any amino acid,
the twelfth x is an amino acid chosen from T, P, N, D, A and H,
the thirteenth x is an amino acid chosen from L, G and V,
the fourteenth x is an amino acid chosen from D, V and E,
the fifteenth x is an amino acid chosen from E and G,
the sixteenth x is an amino acid chosen from G and S,
the seventeenth x is any amino acid,
the eighteenth x is any amino acid,
the nineteenth x is P or no amino acid,
the twentieth x is A or no amino acid,
the twenty-first x is an amino acid chosen from S, H, G and N,
and amino acids in brackets are alternative amino acids at a single position,

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein; and

another monomer domain comprising the amino acids of the following sequence:

Cxxx[EQ]FxCxxxxxC[ILV]xxxWxCDGxNDCxDxSxExxxxC (SEQ ID NO:14),
wherein the first x is an amino acid chosen from P, Q, V, L and E,
the second x is an amino acid chosen from A, S and P,
the third x is an amino acid chosen from G, S, N, and D,
the fourth x is an amino acid chosen from Q, R, T and M,
the fifth x is an amino acid chosen from any amino acid,
the sixth x is any amino acid,
the seventh x is an amino acid chosen from T, G and N,
the eighth x is any amino acid,
the ninth x is an amino acid chosen from R and Q,

the tenth x is an amino acid chosen from P and S,

the eleventh x is any amino acid,

the twelfth x is an amino acid chosen from T, P, N, D, A and H,

the thirteenth x is an amino acid chosen from L, G and V,

the fourteenth x is an amino acid chosen from D, V and E,

the fifteenth x is an amino acid chosen from E and G,

the sixteenth x is an amino acid chosen from G and S,

the seventeenth x is any amino acid,

the eighteenth x is any amino acid,

the nineteenth x is P or no amino acid,

the twentieth x is A or no amino acid,

the twenty-first x is an amino acid chosen from S, H, G and N,

and amino acids in brackets are alternative amino acids at a single position,

or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:14 as defined herein; and

further comprising the following sequence:

CQPNEFQCHSTGRCIPASWLCDGDNDCEDSSDESPANCATPTHT (SEQ ID NO:389).

12. The polypeptide of any one of claims 1 to 11, further comprising a monomer domain having a binding specificity for a blood factor, thereby increasing the serum half-life of the polypeptide when the polypeptide is injected into an animal compared to the serum half-life of a polypeptide lacking the blood factor-binding monomer domain.

13. The polypeptide of claim 12, wherein the blood factor is serum albumin, an immunoglobulin or an erythrocyte.

14. The polypeptide of claim 13, wherein the monomer domain having a binding specificity for a blood factor comprises a sequence selected from:

CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENCSAPASEPPGSL (SEQ ID NO:5), or

CHPTGQFRCRSSGRCVSPTWVCDGDNDCGDNSDEENC (SEQ ID NO:6).

15. An isolated polypeptide that binds to c-MET, wherein the polypeptide comprises the amino acids of SEQ ID NO:389 or a sequence that is at least 95% identical to the amino acids of SEQ ID NO:389.

16. An isolated polypeptide that binds to c-MET, wherein the polypeptide comprises amino acids 1-38 of SEQ ID NO:389 or a sequence that is at least 95% identical to amino acids 1-38 of SEQ ID NO:389.

17. The polypeptide of any one of claims 1 to 16, wherein the polypeptide further comprises polyethylene glycol (PEG).

18. An isolated polynucleotide encoding the polypeptide of any one of claims 1 to 16.

19. A method of treating cancer comprising administering the polypeptide of any one of claims 1 to 17 to a subject, wherein the subject suffers from a cancer that expresses c-MET and/or HGF.

20. The method of claim 19, wherein the cancer is selected from pancreatic cancer, mesothelioma, myeloma, head and neck cancer, lung (NSCLC) cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, glioblastoma, osteosarcoma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, oesophageal cancer, gastric cancer, kidney cancer, liver cancer, lung cancer, nasopharyngeal cancer, gall bladder cancer, prostate cancer, thyroid cancer, osteosarcoma, synovial sarcoma, rhabdomosarcoma, MFH/fibrosarcoma, Kaposi's sarcoma, multiple myeloma, lymphomas, adult T-cell leukemia, glioblastomas, astrocytomas, melanoma, and Wilm's tumor.

21. The method of claim 19 or 20, wherein the subject is a mammal.

22. The method of claim 19 or 20, wherein the subject is a human.

23. The method of any one of claims 19 to 22, wherein the administration is selected from intramuscular, intradermal, subdermal, subcutaneous, oral, intraperitoneal,

intrathecal, intravenous, placed within a cavity of the body, inhalation, vaginal, and rectal administration.

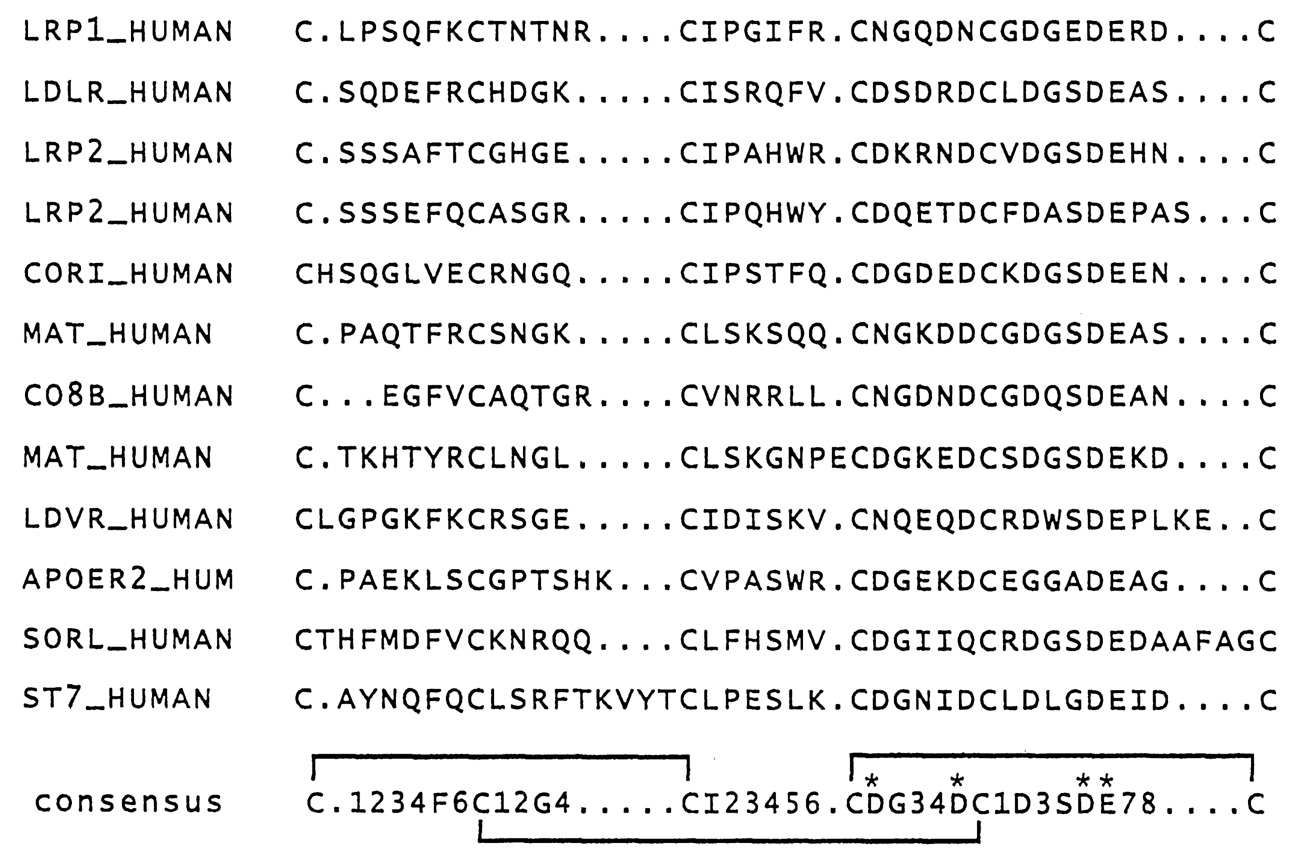
24. The method of any one of claims 19 to 23, further comprising administering an additional therapeutic entity.

25. The method of claim 24, wherein the additional therapeutic entity is selected from a biologic entity and a chemotherapeutic entity.

26. Use of a polypeptide of any one of claims 1 to 17 in the preparation of a medicament for the treatment of cancer wherein the cancer expresses c-MET and/or HGF.

27. An isolated polypeptide according to any one of claims 1 to 17; a polynucleotide according to claim 18; a method of treating cancer according to any one of claims 19 to 25; or use according to claim 26, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

LDL-receptor class A domain



```
LRP1_HUMAN   C.EPYQFRCKNNR.....CVPGRWQ.CDYDNDCGDNSDEES....C
LRP1_HUMAN   C.LPSQFKCTNTNR....CIPGIFR.CNGQDNCGDGEDERD....C
LDLR_HUMAN   C.SQDEFRCHDGK.....CISRQFV.CDSDRDCLDGSDEAS....C
LRP2_HUMAN   C.SSSAFTCGHGE.....CIPAHWR.CDKRNDCVDGSDEHN....C
LRP2_HUMAN   C.SSSEFQCASGR.....CIPQHWY.CDQETDCFDASDEPAS...C
CORI_HUMAN   CHSQGLVECRNGQ.....CIPSTFQ.CDGDEDCKDGSDEEN....C
MAT_HUMAN    C.PAQTFRCSNGK.....CLSKSQQ.CNGKDDCGDGSDEAS....C
CO8B_HUMAN   C...EGFVCAQTGR....CVNRRLL.CNGDNDCGDQSDEAN....C
MAT_HUMAN    C.TKHTYRCLNGL.....CLSKGNPECDGKEDCSDGSDEKD....C
LDVR_HUMAN   CLGPGKFKCRSGE.....CIDISKV.CNQEQDCRDWSDEPLKE..C
APOER2_HUM   C.PAEKLSCGPTSHK...CVPASWR.CDGEKDCEGGADEAG....C
SORL_HUMAN   CTHFMDFVCKNRQQ....CLFHSMV.CDGIIQCRDGSDEDAAFAGC
ST7_HUMAN    C.AYNQFQCLSRFTKVYTCLPESLK.CDGNIDCLDLGDEID....C

                                      *    *    **
consensus     C.1234F6C12G4.....CI23456.CDG34DC1D3SDE78....C
```

FIG. 1

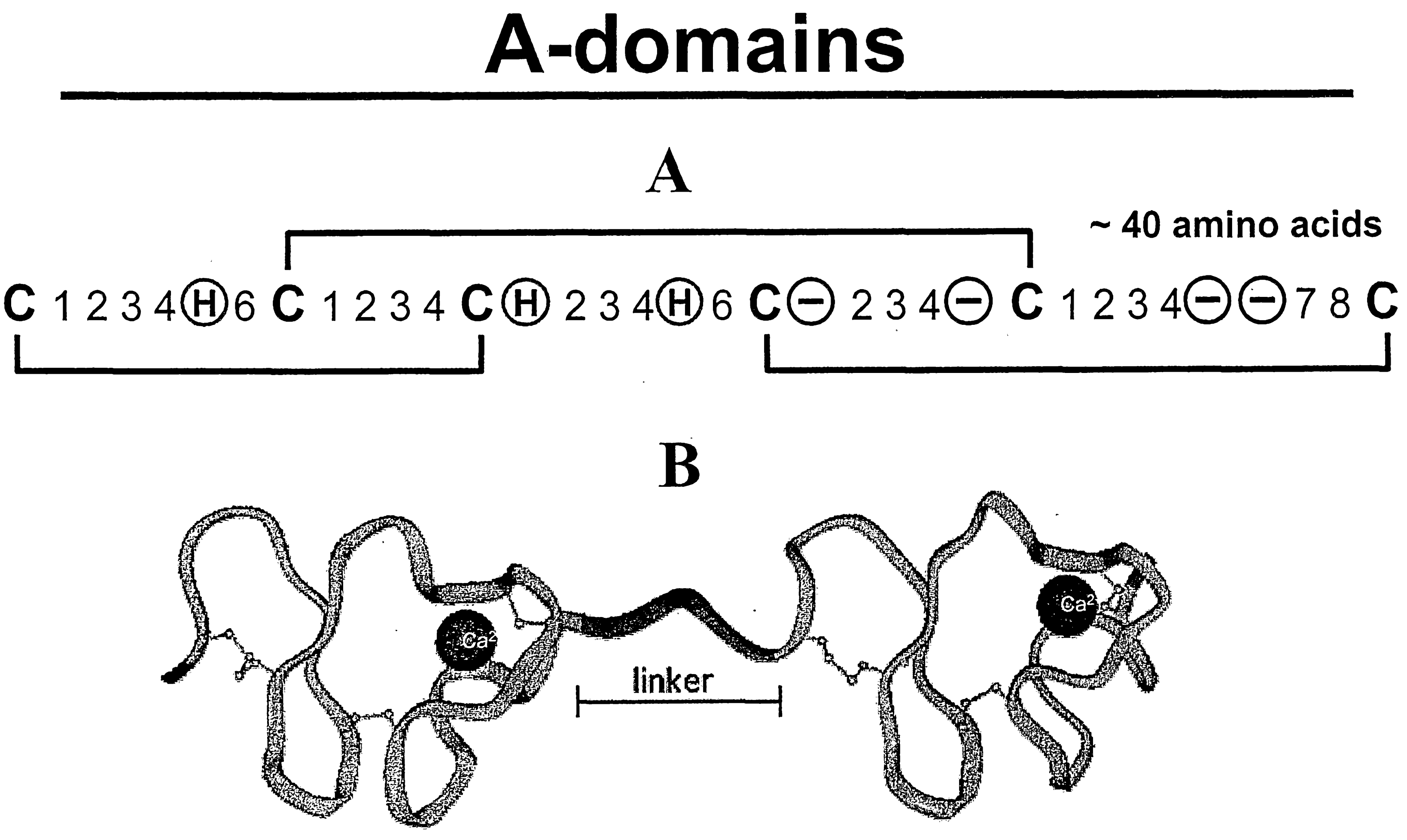

A-domains
A
~ 40 amino acids
C 1 2 3 4 Ⓗ 6 C 1 2 3 4 C Ⓗ 2 3 4 Ⓗ 6 C ⊖ 2 3 4 ⊖ C 1 2 3 4 ⊖ ⊖ 7 8 C
B
Ca2
Ca2
linker

FIG. 2

Ligands recognized by naturally-occurring LDL-receptor family

proteases
- factor IXa
- pro-uPA
- t-PA
- plasminogen
- MMP-9

inhibitors
- α_2-macroglobulin
- PAI-1
- TFPI
- pancreatic trypsin inhibitor

complexes
- protease/
  - α_1-antitrypsin
  - protein C inhibitor
  - protease nexin-1
  - antithrombin
  - C1-inhibitor
- thrombin/heparin cofactor II
- cathepsin G/α_1-antichymotrypsin

vitamin-carrier complexes
- vitamin D-bp, vitamin D
- retinol-bp, vitamin A
- transcobalamin, vitamin B12

proteins involved in lipoprotein metabolism
- apoB100
- apoE
- apoJ (clusterin)
- apoH (β_2-glycoprotein I)
- Lp(a)
- hepatic lipase
- lipoprotein lipase
- IDL
- VLDL
- β-VLDL

non-human
- pseudomonas exotoxin A
- circumsporozoite protein
- trichosanthin
- ricin A
- saporin

antibiotics
- gentamicin
- polymyxin B

viruses
- HRV2 (Rhino)
- HCV (Flavi)
- BVDV (Flavi)

miscellaneous
- albumin
- transthyretin
- β-Amyloid precursor protein
- RAP
- complement C3
- lactoferrin
- thyroglobulin
- thrombospondin
- saposin precursor
- reelin
- insulin
- parathyroid hormone (PTH)
- aprotinin
- α-amylase
- C1q
- α_1-microglobulin
- β_2-microglobulin
- odorant-binding protein
- epidermal growth factor
- prolactin
- lysozyme
- connective tissue growth factor (CTGF)
- cytochrome c
- seminal vesicle secretory protein II
- clara cell secretory protein (CCSP)
- cubulin
- factor VIII

FIG. 3

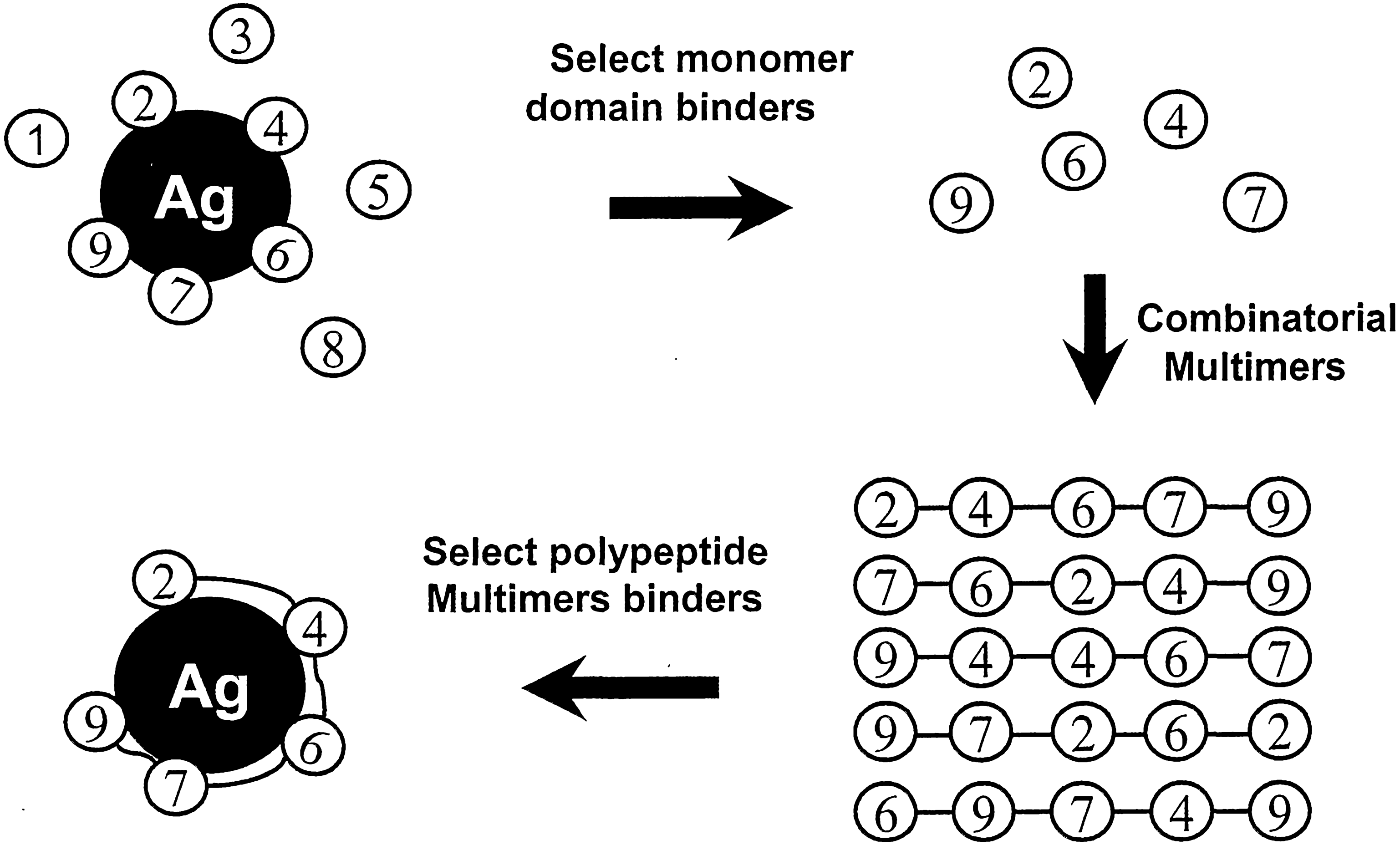

1
2
3
4
5
6
7
8
9
Ag
Select monomer
domain binders
2
4
6
9
7
Combinatorial
Multimers
2 4 6 7 9
7 6 2 4 9
9 4 4 6 7
9 7 2 6 2
6 9 7 4 9
Select polypeptide
Multimers binders
2
4
Ag
9
6
7

FIG. 4

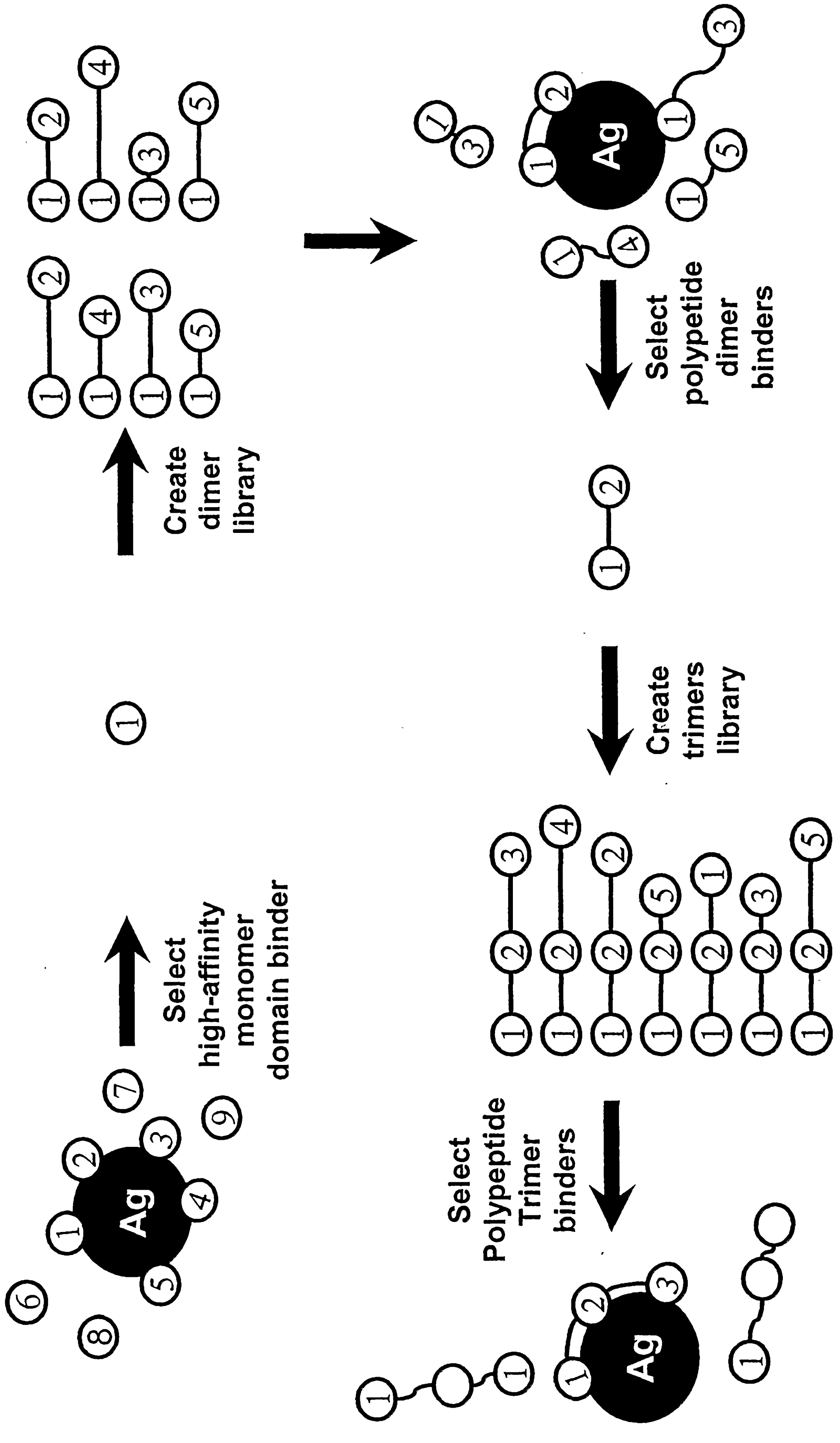

Ag
1
2
3
4
5
6
7
8
9
Select
high-affinity
monomer
domain binder
Create
dimer
library
Select
polypeptide
dimer
binders
Create
trimers
library
Select
Polypeptide
Trimer
binders

FIG. 5

```
                a             b c               de    f ghi  jk lm      nop        q
IDD_HUMAN       C.........NPGQFACRSGTIQ.........CIPLPWQ.CDGWATCEDE......SDEAN......C
LRP3_HUMAN      C.........QADEFRCDNGK...........CLPGPWQ.CNTVDECGDG......SDEGN......C
LRP3_HUMAN      C.........PGGTFPCSGARSTR........CLPVERR.CDGLQDCGDG......SDEAG......C
LRP3_HUMAN      C.........LPWEQPCGSSSDSDGGSLGDQGCFSEPQR.CDGWWHCASG......RDEQG......C
LRP3_HUMAN      C.........PPDQYPCEGGSGL.........CYTPADR.CNNQKSCPDG......ADEKN......C
LRP3_HUMAN      C.........QPGTFHCGTNL...........CIFETWR.CDGQEDCQDG......SDEHG......C
LRP5_HUMAN      C.........SPDQFACATGEID.........CIPGAWR.CDGFPECDDQ......SDEEG......C
LRP5_HUMAN      C.........SAAQFPCARGQ...........CVDLRLR.CDGEADCQDR......SDEVD......C
LRP5_HUMAN      C.........LPNQFRCASGQ...........CVLIKQQ.CDSFPDCIDG......SDELM......C
LRP6_HUMAN      C.........SPQQFTCFTGEID.........CIPVAWR.CDGFTECEDH......SDELN......C
LRP6_HUMAN      C.........SESQFQCASGQ...........CIDGALR.CNGDANCQDK......SDEKN......C
LRP6_HUMAN      C.........LIDQFRCANGQ...........CIGKHKK.CDHNVDCSDK......SDELD......C
ST7_HUMAN       C.........ACDQFRCGNGK...........CIPEAWK.CNNMDECGDS......SDEEI......C
ST7_HUMAN       C.........AYNQFQCLSRFTKVYT......CLPESLK.CDGNIDCLDL......GDEID......C
ST7_HUMAN       C.........LPWEIPCGGNWG..........CYTEQQR.CDGYWHCPNG......RDETN......C
ST7_HUMAN       C.........QKEEFPCSRNGV..........CYPRSDR.CNYQNHCPNG......SDEKN......C
ST7_HUMAN       C.........QPGNFHCKNNR...........CVFESWV.CDSQDDCGDG......SDEEN......C
CORI_HUMAN      C........GRGENFLCASGI...........CIPGKLQ.CNGYNDCDDW......SDEAH......C
CORI_HUMAN      C.........SENLFHCHTGK...........CLNYSLV.CDGYDDCGDL......SDEQN......C
CORI_HUMAN      C........NPTTEHRCGDGR...........CIAMEWV.CDGDHDCVDK......SDEVN......C
CORI_HUMAN      C........HSQGLVECRNGQ...........CIPSTFQ.CDGDEDCKDG......SDEEN......C
CORI_HUMAN      C.........SPSHFKCRSGQ...........CVLASRR.CDGQADCDDD......SDEEN......C
CORI_HUMAN      C........KERDLWECPSNKQ..........CLKHTVI.CDGFPDCPDY......MDEKN......C
CORI_HUMAN      C.........QDDELECANHA...........CVSRDLW.CDGEADCSDS......SDEWD......C
TMS2_HUMAN      C.........SNSGIECDSSGT..........CINPSNW.CDGVSHCPGG......EDENR......C
TMS3_HUMAN      C..........SGKYRCRSSFK..........CIELIAR.CDGVSDCKDG......EDEYR......C
MAT_HUMAN       C..........PGQFTCRTGR...........CIRKELR.CDGWADCTDH......SDELN......C
MAT_HUMAN       C........DAGHQFTCKNKF...........CKPLFWV.CDSVNDCGDN......SDEQG......C
MAT_HUMAN       C.........PAQTFRCSNGK...........CLSKSQQ.CNGKDDCGDG......SDEAS......C
```

FIG. 6A

```
MAT_HUMAN      C.........TKHTYRCLNGL..........CLSKGNPECDGKEDCSDG.....SDEKD......C
ENTK_HUMAN     C.........LPGSSPCTDALT.........CIKADLF.CDGEVNCPDG.....SDEDNKM....C
ENTK_HUMAN     C.........KADHFQCKNGE..........CVPLVNL.CDGHLHCEDG.....SDEAD......C
HAI1_HUMAN     C.........QPTQFRCSNGC..........CIDSFLE.CDDTPNCPDA.....SDEAA......C
CFAI_HUMAN     C.YTQKADSPMDDFFQCVNGK..........YISQMKA.CDGINDCGDQ.....SDEL.......C
CFAI_HUMAN     C.........QGKGFHCKSGV..........CIPSQYQ.CNGEVDCITG.....EDEVG......C
CO6_HUMAN      C..........KNKFRCDSGR..........CIARKLE.CNGENDCGDN.....SDERD......C
CO7_HUMAN      C..........GERFRCFSGQ..........CISKSLV.CNGDSDCDEDS....ADEDR......C
CO8A_HUMAN     C..........GQDFQCKETGR.........CLKRHLV.CNGDQDCLDG.....SDEDD......C
CO8B_HUMAN     C...........EGFVCAQTGR.........CVNRRLL.CNGDNDCGDQ.....SDEAN......C
CO9_HUMAN      C..........GNDFQCSTGR..........CIKMRLR.CNGDNDCGDF.....SDEDD......C
PERL_HUMAN     C.........TEAEFACHSYNE.........CVALEYR.CDRRPDCRDM.....SDELN......C
PERL_HUMAN     C.........GPQEAACRNGH..........CIPRDYL.CDGQEDCEDG.....SDELD......C
PERL_HUMAN     C.........EPNEFPCGNGH..........CALKLWR.CDGDFDCEDR.....TDEAN......C
PERL_HUMAN     C.........GPTQFRCVSTNM.........CIPASFH.CDEESDCPDR.....SDEFG......C
SORL_HUMAN     C.........LRNQYRCSNGN..........CINSIWW.CDFDNDCGDM.....SDERN......C
SORL_HUMAN     C........DLDTQFRCQESGT.........CIPLSYK.CDLEDDCGDN.....SDESH......C
SORL_HUMAN     C.........RSDEYNCSSGM..........CIRSSWV.CDGDNDCRDW.....SDEAN......C
SORL_HUMAN     C.........EASNFQCRNGH..........CIPQRWA.CDGDTDCQDG.....SDEDPVN....C
SORL_HUMAN     C...........NGFRCPNGT..........CIPSSKH.CDGLRDCSDG.....SDEQH......C
SORL_HUMAN     C........THFMDFVCKNRQQ.........CLFHSMV.CDGIIQCRDG.....SDEDAAFAG..C
SORL_HUMAN     C.........DEFGFQCQNGV..........CISLIWK.CDGMDDCGDY.....SDEAN......C
SORL_HUMAN     C........SRYFQFRCENGH..........CIPNRWK.CDRENDCGDW.....SDEKD......C
SORL_HUMAN     C.........LPNYYRCSSGT..........CVMDTWV.CDGYRDCADG.....SDEEA......C
SORL_HUMAN     C.........DRFEFECHQPKT.........CIPNWKR.CDGHQDCQDG.....RDEAN......C
SORL_HUMAN     C.........MSREFQCEDGEA.........CIVLSER.CDGFLDCSDE.....SDEKA......C
APOER2_HUM     C.........EKDQFQCRNER..........CIPSVWR.CDEDDDCLDH.....SDEDD......C
APOER2_HUM     C.........ADSDFTCDNGH..........CIHERWK.CDGEEECPDG.....SDESEAT....C
APOER2_HUM     C.........PAEKLSCGPTSHK........CVPASWR.CDGEKDCEGG.....ADEAG......C
APOER2_HUM     C.........APHEFQCGNRS..........CLAAVFV.CDGDDDCGDG.....SDERG......C
APOER2_HUM     C.........GPREFRCGGDGGGA.......CIPERWV.CDRQFDCEDR.....SDEAAEL....C
APOER2_HUM     C........ATVSQFACRSGE..........CVHLGWR.CDGDRDCKDK.....SDEAD......C
APOER2_HUM     C.........RGDEFQCGDGT..........CVLAIKH.CNQEQDCPDG.....SDEAG......C
```

FIG. 6B

```
LDLR_HUMAN     C.........ERNEFQCQDGK...........CISYKWV.CDGSAECQDG.....SDESQET....C
LDLR_HUMAN     C.........KSGDFSCGGRVNR.........CIPQFWR.CDGQVDCDNG.....SDEQG......C
LDLR_HUMAN     C.........SQDEFRCHDGK...........CISRQFV.CDSDRDCLDG.....SDEAS......C
LDLR_HUMAN     C.........GPASFQCNSST...........CIPQLWA.CDNDPDCEDG.....SDEWPQR....C
LDLR_HUMAN     C.........SAFEFHCLSGE...........CIHSSWR.CDGGPDCKDK.....SDEEN......C
LDLR_HUMAN     C.........RPDEFQCSDGN...........CIHGSRQ.CDREYDCKDM.....SDEVG......C
LDLR_HUMAN     C........EGPNKFKCHSGE...........CITLDKV.CNMARDCRDW.....SDEPIKE....C
LDVR_HUMAN     C.........EPSQFQCTNGR...........CITLLWK.CDGDEDCVDG.....SDEKN......C
LDVR_HUMAN     C.........AESDFVCNNGQ...........CVPSRWK.CDGDPDCEDG.....SDESPEQ....C
LDVR_HUMAN     C.........RIHEISCGAHSTQ.........CIPVSWR.CDGENDCDSG.....EDEEN......C
LDVR_HUMAN     C.........SPDEFTCSSGR...........CISRNFV.CNGQDDCSDG.....SDELD......C
LDVR_HUMAN     C.........GAHEFQCSTSS...........CIPISWV.CDDDADCSDQ.....SDESLEQ....C
LDVR_HUMAN     C.........PASEIQCGSGE...........CIHKKWR.CDGDPDCKDG.....SDEVN......C
LDVR_HUMAN     C.........RPDQFECEDGS...........CIHGSRQ.CNGIRDCVDG.....SDEVN......C
LDVR_HUMAN     C........LGPGKFKCRSGE...........CIDISKV.CNQEQDCRDW.....SDEPLKE....C
LRP1_HUMAN     C.........SPKQFACRDQIT..........CISKGWR.CDGERDCPDG.....SDEAPEI....C
LRP1_HUMAN     C.........QPNEHNCLGTEL..........CVPMSRL.CNGVQDCMDG.....SDEGPH.....C
LRP1_HUMAN     C.........QPGEFACANSR...........CIQERWK.CDGDNDCLDN.....SDEAPAL....C
LRP1_HUMAN     C.........PSDRFKCENNR...........CIPNRWL.CDGDNDCGNS.....EDESNAT....C
LRP1_HUMAN     C.........PPNQFSCASGR...........CIPISWT.CDLDDDCGDR.....SDESAS.....C
LRP1_HUMAN     C........FPLTQFTCNNGR...........CININWR.CDNDNDCGDN.....SDEAG......C
LRP1_HUMAN     C.........SSTQFKCNSGR...........CIPEHWT.CDGDNDCGDY.....SDETHAN....C
LRP1_HUMAN     C.........HTDEFQCRLDGL..........CIPLRWR.CDGDTDCMDS.....SDEKS......C
LRP1_HUMAN     C........DPSVKFGCKDSAR..........CISKAWV.CDGDNDCEDN.....SDEEN......C
LRP1_HUMAN     C.........RPPSHPCANNTSV.........CLPPDKL.CDGNDDCGDG.....SDEGEL.....C
LRP1_HUMAN     C........RAQDEFECANGE...........CINFSLT.CDGVPHCKDK.....SDEKPSY....C
LRP1_HUMAN     C.........KKTFRQCSNGR...........CVSNMLW.CNGADDCGDG.....SDEIP......C
LRP1_HUMAN     C.........GVGEFRCRDGT...........CIGNSSR.CNQFVDCEDA.....SDEMN......C
LRP1_HUMAN     CSSYFRLGVKGVLFQPCERTSL..........CYAPSWV.CDGANDCGDY.....SDERD......C
LRP1_HUMAN     C.........PLNYFACPSGR...........CIPMSWT.CDKEDDCEHG.....EDETH......C
LRP1_HUMAN     C.........SEAQFECQNHR...........CISKQWL.CDGSDDCGDG.....SDEAAH.....C
LRP1_HUMAN     C.........GPSSFSCPGTHV..........CVPERWL.CDGDKDCADG.....ADESIAAG...C
LRP1_HUMAN     C.........DDREFMCQNRQ...........CIPKHFV.CDHDRDCADG.....SDESPE.....C
```

FIG. 6C

```
LRP1_HUMAN      C.........GPSEFRCANGR...........CLSSRQWECDGENDCHDQ......SDEAPKNPH..C
LRP1_HUMAN      C........NASSQFLCSSGR...........CVAEALL.CNGQDDCGDS......SDERG......C
LRP1_HUMAN      C.........TASQFVCKNDK...........CIPFWWK.CDTEDDCGDH......SDEPPD.....C
LRP1_HUMAN      C.........RPGQFQCSTGI...........CTNPAFI.CDGDNDCQDN......SDEAN......C
LRP1_HUMAN      C.........LPSQFKCTNTNR..........CIPGIFR.CNGQDNCGDG......EDERD......C
LRP1_HUMAN      C.........APNQFQCSITKR..........CIPRVWV.CDRDNDCVDG......SDEPAN.....C
LRP1_HUMAN      C.........GVDEFRCKDSGR..........CIPARWK.CDGEDDCGDG......SDEPKEE....C
LRP1_HUMAN      C.........EPYQFRCKNNR...........CVPGRWQ.CDYDNDCGDN......SDEES......C
LRP1_HUMAN      C.........SESEFSCANGR...........CIAGRWK.CDGDHDCADG......SDEKD......C
LRP1_HUMAN      C.........DMDQFQCKSGH...........CIPLRWR.CDADADCMDG......SDEEA......C
LRP1_HUMAN      C.........PLDEFQCNNTL...........CKPLAWK.CDGEDDCGDN......SDENPEE....C
LRP1_HUMAN      C........PPNRPFRCKNDRV..........CLWIGRQ.CDGTDNCGDG......TDEED......C
LRP1_HUMAN      C........KDKKEFLCRNQR...........CLSSSLR.CNMFDDCGDG......SDEED......C
LRP2_HUMAN      C.........DSAHFRCGSGH...........CIPADWR.CDGTKDCSDD......ADEIG......C
LRP2_HUMAN      C.........QQGYFKCQSEGQ..........CIPSSWV.CDQDQDCDDG......SDERQD.....C
LRP2_HUMAN      C.........SSHQITCSNGQ...........CIPSEYR.CDHVRDCPDG......ADEND......C
LRP2_HUMAN      C...........EQLTCDNGA...........CYNTSQK.CDWKVDCRDS......SDEIN......C
LRP2_HUMAN      C.........LHNEFSCGNGE...........CIPRAYV.CDHDNDCQDG......SDEHA......C
LRP2_HUMAN      C.........GGYQFTCPSGR...........CIYQNWV.CDGEDDCKDN......GDEDG......C
LRP2_HUMAN      C.........SPREWSCPESGR..........CISIYKV.CDGILDCPGR......EDENNTSTGKYC
LRP2_HUMAN      C.........GLFSFPCKNGR...........CVPNYYL.CDGVDDCHDN......SDEQL......C
LRP2_HUMAN      C.........SSSAFTCGHGE...........CIPAHWR.CDKRNDCVDG......SDEHN......C
LRP2_HUMAN      C.........LDTQYTCDNHQ...........CISKNWV.CDTDNDCGDG......SDEKN......C
LRP2_HUMAN      C.........QPSQFNCPNHR...........CIDLSFV.CDGDKDCVDG......SDEVG......C
LRP2_HUMAN      C.........TASQFKCASGDK..........CIGVTNR.CDGVFDCSDN......SDEAG......C
LRP2_HUMAN      C.........HSDEFQCQEDGI..........CIPNFWE.CDGHPDCLYG......SDEHNA.....C
LRP2_HUMAN      C.........PSSYFHCDNGN...........CIHRAWL.CDRDNDCGDM......SDEKD......C
LRP2_HUMAN      C.........PSWQWQCLGHNI..........CVNLSVV.CDGIFDCPNG......TDESPL.....C
LRP2_HUMAN      C.........GASSFTCSNGR...........CISEEWK.CDNDNDCGDG......SDEMESV....C
LRP2_HUMAN      C.........SPTAFTCANGR...........CVQYSYR.CDYYNDCGDG......SDEAG......C
LRP2_HUMAN      C........NATTEFMCNNRR...........CIPREFI.CNGVDNCHDNNT....SDEKN......C
LRP2_HUMAN      C.........QSGYTKCHNSNI..........CIPRVYL.CDGDNDCGDN......SDENPTY....C
LRP2_HUMAN      C.........SSSEFQCASGR...........CIPQHWY.CDQETDCFDA......SDEPAS.....C
```

FIG. 6D

```
LRP2_HUMAN    C.........LADEFKCDGGR...........CIPSEWI.CDGDNDCGDM.....SDEDKRHQ...C
LRP2_HUMAN    C.........SDSEFLCVNDRPPDRR......CIPQSWV.CDGDVDCTDG.....YDENQN.....C
LRP2_HUMAN    C.........SENEFTCGYGL...........CIPKIFR.CDRHNDCGDY.....SDERG......C
LRP2_HUMAN    C.........QQNQFTCQNGR...........CISKTFV.CDEDNDCGDG.....SDELMHL....C
LRP2_HUMAN    C.........PPHEFKCDNGR...........CIEMMKL.CNHLDDCLDN.....SDEKG......C
LRP2_HUMAN    C.........SSTQFLCANNEK..........CIPIWWK.CDGQKDCSDG.....SDELAL.....C
LRP2_HUMAN    C.........RLGQFQCSDGN...........CTSPQTL.CNAHQNCPDG.....SDEDRLL....C
LRP2_HUMAN    C.........DSNEWQCANKR...........CIPESWQ.CDTFNDCEDN.....SDEDSSH....C
LRP2_HUMAN    C.........RPGQFRCANGR...........CIPQAWK.CDVDNDCGDH.....SDEPIEE....C
LRP2_HUMAN    C........DNFTEFSCKTNYR..........CIPKWAV.CNGVDDCRDN.....SDEQG......C
LRP2_HUMAN    C........HPVGDFRCKNHH...........CIPLRWQ.CDGQNDCGDN.....SDEEN......C
LRP2_HUMAN    C.........TESEFRCVNQQ...........CIPSRWI.CDHYNDCGDN.....SDERD......C
LRP2_HUMAN    C.........HPEYFQCTSGH...........CVHSELK.CDGSADCLDA.....SDEAD......C
LRP2_HUMAN    C.........QATMFECKNHV...........CIPPYWK.CDGDDDCGDG.....SDEELHL....C
LRP2_HUMAN    C........NSPNRFRCDNNR...........CIYSHEV.CNGVDDCGDG.....TDETEEH....C
LRP2_HUMAN    C.........TEYEYKCGNGH...........CIPHDNV.CDDADDCGDW.....SDELG......C
LR1B_HUMAN    C.........DPGEFLCHDHVT..........CVSQSWL.CDGDPDCPDD.....SDESLDT....C
LR1B_HUMAN    C.........PLNHIACLGTNK..........CVHLSQL.CNGVLDCPDG.....YDEGVH.....C
LR1B_HUMAN    C.........KAGEFRCKNRH...........CIQARWK.CDGDDDCLDG.....SDEDSVN....C
LR1B_HUMAN    C.........PDDQFKCQNNR...........CIPKRWL.CDGANDCGSN.....EDESNQT....C
LR1B_HUMAN    C.........QVDQFSCGNGR...........CIPRAWL.CDREDDCGDQ.....TDEMAS.....C
LR1B_HUMAN    C........EPLTQFVCKSGR...........CISSKWH.CDSDDDCGDG.....SDEVG......C
LR1B_HUMAN    C.........FDNQFRCSSGR...........CIPGHWA.CDGDNDCGDF.....SDEAQIN....C
LR1B_HUMAN    C.........NGNEFQCHPDGN..........CVPDLWR.CDGEKDCEDG.....SDEKG......C
LR1B_HUMAN    C........DHKTKFSCWSTGR..........CINKAWV.CDGDIDCEDQ.....SDEDD......C
LR1B_HUMAN    C.........GPPKHPCANDTSV.........CLQPEKL.CNGKKDCPDG.....SDEGYL.....C
LR1B_HUMAN    C........NAYSEFECGNGE...........CIDYQLT.CDGIPHCKDK.....SDEKLLY....C
LR1B_HUMAN    C.........RRGFKPCYNRR...........CIPHGKL.CDGENDCGDN.....SDELD......C
LR1B_HUMAN    C.........ATVEFRCADGT...........CIPRSAR.CNQNIDCADA.....SDEKN......C
LR1B_HUMAN    CTHFYKLGVKTTGFIRCNSTSL..........CVLPTWI.CDGSNDCGDY.....SDELK......C
LR1B_HUMAN    C.........EENYFSCPSGR...........CILNTWI.CDGQKDCEDG.....RDEFH......C
LR1B_HUMAN    C.........SWNQFACSAQK...........CISKHWI.CDGEDDCGDG.....LDESDSI....C
LR1B_HUMAN    C.........AADMFSCQGSRA..........CVPRHWL.CDGERDCPDG.....SDELSTAG...C
```

FIG. 6E

```
LR1B_HUMAN      C.........DENAFMCHNKV..........CIPKQFV.CDHDDDCGDG.....SDESPQ.....C
LR1B_HUMAN      C.........GTEEFSCADGR..........CLLNTQWQCDGDFDCPDH.....SDEAPLNPK..C
LR1B_HUMAN      C.........NSSFFMCKNGR..........CIPSGGL.CDNKDDCGDG.....SDERN......C
LR1B_HUMAN      C.........TASQFRCKTDK..........CIPFWWK.CDTVDDCGDG.....SDEPDD.....C
LR1B_HUMAN      C.........QPGRFQCGTGL..........CALPAFI.CDGENDCGDN.....SDELN......C
LR1B_HUMAN      C.........LSGQFKCTKNQK.........CIPVNLR.CNGQDDCGDE.....EDERD......C
LR1B_HUMAN      C.........SPDYFQCKTTKH.........CISKLWV.CDEDPDCADA.....SDEAN......C
LR1B_HUMAN      C.........GPHEFQCKNNN..........CIPDHWR.CDSQNDCSDN.....SDEEN......C
LR1B_HUMAN      C.........TLKDFLCANGD..........CVSSRFW.CDGDFDCADG.....SDERN......C
LR1B_HUMAN      C.........SKDQFRCSNGQ..........CIPAKWK.CDGHEDCKYG.....EDEKS......C
LR1B_HUMAN      C.........SSREYICASDG..........CISASLK.CNGEYDCADG.....SDEMD......C
LR1B_HUMAN      C.........KEDQFRCKNKAH.........CIPIRWL.CDGIHDCVDG.....SDEEN......C
LR1B_HUMAN      C.........RADEFLCNNSL..........CKLHFWV.CDGEDDCGDN.....SDEAPDM....C
LR1B_HUMAN      C........PSTRPHRCRNNRI.........CLQSEQM.CNGIDECGDN.....SDEDH......C
LR1B_HUMAN      C.........KKDEFACSNKK..........CIPMDLQ.CDRLDDCGDG.....SDEQG......C


O75851          C.........AEGEALCQENGH.........CVPHGWL.CDNQDDCGDG.....SDEEGE.....C
O75851          C.........GEGQMTCSSGH..........CLPLALL.CDRQDDCGDG.....TDEPSYP....C
O75851          C.........PQGLLACADGR..........CLPPALL.CDGHPDCLDA.....ADEES......C
O75851          C.........VPGEVSCVDGT..........CLGAIQL.CDGVWDCPDG.....ADEGPGH....C
ENSP00000262089
= O75851        C.........GPFEFRCGSGE..........CTPRGWR.CDQEEDCADG.....SDERG......C
ENSP00000262089
                C.........APHHAPCARGPH.........CVSPEQL.CDGVRQCPDG.....SDEGPDA....C
O75851          C..........PGLFPCGVAPGL........CLTPEQL.CDGIPDCPQG.....EDELD......C
O75851          C...........PEYTCPNGT..........CIGFQLV.CDGQPDCGRPGQVGPSPEEQG......C
O75851          C........EPGVGLRCASGE..........CVLRGGP.CDGVLDCEDG.....SDEEG......C
ENSP00000262089
                C.........GPGQTPCEVLG..........CVEQAQV.CDGREDCLDG.....SDERH......C
O75851          C.........SPSQLSCGSGE..........CLSAERR.CDLRPDCQDG.....SDEDG......C
C18oRF1         C............KFTCTSGK..........CLYLGSLVCNQQNDCGDN.....SDEEN......C
AAH07083/Q9NPF0
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FIG. 6F

```
                 C.........PPTKFQCRTSGL..........CVPLTWR.CDRDLDCSDG......SDEEE......C
AAH07083/Q9NPF0
                 C.........LAGELRCTLSDD..........CIPLTWR.CDGHPDCPDS......SDELG......C
Q9HBX9           C.........SLGYFPCGNITK..........CLPQLLH.CNGVDDCGNQ......ADEDN......C
Q9BY79/Q96DQ9    C.........AHDEFRCDQLI...........CLLPDSV.CDGFANCADG......SDETN......C
Q9BY79/Q96DQ9    C.........GPSELSCQAGG...........CKGVQWM.CDMWRDCTDG......SDDN.......C
BAB55257 =
ENSP00000239367
                 C.........SRYHFFCDDGC...........CIDITLA.CDGVQQCPDG......SDEDF......C
O95518 =         C..........PGEFLCSVNGL..........CVPA....CDGVKDCPNG......LDERN......C
ENSP00000255793
ENSP00000255793
                 C..........RATFQCKEDST..........CISLPKV.CDGQPDCLNG......SDEEQ......C
ENSP00000255793
                 C.........GTFTFQCEDRS...........CVKKPNPQCDGRPDCRDG......SDEEH......C

Q8WXD0           C         QKGYFPCGNLTK          CLPRAFH CDGKDDCGNG      ADEEN      C
Q8NBJ0           C         STARYHCKNGL           CIDKSFI CDGQNNCQDN      SDEES      C
Q8NBJ0           C         GPTFFPCASGIH          CIIGRFR CNGFEDCPDG      SDEEN      C
Q8NBJ0           C        NIPGNFMCSNGR           CIPGAWQ CDGLPDCFDK      SDEKE      C
MEGF7            C         ALDQFLCWNGR           CIGQRKL CNGVNDCGDN      SDESPQQN   C
MEGF7            C         EEDEFPCQNGY           CIRSLWH CDGDNDCGDN      SDEQ       C
MEGF7            C         RSGEFMCDSGL           CINAGWR CDGDADCDDQ      SDERN      C
MEGF7            C         TAEQFRCHSGR           CVRLSWR CDGEDDCADN      SDEEN      C
MEGF7            C         SPLDFHCDNGK           CIRRSWV CDGDNDCEDD      SDEQD      C
MEGF7            C         NLEEFQCAYGR           CILDIYH CDGDDDCGDW      SDESD      C
MEGF7            C         SDKEFRCSDGS           CIAEHWY CDGDTDCKDG      SDEEN      C
MEGF7            C         GRSHFTCAVSALGECT      CIPAQWQ CDGDNDCGDH      SDEDG      C
CAD61944         C         LQEEFQCLNHR           CVSAVQR CDGVDACGDG      SDEAG      C
CAD61944         C         PPGHFPCGAAGTSGATA     CYLPADR CNYQTFCADG      ADERR      C
CAD61944         C         QPGNFRCRDEK           CVYETWV CDGQPDCADG      SDEWD      C
ENSG00000181006
                 C        PEITDFLCRDKK           CIASHLL CDYKPDCSDR      SDEAH      C
```

FIG. 6G

```
ENSP00000320248
               C        NNRTFKCGNDI           CFRKQNAKCDGTVDCPDG      SDEEG        C
ENSP00000277547
               C        PPGHHHCQNKV           CVEPQQL CDGEDNCGDL      SDENPLT      C
ENSP00000320022
               C        KQGHLACGDL            CVPPEQL CDFEEQCAGG      EDEQA        C
ENSP00000313222
               C        PGNSFSCGNSQ           CVTKVNPECDDQEDCSDG      SDEAH        C
```

FIG. 6H

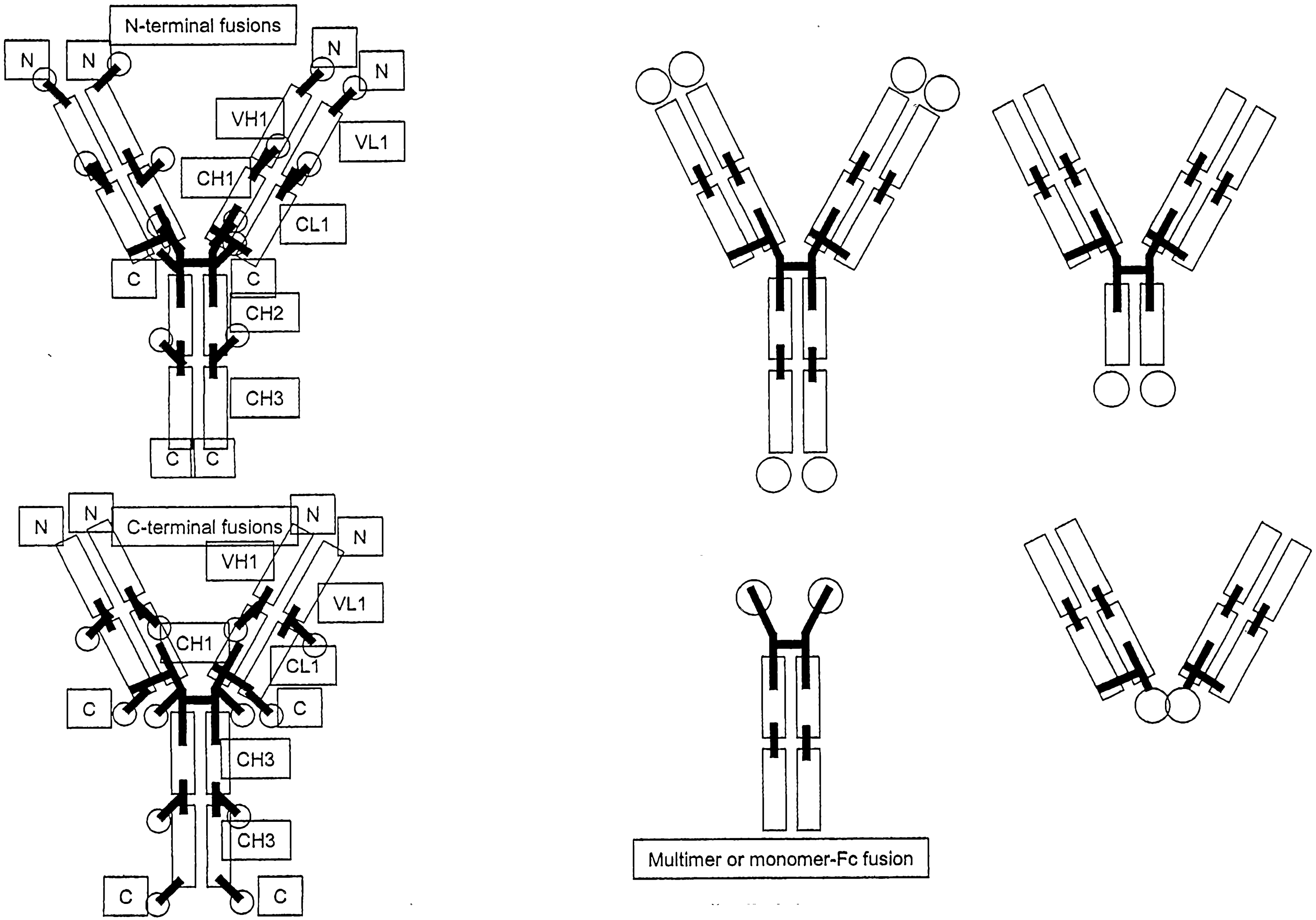
N-terminal fusions
N
N
N
N
VH1
VL1
CH1
CL1
C
C
CH2
CH3
C
C
C-terminal fusions
N
N
N
N
VH1
VL1
CH1
CL1
C
C
CH3
CH3
C
C
Multimer or monomer-Fc fusion

FIG. 7

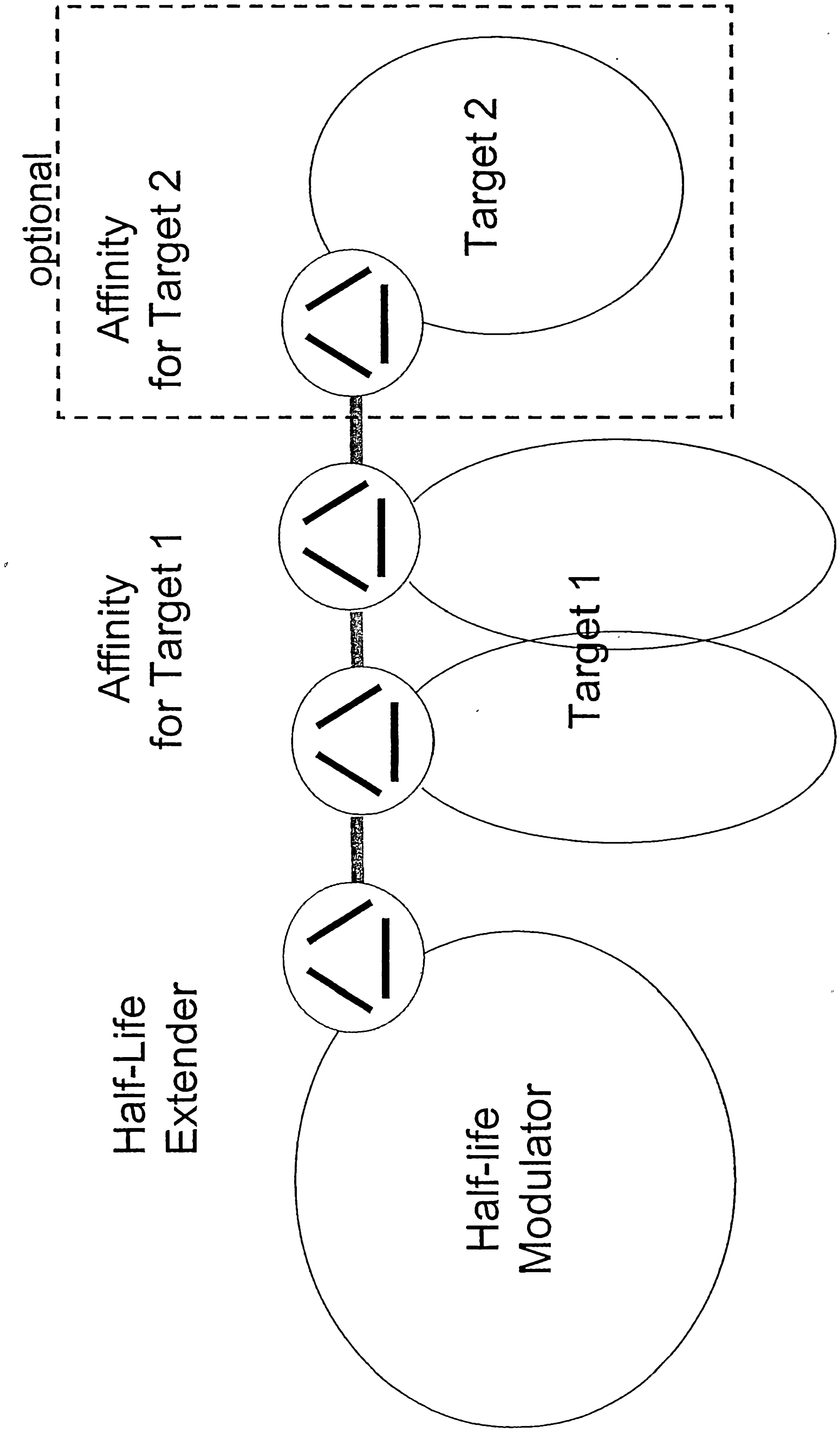
optional
Affinity for Target 2
Target 2
Affinity for Target 1
Target 1
Half-Life Extender
Half-life Modulator

FIG. 8

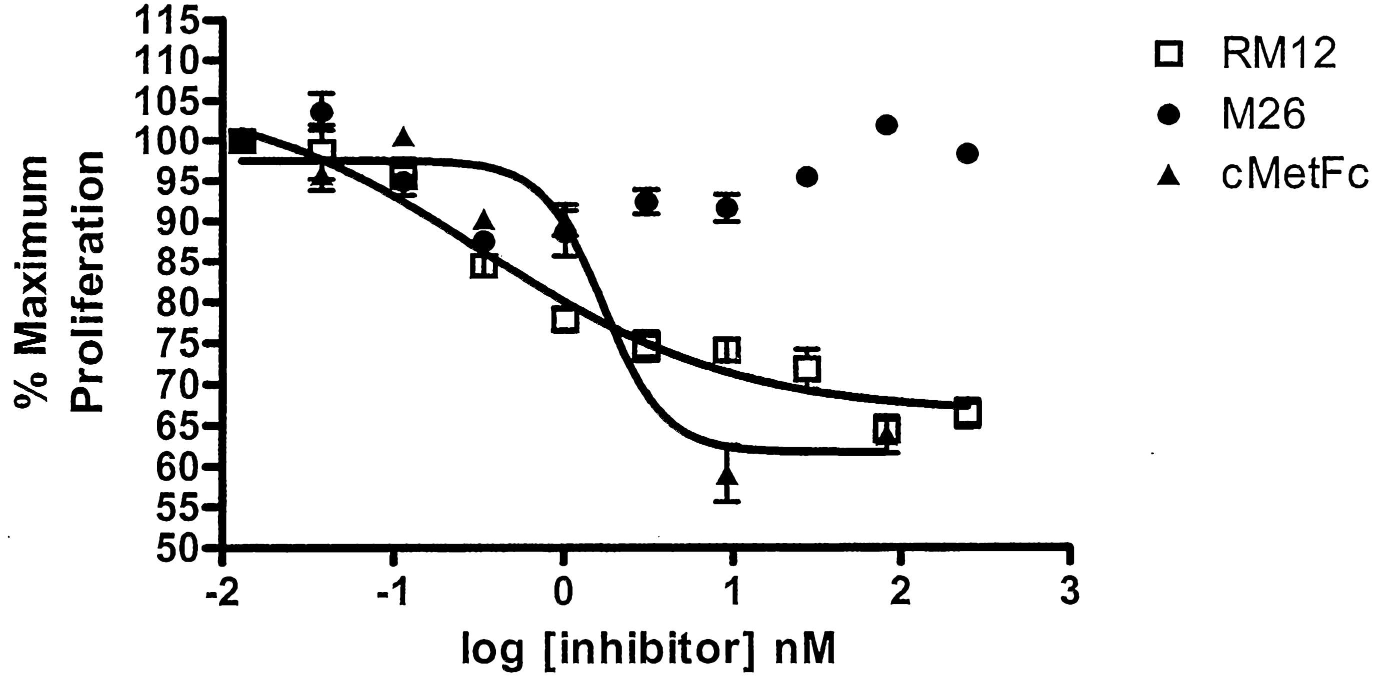
% Maximum Proliferation
115
110
105
100
95
90
85
80
75
70
65
60
55
50
-2
-1
0
1
2
3
log [inhibitor] nM
RM12
M26
cMetFc

FIG. 9

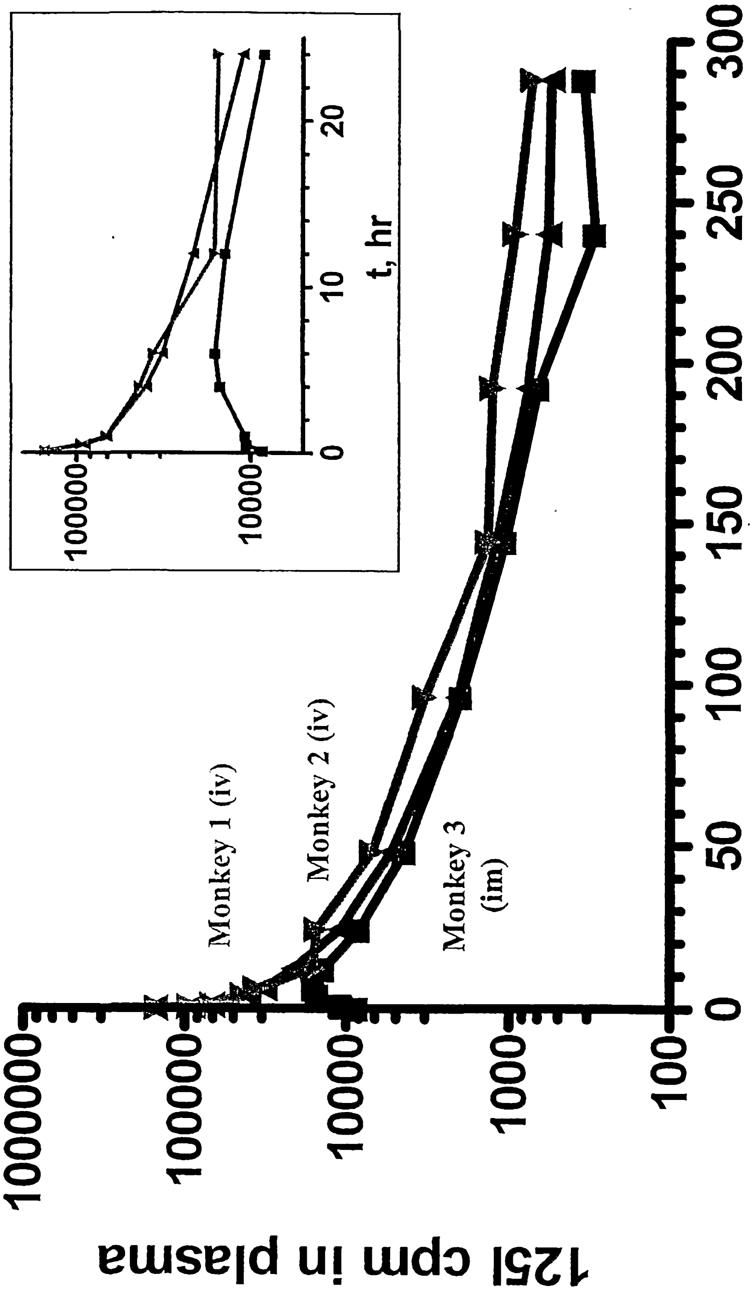
125I cpm in plasma
1000000
100000
10000
1000
100
0
50
100
150
200
250
300
t, hr
Monkey 1 (iv)
Monkey 2 (iv)
Monkey 3 (im)
100000
10000
0
10
20
t, hr

FIG. 10

SEQUENCE LISTING

<110> AMGEN MOUNTAIN VIEW INC.
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SATYAL, SANJEEV
ALBA, BENJAMIN M.
BAKKER, ALICE
DUGUAY, AMY N.
LIU, QIANG
SILVERMAN, JOSHUA
SMITH, RICHARD
SWIMMER, CANDACE

<120> C-MET KINASE BINDING PROTEINS

<130> 10398.0001-00131

<140> CA 2,569,191
<141> 2005-06-17

<150> PCT/US2005/021558
<151> 2005-06-17

<150> 10/871,602
<151> 2004-06-17

<150> 10/957,351
<151> 2004-09-30

<160> 967

<170> PatentIn version 3.3

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<213> Homo sapiens

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
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Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
            20                  25                  30


Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
        35                  40                  45


Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
    50                  55                  60


Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65                  70                  75                  80


Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
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```
                85                  90                  95

Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
            100                 105                 110

Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
        115                 120                 125

Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
    130                 135                 140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
145                 150                 155                 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
                165                 170                 175

Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
            180                 185                 190

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

His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
    210                 215                 220

Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225                 230                 235                 240

Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
                245                 250                 255

Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
            260                 265                 270

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
        275                 280                 285

His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
    290                 295                 300

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

Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
                325                 330                 335
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Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
            340                 345                 350

Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
        355                 360                 365

Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
    370                 375                 380

Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385                 390                 395                 400

Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
                405                 410                 415

Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
            420                 425                 430

Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
        435                 440                 445

Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
    450                 455                 460

Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
465                 470                 475                 480

Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
                485                 490                 495

Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
            500                 505                 510

Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
        515                 520                 525

Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
    530                 535                 540

Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
545                 550                 555                 560

Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu
                565                 570                 575
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Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
            580   585   590

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

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
    610   615   620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
625   630   635   640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
                645   650   655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
            660   665   670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
        675   680   685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
    690   695   700

Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
705   710   715   720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
                725   730   735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
            740   745   750

Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn
        755   760   765

Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg
    770   775   780

Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
785   790   795   800

Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
                805   810   815

Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
820 825 830

Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
835 840 845

Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
850 855 860

Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
865 870 875 880

Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
885 890 895

Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
900 905 910

Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
915 920 925

Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Thr Ala
930 935 940

Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg Lys Gln
945 950 955 960

Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His
965 970 975

Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr
980 985 990

Thr Glu Met Val Ser Asn Glu Ser Val Asp Tyr Arg Ala Thr Phe Pro
995 1000 1005

Glu Asp Gln Phe Pro Asn Ser Ser Gln Asn Gly Ser Cys Arg Gln
1010 1015 1020

Val Gln Tyr Pro Leu Thr Asp Met Ser Pro Ile Leu Thr Ser Gly
1025 1030 1035

Asp Ser Asp Ile Ser Ser Pro Leu Leu Gln Asn Thr Val His Ile
1040 1045 1050

Asp Leu Ser Ala Leu Asn Pro Glu Leu Val Gln Ala Val Gln His

1055 1060 1065

Val Val Ile Gly Pro Ser Ser Leu Ile Val His Phe Asn Glu Val
1070 1075 1080

Ile Gly Arg Gly His Phe Gly Cys Val Tyr His Gly Thr Leu Leu
1085 1090 1095

Asp Asn Asp Gly Lys Lys Ile His Cys Ala Val Lys Ser Leu Asn
1100 1105 1110

Arg Ile Thr Asp Ile Gly Glu Val Ser Gln Phe Leu Thr Glu Gly
1115 1120 1125

Ile Ile Met Lys Asp Phe Ser His Pro Asn Val Leu Ser Leu Leu
1130 1135 1140

Gly Ile Cys Leu Arg Ser Glu Gly Ser Pro Leu Val Val Leu Pro
1145 1150 1155

Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg Asn Glu Thr
1160 1165 1170

His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe Gly Leu Gln Val
1175 1180 1185

Ala Lys Gly Met Lys Tyr Leu Ala Ser Lys Lys Phe Val His Arg
1190 1195 1200

Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe Thr Val
1205 1210 1215

Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr Asp Lys Glu
1220 1225 1230

Tyr Tyr Ser Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys
1235 1240 1245

Trp Met Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys
1250 1255 1260

Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu Met Thr
1265 1270 1275

Arg Gly Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe Asp Ile Thr
1280 1285 1290

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Val Tyr  Leu Leu Gln Gly Arg  Arg Leu Leu Gln Pro  Glu Tyr Cys
    1295                1300                1305

Pro Asp  Pro Leu Tyr Glu Val  Met Leu Lys Cys Trp  His Pro Lys
    1310                1315                1320

Ala Glu  Met Arg Pro Ser Phe  Ser Glu Leu Val Ser  Arg Ile Ser
    1325                1330                1335

Ala Ile  Phe Ser Thr Phe Ile  Gly Glu His Tyr Val  His Val Asn
    1340                1345                1350

Ala Thr  Tyr Val Asn Val Lys  Cys Val Ala Pro Tyr  Pro Ser Leu
    1355                1360                1365

Leu Ser  Ser Glu Asp Asn Ala  Asp Asp Glu Val Asp  Thr Arg Pro
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Ala Ser  Phe Trp Glu Thr Ser
    1385                1390


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            20                  25


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            20   25

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Ser Pro Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser
            20                  25                  30


Asp Glu Glu Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35                  40                  45


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Ser Pro Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser
            20                  25                  30


Asp Glu Glu Asn Cys
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Glu Xaa

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Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu Asp Xaa Ser
            20                  25                  30
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Asp Glu Xaa
        35


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Pro Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Glu Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa Xaa
        35
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1               5                   10                  15


Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Xaa Xaa Cys
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
        35
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Xaa Xaa Trp Xaa Cys Xaa Gly Xaa Asn Asp Cys Glu Asp Xaa Ser Asp
            20   25   30

Glu Xaa

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1   5   10   15

Xaa Xaa Xaa Trp Xaa Cys Xaa Xaa Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20   25   30

Asp Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35   40

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Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Xaa Asp Xaa Ser Xaa
            20   25   30

Glu Xaa Xaa Xaa Xaa Cys
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<400> 15

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Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Xaa Arg Cys Xaa
1               5                   10                  15
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Pro Xaa Xaa Trp Xaa Cys Xaa Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
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<223> Ile, Leu or Val

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1               5                   10                  15


Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
        35


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      polypeptide


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<223> Variable amino acid

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<400> 17
Glu Phe Xaa Cys Xaa Asn Gly Xaa Cys Ile Pro Xaa Xaa Trp Xaa Cys
1   5   10   15

Asp Gly Xaa Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20   25

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<223> Variable amino acid

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<400> 18
Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1   5   10   15

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Cys
        35

<210> 19
<211> 51
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<220>
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      polypeptide

<400> 19
Cys Arg Ser Ser Gln Phe Gln Cys Asn Asp Ser Arg Ile Cys Ile Pro
1   5   10   15

Gly Arg Trp Arg Cys Asp Gly Asp Asn Asp Cys Gln Asp Gly Ser Asp
            20   25   30

Glu Thr Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35   40   45

Pro Ser Thr
    50

<210> 20
<211> 48
<212> PRT
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<220>
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      polypeptide

<400> 20
Cys Pro Ala Gly Glu Phe Pro Cys Lys Asn Gly Gln Cys Leu Pro Val
1   5   10   15

Thr Trp Leu Cys Asp Gly Val Asn Asp Cys Leu Asp Gly Ser Asp Glu
            20   25   30

Lys Gly Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Pro Ala Ala
        35   40   45

<210> 21
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<220>
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      polypeptide

<400> 21
Cys Pro Pro Asp Glu Phe Pro Cys Lys Asn Gly Gln Cys Ile Pro Gln
1 5 10 15

Asp Trp Leu Cys Asp Gly Val Asn Asp Cys Leu Asp Gly Ser Asp Glu
20 25 30

Lys Asp Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Pro Ala Ala
35 40 45

<210> 22
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
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polypeptide

<400> 22
Cys Gly Ala Gly Gln Phe Pro Cys Lys Asn Gly His Cys Leu Pro Leu
1 5 10 15

Asn Leu Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Asn Ser Asp Glu
20 25 30

Pro Ser Glu Leu Cys Lys Ala Leu Thr
35 40

<210> 23
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<223> Variable amino acid and this region may encompass
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<220>
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<223> Ser, Thr, Ala, Asp or Glu

<220>
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<223> Asp, Glu or His

<220>
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<222> (21)..(21)
<223> Asp or Glu

<220>
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<222> (22)..(26)
<223> Variable amino acid and this region may encompass
1 to 5 residues

<400> 23

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Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
            20                  25
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<210> 24
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<220>
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polypeptide

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3 to 15 residues

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<223> Variable amino acid and this region may encompass
      4 to 15 residues

<220>
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<222> (34)..(40)
<223> Variable amino acid and this region may encompass
      6 or 7 residues

<220>
<221> MOD_RES
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<223> Asn or Asp

<220>
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<223> Asp, Glu, Asn, Gln, His, Ser or Thr

<220>
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<220>
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<223> Variable amino acid and this region may encompass
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Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10                  15


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
    50                  55                  60


<210> 25
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      3 to 15 residues

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      2 to 8 residues

<400> 25
Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10                  15


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
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      1 or 2 residues

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<223> Variable amino acid and this region may encompass
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<400> 26
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60


Xaa Xaa Xaa Cys
65
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<210> 27
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Cys
    50
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<210> 28
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polypeptide

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<400> 28
Trp Xaa Xaa Trp Xaa Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa Gly Xaa Xaa
1               5                   10                  15


Xaa Xaa Arg Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Cys
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<210> 29
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      polypeptide


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<223> May or may not be present

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<223> Variable amino acid that may or may not be present

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<223> Variable amino acid

<400> 29
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Trp Xaa Xaa Trp Xaa Xaa Cys Ser Xaa Thr Cys Xaa Xaa Gly Xaa Xaa
1               5                   10                  15


Xaa Xaa Arg Xaa Arg Xaa Cys Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Cys
    50
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<210> 30
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<220>
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      polypeptide

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<223> May or may not be present

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<223> Val, Lys, Ala or Gln

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<222> (10)..(10)
<223> Thr, Ser, Pro or Leu

<220>
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<223> Arg or Glu

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Cys
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1   5   10   15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35   40   45

Xaa Xaa Xaa Xaa Cys
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      Thr or Val

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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
        35                  40                  45


Xaa Cys
    50


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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Cys Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
        35                  40
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Cys Xaa Xaa
            20                  25                  30
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
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1               5                   10                  15


Pro Xaa Ile Thr Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly Cys Cys Phe Asp
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Trp Cys Phe
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1   5   10   15

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Cys Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35                  40


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1   5   10   15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Cys Xaa
            20   25   30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35   40

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1   5   10   15

Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys Cys Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Xaa Xaa Trp Cys
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Xaa Xaa
    50                  55                  60


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Cys
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Tyr Xaa Pro Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Gln
        35                  40                  45


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Trp Cys Val Xaa
    50                  55                  60


Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80


Xaa Xaa Xaa Xaa Cys
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Tyr Xaa Pro Xaa Cys Xaa Xaa Xaa Gly Xaa Tyr Xaa Xaa Xaa Gln
35 40 45

Cys Xaa Xaa Ser Xaa Xaa Xaa Xaa Xaa Gly Xaa Cys Trp Cys Val Asp
50 55 60

Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Gly Xaa
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Xaa Xaa Xaa Xaa Cys
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Pro Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Gln
        35                  40                  45


Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Val Xaa
    50                  55                  60


Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa
65                  70                  75                  80


Xaa Xaa Xaa Xaa Cys
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<210> 43
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Xaa Pro Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Gln
        35   40   45

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Val Xaa
    50   55   60

Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa
65   70   75   80

Xaa Xaa Xaa Xaa Cys
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<210> 44
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
    50                  55                  60
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Cys Xaa Cys Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Gly Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
    50                  55                  60
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<210> 46

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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Cys Xaa Cys Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Gly Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
        35                  40                  45
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
    50                  55                  60
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<210> 47
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Asn Xaa Xaa Gly Xaa Phe Xaa Cys
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
    50                  55
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<210> 48
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1               5                   10                  15


Xaa Cys Xaa Xaa Xaa Cys Asn Xaa Xaa Xaa Cys Xaa Xaa Asp Gly Xaa
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            20   25   30

Asp Cys

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Xaa Xaa Asp Xaa Xaa Xaa His Xaa Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa
            20                  25                  30


Xaa Cys Xaa Xaa Gly Trp Xaa Gly Xaa Xaa Cys
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Glu Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa
            20                  25                  30


Xaa Phe Xaa Xaa Cys Cys
        35
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Xaa Xaa Phe Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Arg Cys Asp Xaa
            20                  25                  30


Xaa Xaa Xaa Leu Xaa Xaa Xaa Gly Cys
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1               5                   10                  15
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Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Asn Xaa Xaa Gly Xaa Xaa Xaa Cys
20 25 30

Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
50 55

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not present

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<400> 53
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1               5                   10                  15
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Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Asp Gly Xaa
            20                  25                  30


Asp Cys



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1   5   10   15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa
            20   25   30

Xaa Cys Xaa Xaa Gly Xaa Xaa Gly Xaa Xaa Cys
        35   40

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Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Cys Cys
        35


<210> 56
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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Arg Cys Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Cys
        35                  40


<210> 57
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Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Asn Xaa Xaa Gly Xaa Xaa Xaa Cys
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
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<210> 58
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<212> PRT
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1               5                   10                  15


Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Asp Gly Xaa
            20                  25                  30


Asp Cys
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<223> Tyr, Phe or His

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<222> (16)..(16)
<223> Pro, Ala or Glu

<220>
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<222> (17)..(18)
<223> Variable amino acid

<220>
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<222> (19)..(19)
<223> Asp or Ala

<220>
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<222> (20)..(21)
<223> Variable amino acid

<220>
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<222> (22)..(22)
<223> Gly, Leu, Ala, Ser or Thr

<220>
<221> MOD_RES
<222> (23)..(23)
<223> His, Arg, Gly or Lys

<220>
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<222> (24)..(24)
<223> Tyr, Lys, Phe or Trp

<220>
<221> MOD_RES
<222> (25)..(25)
<223> Variable amino acid

<220>
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<222> (27)..(27)
<223> Asp, Ser, Gly or Asn

<220>
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<222> (28)..(29)
<223> Variable amino acid

<220>
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<222> (31)..(33)
<223> Variable amino acid

<220>
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<222> (35)..(36)
<223> Variable amino acid

<220>
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<222> (38)..(38)
<223> Trp, Leu, Phe or Tyr

<220>
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<222> (39)..(39)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (41)..(42)
<223> Variable amino acid

<400> 59
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Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa
            20                  25                  30


Xaa Cys Xaa Xaa Gly Xaa Xaa Gly Xaa Xaa Cys
        35                  40
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<210> 60
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<220>
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<223> Variable amino acid

<220>
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<222> (4)..(4)
<223> Ala, Asp, Glu, His, Leu or Thr

<220>
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<222> (6)..(13)
<223> Variable amino acid

<220>
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<222> (14)..(14)
<223> Variable amino acid that may or may not be present

<220>
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<223> Asp, Glu, Arg, Ser or Thr

<220>
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<223> Variable amino acid

<220>
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<222> (26)..(27)
<223> Variable amino acid that may or may not be present

<220>
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<223> Ala, Glu, Arg, Ser, Val or not present

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<222> (30)..(31)
<223> Variable amino acid

<220>
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<222> (32)..(32)
<223> Ala, Pro, Val or Thr

<220>
<221> MOD_RES
<222> (33)..(33)
<223> Phe, Met or Gln

<220>
<221> MOD_RES
<222> (34)..(34)

<223> Glu, Lys, Leu, Gln, Arg, Thr or Val

<220>
<221> MOD_RES
<222> (35)..(35)
<223> Ala, Asp, Glu, His, Gln, Arg, Ser or Lys

<220>
<221> MOD_RES
<222> (36)..(36)
<223> Variable amino acid that may or may not be present

<400> 60
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Cys Cys Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Cys Cys
        35
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<210> 61
<211> 41
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
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<223> Ala, Glu, Gly, Lys, Gln, Arg, Ser or Thr

<220>
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<222> (3)..(3)
<223> Lys, Arg, Glu, Gln or Asp

<220>
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<222> (5)..(5)
<223> Ile or Leu

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Ala, Glu, Leu, Gln, Arg or Val

<220>
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<222> (7)..(7)
<223> Val, Ile, Leu, Ala or Ser

<220>

<221> MOD_RES
<222> (8)..(8)
<223> Asp, Gly, His or Ser

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Lys or Pro

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Gly, Ala, Ser or Thr

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Trp or Tyr

<220>
<221> MOD_RES
<222> (15)..(18)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (19)..(19)
<223> Phe or Leu

<220>
<221> MOD_RES
<222> (20)..(23)
<223> Variable amino acid

<220>
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<223> Variable amino acid that may or may not be present

<220>
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<222> (28)..(28)
<223> Val, Ile, Leu, Ala, Arg or not present

<220>
<221> MOD_RES
<222> (29)..(29)
<223> May or may not be present

<220>
<221> MOD_RES
<222> (31)..(31)
<223> Ala, Asn or Asp

<220>
<221> MOD_RES

<222> (32)..(32)
<223> Asp, Ile, Leu, Arg or Thr

<220>
<221> MOD_RES
<222> (33)..(33)
<223> Ile, Lys, Leu, Pro, Gln, Arg or Val

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Ala, Asp, Glu, Pro or Ser

<220>
<221> MOD_RES
<222> (35)..(35)
<223> Ala, Glu, Asn or Gln

<220>
<221> MOD_RES
<222> (37)..(37)
<223> Ile, Lys, Leu, Gln or Val

<220>
<221> MOD_RES
<222> (38)..(38)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (39)..(39)
<223> Ala, Asp, Lys, Asn or Arg

<220>
<221> MOD_RES
<222> (40)..(40)
<223> Gly or Asn

<400> 61

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Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Arg Cys Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Cys
        35                  40
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<210> 62
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 62

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agcttataac ttcgtataga aaggtatata cgaagttata gatctcgtgc tgcatgcggt     60

gcg                                                                   63


<210> 63
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 63
aattcgcacc gcatgcagca cgagatctat aacttcgtat atacctttct atacgaagtt     60

ataagct                                                               67


<210> 64
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 64
ataacttcgt atagcataca ttatacgaag ttatcgag                             38


<210> 65
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 65
ctcgataact tcgtataatg tatgctatac gaagttatg                            39


<210> 66
<211> 79
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 66
ccgggagcag ggcatgctaa gtgagtaata agtgagtaaa taacttcgta tatacctttc     60

tatacgaagt tatcgtctg                                                  79
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<210> 67
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 67
acgataactt cgtatagaaa ggtatatacg aagttattta ctcacttatt actcacttag 60

catgccctgc tc 72

<210> 68
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 68
ccgggaccag tggcctctgg ggccataact tcgtatagca tacattatac gaagttatg 59

<210> 69
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 69
cataacttcg tataatgtat gctatacgaa gttatggccc cagaggccac tggtc 55

<210> 70
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 70
atggcgaatt ctcattgtcg gcgcaactat 30

<210> 71
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

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      oligonucleotide

<400> 71
gataagcttt cattaagact ccttattacg cag                                  33


<210> 72
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (1)..(5)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (7)..(12)
<223> Variable amino acid and this region may encompasss
      4 to 6 residues

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Variable amino acid and this region may encompasss
      4 or 5 residues

<220>
<221> MOD_RES
<222> (20)..(27)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (31)..(42)
<223> Variable amino acid and this region may encompasss
      8 to 12 residues

<400> 72
Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1               5                   10                  15


Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
        35                  40
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<210> 73
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Val, Thr, Ile, Lys, Glu or Ala

<220>
<221> MOD_RES
<222> (3)..(3)
<223> Val or Ile

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Asn or Asp

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Val, Ser, Leu, Ala, Asp, Glu, Gly, Lys, Asn,
      Arg or Thr

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Ser, Pro, Glu, Leu, Gln or Val

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Ser, Gly, Asn, Asp, Ile or Val

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Pro, Ala or Ser

<220>
<221> MOD_RES
<222> (11)..(11)
<223> Asp, Gly, His, Asn, Arg, Ser or not present

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Ala, Ile, Leu, Pro, Thr, Val or not present

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Val, Thr, Ser, Arg, Gln, Pro, Asn, Met, Leu, Lys,

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      Ile, Met, Gly, Glu, Asp or Ala

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Ser, Arg, Asn or His

<220>
<221> MOD_RES
<222> (16)..(16)
<223> Gly, Asp, Asn or Ser

<220>
<221> MOD_RES
<222> (17)..(17)
<223> Ser, Arg, Gln, Asn, Leu, Lys, Ile, His, Ala or Gly

<220>
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<222> (18)..(18)
<223> Ile, Lys, Asn, Arg, Ser, Thr or not present

<220>
<221> MOD_RES
<222> (20)..(20)
<223> Val, Gln, Leu, Lys, Ile or Glu

<220>
<221> MOD_RES
<222> (21)..(21)
<223> Asn or Asp

<220>
<221> MOD_RES
<222> (22)..(22)
<223> Thr, Ser, Leu or Ile

<220>
<221> MOD_RES
<222> (23)..(23)
<223> Val, Gln, Pro, Leu, Glu or Ala

<220>
<221> MOD_RES
<222> (25)..(25)
<223> Ser or Gly

<220>
<221> MOD_RES
<222> (26)..(26)
<223> Thr or Phe

<220>
<221> MOD_RES
<222> (27)..(27)
<223> Ser, Arg, Gln, Lys or His

<220>
<221> MOD_RES
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<223> Val, Ser, Arg, Gln, Asn, Met, Leu, Lys, Ile, His,
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      Gly, Glu, Asp

<220>
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<222> (31)..(31)
<223> Val, Pro, Leu, Ala, His, Asn, Arg, Ser or Thr

<220>
<221> MOD_RES
<222> (32)..(32)
<223> Gln, Pro, Glu, Ala, Lys or Thr

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Tyr or Phe

<220>
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<222> (35)..(35)
<223> Thr, Ser, Ala, Glu, Lys, Leu, Met, Pro, Gln or Val

<220>
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<222> (36)..(36)
<223> Gly, Leu, Pro, Gln or Arg

<220>
<221> MOD_RES
<222> (37)..(37)
<223> Val, Thr, Gln, Pro, Leu, Lys, Ile, Glu, Ala, Asp,
      Gly, Asn or Ser

<220>
<221> MOD_RES
<222> (38)..(38)
<223> Ser, Arg, Asn, Leu, Ile, His, Ala, Glu, Gly,
      Pro or Gln

<220>
<221> MOD_RES
<222> (39)..(39)
<223> Ala, Asp, Asn, Thr or not present

<220>
<221> MOD_RES
<222> (40)..(40)
<223> Gly, Arg, Ser or not present

<220>
<221> MOD_RES
<222> (41)..(41)
<223> Lys, Asn, Arg, Ser, Thr or not present

<220>
<221> MOD_RES
<222> (42)..(42)
<223> Ala, Asp, Glu, Gly, Lys, Asn, Arg, Ser, Thr
      or not present

<400> 73
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Xaa Asp Xaa Xaa Glu Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1               5                   10                  15


Xaa Xaa Cys Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Cys Xaa Cys Xaa Xaa
            20                  25                  30


Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
        35                  40


<210> 74
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 74
aaaaggcctc gagggcctgg gtggcaatgg t                                   31


<210> 75
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide


<220>
<221> modified_base
<222> (25)..(25)
<223> a, c, g, t, unknown or other

<400> 75
cctgaaccac cacakhkacc gyksnbgcac ggayycgrcr macattcaty aayatctdya     60

ccattgccac cc                                                          72


<210> 76
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide


<220>
<221> modified_base
<222> (16)..(16)
<223> a, c, g, t, unknown or other
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<400> 76
cctgaaccac cacakntgsc gyygykmhsg cacggayycg rcrmacattc atyaayatct   60

dyaccattgc caccc   75

<210> 77
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<220>
<221> modified_base
<222> (25)..(25)
<223> a, c, g, t, unknown or other

<400> 77
cctgaaccac cacakhkacc gyksnbgcaa rbaybcgvah ycwskbyaca ttcatyaaya   60

tctdyaccat tgccaccc   78

<210> 78
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<220>
<221> modified_base
<222> (16)..(16)
<223> a, c, g, t, unknown or other

<400> 78
cctgaaccac cacakntgsc gyygykmhsg caarbaybcg vahycwskby acattcatya   60

ayatctdyac cattgccacc c   81

<210> 79
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 79
tgaattttct gtatgaggtt ttgctaaaca actttcaaca gtttcggccc cagaggccct   60

ggagccacct gaaccaccac a   81

<210> 80
<211> 50
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 80
acggtgccta cccgtatgat gttccggatt atgccccggg tggcaatggt   50

<210> 81
<211> 84
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 81
cctgaaccac cacaghktdb accgghawag cctkscrsgc ashbacakyk awagcyaccc   60

dstrwatytw baccattgcc accc   84

<210> 82
<211> 96
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<220>
<221> modified_base
<222> (34)..(34)
<223> a, c, g, t, unknown or other

<400> 82
cctgaaccac cacakbykbt kcygkycbsa bycngcdbaw agcctkbgbk gcashbacak   60

ykawagcyac ccdstrwaty twbaccattg ccaccc   96

<210> 83
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 83

aaaaggcccc agaggcccct gaaccaccac a   31

<210> 84
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 84
aaaaggcctc gagggcctgg gtggcaatgg t   31

<210> 85
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 85
aaaaggcccc agaggcccct gaaccaccac a   31

<210> 86
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (2)..(7)
<223> Variable amino acid and this region may encompass
      4 to 6 residues

<220>
<221> MOD_RES
<222> (13)..(16)
<223> Variable amino acid and this region may encompass
      2 to 4 residues

<220>
<221> MOD_RES
<222> (39)..(44)
<223> Variable amino acid and this region may encompass
      4 to 6 residues

<400> 86
Cys Xaa Xaa Xaa Xaa Xaa Xaa Glu Phe Arg Cys Ala Xaa Xaa Xaa Xaa
1   5   10   15

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Gly Arg Cys Ile Pro Ser Ser Trp Val Cys Asp Gly Glu Asp Asp Cys
            20                  25                  30


Gly Asp Gly Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys
        35                  40                  45


<210> 87
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide


<220>
<221> modified_base
<222> (36)..(37)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (39)..(40)
<223> a, c, g, t, unknown or other

<220>
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<222> (42)..(43)
<223> a, c, g, t, unknown or other

<220>
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<222> (45)..(46)
<223> a, c, g, t, unknown or other

<400> 87
atatcccggg tctggaggcg tctggtggtt cgtgtnnknn knnknnkgaa ttccga         56


<210> 88
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide


<220>
<221> modified_base
<222> (36)..(37)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (39)..(40)
<223> a, c, g, t, unknown or other
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<220>
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<223> a, c, g, t, unknown or other

<220>
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<222> (45)..(46)
<223> a, c, g, t, unknown or other

<220>
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<222> (48)..(49)
<223> a, c, g, t, unknown or other

<400> 88
atatcccggg tctggaggcg tctggtggtt cgtgtnnknn knnknnknnk gaattccga   59

<210> 89
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
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      oligonucleotide

<220>
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<223> a, c, g, t, unknown or other

<220>
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<222> (39)..(40)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (42)..(43)
<223> a, c, g, t, unknown or other

<220>
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<222> (45)..(46)
<223> a, c, g, t, unknown or other

<220>
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<222> (48)..(49)
<223> a, c, g, t, unknown or other

<220>
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<222> (51)..(52)
<223> a, c, g, t, unknown or other

<400> 89

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ga                                                                    62


<210> 90
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
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      oligonucleotide


<220>
<221> modified_base
<222> (39)..(40)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (42)..(43)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (45)..(46)
<223> a, c, g, t, unknown or other

<400> 90
atatcccggg tctggaggcg tctggtggtt cgtgttatnn knnknnkgaa ttccga         56


<210> 91
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide


<220>
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<222> (36)..(37)
<223> a, c, g, t, unknown or other

<220>
<221> modified_base
<222> (42)..(43)
<223> a, c, g, t, unknown or other

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<210> 92
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<400> 96
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<210> 97
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<212> DNA
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<210> 102
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<210> 103
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<210> 104
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<220>
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<210> 105
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atccgt   66

<210> 106
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cagatccgt   69

<210> 107
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cgtcagatcc gt   72

<210> 108
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atccgt                                                                66


<210> 109
<211> 69
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cagatccgt                                                             69


<210> 110
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<211> 66
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atccgt                                                                66


<210> 111
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<213> Artificial Sequence

<220>
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<400> 111
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atccgt                                                                66
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<210> 112
<211> 66
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<213> Artificial Sequence

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<400> 112
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atccgt 66

<210> 113
<211> 69
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<220>
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<220>
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<223> a, c, g, t, unknown or other

<400> 113
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cagatccgt 69

<210> 114
<211> 35
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<220>
<223> Description of Artificial Sequence: Synthetic
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<223> Variable amino acid

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<400> 114
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Cys Ile Xaa Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Cys
        35


<210> 115
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 115
attatgcccc gggtctggag gcgtc                                           25


<210> 116
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 116
cgccgtcgca a                                                          11


<210> 117
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 117
ttgcgacggc g                                                          11


<210> 118
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer
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<400> 118
tcggccccag aggcctgcaa tg                                                22


<210> 119
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 119
ccggattatg ccccgggtct gga                                               23


<210> 120
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 120
aacagtttcg gccccagagg cctgc                                             25


<210> 121
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 121
atcatctggc cggtccggcc tacccgtatg atgttccgga                             40


<210> 122
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
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      primer

<400> 122
aaaaggcccc agaggccttc tgcaatgac                                         29


<210> 123
<211> 22
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 123
acccgtatga tgttccggat ta   22

<210> 124
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 124
gatgtattcg gccccagagg cctgcaatga c   31

<210> 125
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 125
gaaattcacc tcgaaagcaa   20

<210> 126
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      primer

<400> 126
atgggttcct attgggct   18

<210> 127
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 127
Cys Pro Ser Asp Glu Phe Lys Cys His Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Val Glu Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35   40   45

Leu Gln
    50

<210> 128
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 128
Cys Gln Ser Asn Glu Phe Thr Cys Gln Ser Thr Asn Arg Cys Leu Pro
1   5   10   15

Leu Pro Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asn Cys Gly Gln Arg Thr Ser Leu Gln
        35   40

<210> 129
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 129
Cys Glu Ala Asn Glu Phe Arg Cys Lys Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Gln Thr Trp Arg Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asn Cys Lys Pro Pro Thr Ser Leu Gln
        35   40

<210> 130
<211> 54
<212> PRT
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 130
Cys Leu Ser Asn Glu Phe Arg Cys Ser Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15


Arg Pro Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


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


Pro Ala Ala Ser Leu Gln
    50


<210> 131
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 131
Cys Asn Thr Thr Gln Phe Ser Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Asp Trp Gln Cys Asp Gly Val Thr Asp Cys Glu Asp Asn Ser Asp
            20                  25                  30


Glu Ala Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35                  40                  45


Leu Gln
    50


<210> 132
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 132
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15
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Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr Ser Leu Gln
35 40 45

<210> 133
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
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polypeptide

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<222> (2)..(2)
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<400> 133
Cys Xaa Ala Thr Gln Phe Arg Cys Pro Arg Thr Arg Leu Cys Ile Pro
1 5 10 15

Pro Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Asn Cys Thr Ala Ser Glu Ser Lys Pro Leu Gly Ser Leu Gln
35 40 45

<210> 134
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
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polypeptide

<400> 134
Cys Gln Ser Ser Glu Phe Thr Cys Lys Ser Thr Glu Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Glu Asn Cys Ser Gln Asp Pro Glu Phe His Lys Val Ser Leu Gln
35 40 45

<210> 135
<211> 52
<212> PRT

<213> Artificial Sequence

<220>
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      polypeptide

<400> 135
Cys Leu Ala Ser Glu Phe Thr Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

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

Ala Ser Leu Gln
    50

<210> 136
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 136
Cys Gln Pro Asp Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Pro Asp Trp Val Cys Asp Gly Val Asp Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Gly Cys Ser Gln Asp Pro Glu Phe His Lys Val Ser Leu Gln
        35   40   45

<210> 137
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 137
Cys Leu Ala Ser Glu Phe Thr Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Asp Asn Ala His Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
35 40 45

Pro Ala Ala Ser Leu Gln
50

<210> 138
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 138
Cys Glu Ser Ser Gln Phe Thr Cys Asn Ser Thr Lys Arg Cys Ile Pro
1 5 10 15

Leu Ala Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Lys Ser Cys Glu Ala Pro Ala His Thr Ser Leu Gln
35 40 45

<210> 139
<211> 48
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 139
Cys Leu Ala Asp Glu Phe Gln Cys His Ser Thr Lys Arg Cys Val Pro
1 5 10 15

Arg His Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Lys Ser Cys Ser Gln Asp Pro Glu Phe His Lys Val Ser Leu Gln
35 40 45

<210> 140
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

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      polypeptide

<400> 140
Cys Ala Pro Asn Glu Phe Thr Cys Ser Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15


Arg Ala Trp Val Cys Asp Gly Val Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Ser Cys Gly Ala Thr Val His Thr Ser Leu Gln
        35                  40                  45


<210> 141
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 141
Cys Ala Pro Asp Glu Phe Pro Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Leu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Ser Ala Thr Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala Ser Leu Gln
    50


<210> 142
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 142
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr Ser Leu Gln
        35                  40                  45
```

<210> 143
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 143
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Gln Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Gly Cys Ala Ala Ser Gly Pro Thr Ser Leu Gln
35 40 45

<210> 144
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 144
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Asn Cys Thr Ala Ala Val His Thr Ser Leu Gln
35 40 45

<210> 145
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 145
Cys Glu Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Gly Gly Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp

```
            20                  25                  30

Glu Thr Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35                  40                  45

Leu Gln
    50


<210> 146
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 146
Cys Glu Ala Asp Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Ser
1               5                   10                  15

Val Asp Trp Arg Cys Asp Gly Val Ser Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30

Glu Glu Ser Cys Glu Ser Thr Ala Pro Thr Ser Leu Gln
        35                  40                  45


<210> 147
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 147
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1               5                   10                  15

Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30

Glu Thr Gly Cys Pro Lys His Thr Ser Leu Gln
        35                  40


<210> 148
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
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<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 148
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr Ser Leu Gln
        35   40

<210> 149
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 149
Cys Ala Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Leu Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Asn Cys Arg Ala Pro Thr Ser Glu Pro Lys Gly Ser Val Ser
        35   40   45

Leu Gln
    50

<210> 150
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 150
Cys Pro Pro Asp Glu Phe Arg Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Ala Trp Leu Cys His Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asp Cys Lys Pro His Thr Ser Leu Gln

35 40

<210> 151
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 151
```
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr Ser Leu Gln
        35                  40
```

<210> 152
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 152
```
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Ser Pro Ala Asn Cys Ala Thr Pro Ala His Thr Ser Leu Gln
        35                  40                  45
```

<210> 153
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 153
```
Cys Val Ala Ser Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15
```

```
Glu Ser Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Pro Asp Leu Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser
        35                  40                  45


Leu Gln
    50


<210> 154
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 154
Cys Gly Ser Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Glu Asn Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Ser Cys Thr Ser Ala Ala Pro Thr Ser Leu Gln
        35                  40                  45


<210> 155
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 155
Cys Gln Ala Gly Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr Ser Leu Gln
        35                  40                  45


<210> 156
<211> 45
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 156
Cys Gln Ala Gly Gln Phe Glu Cys Arg Asn Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr Ser Leu Gln
        35   40   45

<210> 157
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 157
Cys Leu Pro Ser Glu Phe Gln Cys Lys Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Ala Trp Leu Tyr Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35   40   45

Leu Gln
    50

<210> 158
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 158
Cys Gln Pro Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Gln Leu Cys Thr Ala His Thr Ser Leu Gln
35 40

<210> 159
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 159
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Gly Cys Ala Thr Ser Gly Pro Thr Ser Leu Gln
35 40 45

<210> 160
<211> 93
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 160
Cys Pro Ser Ser Gln Phe Thr Cys His Ser Thr Arg Arg Cys Ile Pro
1 5 10 15

Gln Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Asp Cys Pro Pro His Thr Ser Leu Gln Lys Ala Ser Ser Gly
35 40 45

Gly Ser Cys Leu Ala Asn Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys
50 55 60

Ile Pro Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser
65 70 75 80

Ser Asp Glu Lys Asp Cys Lys Gln His Thr Ser Leu Gln
85 90

<210> 161

<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 161
Cys Ser Ser Asp Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Arg Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Leu Ala Pro Cys Thr Ser Thr Ala His Thr Ser Leu Gln
35 40 45

<210> 162
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 162
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Arg Cys Asp Arg Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Asn Cys Thr Ala Ala Val His Thr Ser Leu Gln
35 40 45

<210> 163
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 163
Cys Gly Ala Asn Glu Phe Thr Cys Gln Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Gln Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Pro Val Leu Cys Ala Thr Thr Val His Thr Ser Leu Gln
        35   40   45

<210> 164
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 164
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1   5   10   15

Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Gly Cys Pro Lys His Thr Ser Leu Gln
        35   40

<210> 165
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 165
Cys Val Ser Asn Glu Phe Pro Cys Gln Ser Thr Asp Arg Cys Ile Pro
1   5   10   15

Arg Ser Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Lys Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35   40   45

Leu Gln
    50

<210> 166
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

```
<400> 166
Cys Leu Pro Ser Glu Phe Gln Cys Lys Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Leu Tyr Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser
        35                  40                  45


Leu Gln
    50


<210> 167
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 167

Cys Pro Ala Gly Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Pro Ala Ile Cys Ala Thr Thr Gly Pro Thr Ser Leu Gln Lys
        35                  40                  45


Ala Ser Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Pro Gly Leu
    50                  55                  60


Glu Ala Ser Gly Gly Ser Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser
65                  70                  75                  80


Thr Gly Arg Cys Val Pro Val Ala Trp Val Cys Asp Gly Asp Asn Asp
                85                  90                  95


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


Gln



<210> 168
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```
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 168
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Cys Pro Gly Pro Gly Ala Thr Ser Ala Pro Ala
        35                  40                  45


Ala Ser Leu Gln
    50


<210> 169
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 169
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Lys Asp Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro
        35                  40                  45


Gly Pro Ser Thr Ser Leu Gln Lys Ala Ser Ala Ala Tyr Pro Tyr Asp
    50                  55                  60


Val Pro Asp Tyr Ala Pro Gly Leu Glu Ala Ser Gly Cys Asp Pro Ile
65                  70                  75                  80


Ala Glu Phe Lys Cys His Ser Thr Gly Arg Cys Ile Pro Leu Asp Trp
                85                  90                  95


Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp Glu Ser Pro
            100                 105                 110
```

Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu Ser Leu
115 120 125

Gln

<210> 170
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 170
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Val Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ser Ser Asp Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser
35 40 45

Leu Ser Leu Gln
50

<210> 171
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 171
Cys His Pro Thr Ala Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1 5 10 15

Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
20 25 30

Asp Glu Lys Asn Cys Lys Ala His Thr Ser Leu Gln
35 40

<210> 172
<211> 102
<212> PRT

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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 172
Cys Gln Ala Ser Asp Gln Phe Glu Cys Lys Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Leu Ala Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Glu Ala Ser Gly
        35                  40                  45


Gly Ser Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys
    50                  55                  60


Ile Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly
65                  70                  75                  80


Ser Asp Glu Ala Ser Cys Gly Arg Pro Gly Pro Gly Gly Ser Thr Ala
                85                  90                  95


Pro Ala Ala Ser Leu Gln
            100


<210> 173
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 173
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Asn Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Cys Ser Leu Ser
        35                  40                  45


Leu Gln
    50
```

```
<210> 174
<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 174
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Ser Pro Ala Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


Ser Leu Ser Leu Gln
    50


<210> 175
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 175
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Asp Ser His Ile Leu Pro Phe Gly Thr Pro Gly
        35                  40                  45


Pro Ser Thr Ser Leu Gln
    50


<210> 176
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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<400> 176
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr Ser Leu Gln Ala
        35   40   45

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

Glu Cys Arg Ser Thr Gly Arg Cys Ile Pro Ala Ala Trp Val Cys Asp
65   70   75   80

Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Ser Pro Ala Ile Cys
                85   90   95

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

<210> 177
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 177
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Gly Leu Glu Ala Ser
        35   40   45

Gly Gly Ser Cys Pro Ala Ser Gln Phe Pro Cys Arg Ser Thr Gly Arg
    50   55   60

Cys Ile Pro Ala Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp
65   70   75   80

Ser Ser Asp Glu Ala Ser Arg Gly Asp Ser His Ile Leu Pro Phe Ser
                85   90   95

Thr Pro Gly Pro Ser Thr Ser Leu Gln
            100   105

<210> 178
<211> 99
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 178
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Leu Glu Ala
        35   40   45

Ser Gly Gly Ser Cys Pro Ala Ser Glu Phe Thr Cys Arg Ser Thr Gly
    50   55   60

Arg Cys Ile Ser Gln Gly Trp Val Cys Asp Gly Asp Asn Asp Cys Glu
65   70   75   80

Asp Ser Ser Asp Glu Ser Pro Ala Ile Cys Ala Thr Thr Gly Pro Thr
                85   90   95

Ser Leu Gln

<210> 179
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 179
Cys Ala Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

```
Glu Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser Gly Gly Ser Cys Gln Thr Gly Glu Phe Arg Cys Arg
    50                  55                  60


Ser Thr Asp Arg Cys Ile Pro Ala Glu Trp Val Cys Asp Gly Asp Ser
65                  70                  75                  80


Asp Cys Glu Asp Gly Ser Asp Glu Thr Asn Cys Gly Asp Ser His Ile
                85                  90                  95


Leu Pro Phe Ser Thr Pro Gly Pro Ser Thr Ser Leu Gln
            100                 105


<210> 180
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 180
Cys Glu Pro Asp Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Thr Gly Cys Ala Lys Pro Thr Ser Leu Gln
        35                  40


<210> 181
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(4)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (5)..(5)
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<223> Glu or Gln

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Ile or Val

<220>
<221> MOD_RES
<222> (16)..(18)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (20)..(20)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (30)..(30)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Variable amino acid

<400> 181
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Xaa Arg Cys Xaa Xaa
1   5   10   15

Xaa Xaa Trp Xaa Cys Asp Gly Asp Asn Asp Cys Glu Asp Xaa Ser Asp
            20   25   30

Glu Xaa

<210> 182
<211> 35
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (2)..(5)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Glu or Gln

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (16)..(16)
<223> Ile or Val

<220>
<221> MOD_RES
<222> (17)..(19)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (21)..(21)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (25)..(25)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (31)..(31)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (35)..(35)
<223> Variable amino acid

<400> 182

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Cys Xaa Xaa Xaa Xaa Xaa Phe Glu Cys Xaa Ser Thr Xaa Arg Cys Xaa
1               5                   10                  15


Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu Asp Xaa Ser
            20                  25                  30
```

```
Asp Glu Xaa
        35


<210> 183
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(5)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Glu or Gln

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (16)..(16)
<223> Ile, Leu or Val

<220>
<221> MOD_RES
<222> (18)..(19)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (21)..(21)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (25)..(26)
<223> Variable amino acid
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<220>
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<220>
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<400> 183
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Xaa Arg Cys Xaa
1               5                   10                  15


Pro Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Glu Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa Xaa
        35


<210> 184
<211> 36
<212> PRT
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<220>
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      polypeptide


<220>
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<223> Glu or Gln

<220>
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<220>
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<223> Ile or Val

<220>
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<223> Variable amino acid

<220>
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<223> Variable amino acid

<400> 184
Cys Xaa Xaa Xaa Xaa Phe Gln Cys Xaa Ser Thr Xaa Arg Cys Xaa Pro
1               5                   10                  15


Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Xaa Xaa Cys
        35


<210> 185
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
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      polypeptide


<220>
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<220>
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<223> Glu or Gln

<220>
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<223> Variable amino acid

<220>
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<223> Variable amino acid

<220>
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<223> Ile, Leu or Val

<220>
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<223> Variable amino acid

<220>
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<223> Variable amino acid

<400> 185
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
        35


<210> 186
<211> 34
<212> PRT
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<220>
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      polypeptide


<220>
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<220>
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<220>
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<220>
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<223> Variable amino acid

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<220>
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<223> Variable amino acid

<400> 186
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Gly Arg Cys Xaa Pro
1               5                   10                  15


Xaa Xaa Trp Xaa Cys Xaa Gly Xaa Asn Asp Cys Glu Asp Xaa Ser Asp
            20                  25                  30


Glu Xaa



<210> 187
<211> 40
<212> PRT
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<220>
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polypeptide

<220>
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<223> Variable amino acid

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<220>
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<223> Ile, Leu or Val

<220>
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<223> Variable amino acid

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<223> Variable amino acid

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<223> Variable amino acid

<220>
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<222> (40)..(40)
<223> Variable amino acid

<400> 187
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Xaa Arg Cys Xaa
1   5   10   15

Xaa Xaa Xaa Trp Xaa Cys Xaa Xaa Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20   25   30

Asp Xaa Xaa Xaa Xaa Xaa Cys Xaa
        35   40

<210> 188
<211> 38
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
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<223> Variable amino acid

<220>
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<223> Glu or Gln

<220>
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<223> Variable amino acid

<220>
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<223> Variable amino acid

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<223> Ile, Leu or Val

<220>
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<220>

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<223> Variable amino acid

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<223> Variable amino acid

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<223> Variable amino acid

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<223> Variable amino acid

<220>
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<223> Variable amino acid

<400> 188
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Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa
1               5                   10                  15


Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Xaa Asp Xaa Ser Xaa
            20                  25                  30


Glu Xaa Xaa Xaa Xaa Cys
        35
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<210> 189
<211> 35
<212> PRT
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<220>
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<223> Glu or Gln

<220>
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<223> Variable amino acid

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<220>
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<223> Ile, Leu or Val

<220>
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<222> (35)..(35)
<223> Variable amino acid

<400> 189
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Ser Thr Xaa Arg Cys Xaa
1   5   10   15

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Pro Xaa Xaa Trp Xaa Cys Xaa Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
        35


<210> 190
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
<221> MOD_RES
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<223> Variable amino acid

<220>
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<223> Ile, Leu or Val

<220>
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<223> Variable amino acid

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<222> (29)..(29)
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<222> (31)..(31)
<223> Variable amino acid

<220>
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<222> (35)..(35)
<223> Variable amino acid

<400> 190
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
1               5                   10                  15


Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa
        35


<210> 191
<211> 43
<212> PRT
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<220>
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      polypeptide


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<220>
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<222> (10)..(13)
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<220>
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<220>
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<223> Variable amino acid that may or may not be present

<400> 191
Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Cys Asp Xaa Xaa Xaa Asp Cys Xaa Asp Xaa Ser
            20                  25                  30


Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
        35                  40


<210> 192
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


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<220>
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<223> Variable amino acid that may or may not be present

<400> 192
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Cys Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Cys
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        35                  40


<210> 193
<211> 40
<212> PRT
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<220>
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      polypeptide


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<223> Variable amino acid that may or may not be present

<400> 193
Cys Xaa Ala Xaa Xaa Glu Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys
1   5   10   15

Ile Pro Xaa Xaa Leu Leu Cys Asp Gly Asp Pro Asp Cys Xaa Asp Xaa
            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Cys
        35   40

<210> 194
<211> 40
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<220>
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<220>
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<223> Variable amino acid that may or may not be present

<400> 194
Cys Xaa Pro Xaa Xaa Gln Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys
1               5                   10                  15


Leu Ser Xaa Xaa Trp Arg Cys Asp Gly Glu Asn Asp Cys Xaa Asp Xaa
            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Cys
        35                  40


<210> 195
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
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      polypeptide


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<223> Variable amino acid that may or may not be present

<400> 195
Cys Xaa Ser Xaa Xaa Lys Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys
1   5   10   15

Val Xaa Xaa Xaa Xaa Val Cys Asp Gly Val Asp Asp Cys Xaa Asp Xaa
            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Cys
        35   40

<210> 196
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 196
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35   40

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<210> 197
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 197
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35                  40


<210> 198
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 198
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35                  40


<210> 199
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 199
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
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Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
35 40

<210> 200
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 200
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
35 40

<210> 201
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 201
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
35 40

<210> 202
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 202
Cys Ala Pro Ser Gln Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

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Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ile Ala Ala Pro Thr
        35                  40


<210> 203
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 203
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35                  40


<210> 204
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 204
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35                  40


<210> 205
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
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polypeptide

<400> 205
Cys Glu Ser Asn Glu Phe Gln Cys Ser Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Gln Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35   40

<210> 206
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 206
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr
        35   40

<210> 207
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 207
Cys Glu Pro Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Ala Leu Cys Lys Ala Ser Val Pro Thr
        35   40

<210> 208
<211> 44

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 208
Cys Pro Ala Ser Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Gln Gly Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Pro Ala Ile Cys Ala Thr Thr Gly Pro Thr
        35   40

<210> 209
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 209
Cys Pro Ala Gly Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Pro Ala Ile Cys Ala Thr Thr Gly Pro Thr
        35   40

<210> 210
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 210
Cys Pro Ala Ser Gln Phe Thr Cys Arg Ser Thr Asp Arg Cys Ile Pro
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Pro Glu Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly

```
        35                  40                  45


<210> 211
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 211
Cys Gln Ala Ser Gln Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Asp Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Pro Glu Ile Cys Ala Ala Pro Ala Pro Thr
        35                  40


<210> 212
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 212
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Leu Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Pro Ala Ile Cys Lys Thr Pro Gly His Thr
        35                  40


<210> 213
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 213
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15
```

Gln Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Ala Ile Cys Lys Thr Pro Gly His Thr
        35   40

<210> 214
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (36)..(36)
<223> Variable amino acid

<400> 214
Cys Arg Ser Asn Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1   5   10   15

Leu Gly Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Glu
            20   25   30

Glu Ala Pro Xaa Ile Arg Lys Thr Pro Gly His Thr
        35   40

<210> 215
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 215
Cys Pro Ala Asn Glu Phe Lys Cys His Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Arg Gly Pro Gly His Thr
        35   40

<210> 216
<211> 45
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 216
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Pro Ala Thr Cys Ala Thr Pro Gly His Thr
        35   40   45

<210> 217
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 217
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Pro Ala Asn Cys Ala Thr Pro Ala His Thr
        35   40   45

<210> 218
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 218
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ala Pro Ala Ile Cys Lys Thr Pro Gly His Thr
        35   40   45

```
<210> 219
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 219
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Glu Gly Cys Glu Ala Ala Ala Pro Thr
        35                  40


<210> 220
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 220
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 221
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 221
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
```

```
            20                  25                  30


Asp Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 222
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 222
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 223
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 223
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Lys Ser Cys Pro Ala His Thr
        35                  40


<210> 224
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 224
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Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Lys Asn Cys Gln Pro Pro Thr
        35                  40


<210> 225
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 225
Cys His Pro Thr Ala Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 226
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 226
Cys His Pro Ile Ala Glu Phe Glu Cys His Ser Thr Ser Arg Cys Ile
1               5                   10                  15


Pro Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Ala Asn Cys Gln Pro Pro Thr
        35                  40


<210> 227
<211> 43
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 227
Cys His Pro Thr Ala Glu Phe Glu Cys Asn Ser Thr Gly Arg Cys Val
1               5                   10                  15


Ser Ala Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Pro Ala Leu Cys Lys Ala Pro Thr
        35                  40


<210> 228
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 228
Cys His Pro Thr Ala Glu Phe Glu Cys Asn Ser Thr Gly Arg Cys Val
1               5                   10                  15


Ser Ala Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Pro Ala Leu Cys Lys Ala Pro Thr
        35                  40


<210> 229
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 229
Cys His Pro Thr Ala Glu Phe Glu Cys Asn Ser Thr Gly Arg Cys Val
1               5                   10                  15


Ser Ala Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Ser Ala Pro Cys Glu Thr Thr Gly Pro Thr
        35                  40                  45
```

<210> 230
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 230
Cys His Pro Thr Ser Glu Phe Glu Cys Arg Ser Thr Ala Arg Cys Ile
1 5 10 15

Pro Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
20 25 30

Asp Glu Lys His Cys Gln Pro Pro Thr
35 40

<210> 231
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 231
Cys His Pro Thr Ser Glu Phe Glu Cys Arg Ser Thr Ala Arg Cys Ile
1 5 10 15

Pro Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
20 25 30

Asp Glu Ala Pro Ala Ile Cys Lys Thr Pro Gly His Thr
35 40 45

<210> 232
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 232
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile
1 5 10 15

Pro Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
20 25 30

```
Asp Glu Thr Gly Cys Ala Lys Pro Thr
        35                  40


<210> 233
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 233
Cys His Thr Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Thr Gly Cys Ala Lys Pro Thr
        35                  40


<210> 234
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 234
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Ser Leu Ala Thr Cys Gln Gln His Thr
        35                  40


<210> 235
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 235
Cys Asn Ala Pro Asn Gln Phe Glu Cys Arg Ser Thr Ser Arg Cys Ile
1               5                   10                  15
```

Pro Leu Gly Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser
20 25 30

Asp Glu Thr Asp Cys Gln Glu Pro Thr
35 40

<210> 236
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 236
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1 5 10 15

Pro Arg Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
20 25 30

Asp Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
35 40

<210> 237
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 237
Cys Gln Ala Ser Asp Gln Phe Glu Cys Lys Ser Thr Gly Arg Cys Ile
1 5 10 15

Pro Leu Ala Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
20 25 30

Asp Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Glu Ala Ser Gly
35 40 45

Gly Ser
50

<210> 238
<211> 43
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 238
Cys Gln Ala Ser Asp Gln Phe Glu Cys Lys Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Leu Ala Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser
            20   25   30

Asp Glu Ala Gly Cys Ala Ala Ser Gly Pro Thr
        35   40

<210> 239
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 239
Cys Gln Ala Ser Asp Gln Phe Glu Cys Lys Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Leu Asp Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ala Leu Glu Asn Cys Ala Gln His Thr
        35   40

<210> 240
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 240
Cys Gly Ser Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Asn Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Thr Ser Ala Ala Pro Thr
        35   40

<210> 241
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 241
Cys Gly Ser Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Asn Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Thr Ser Ala Ala Pro Thr
        35   40

<210> 242
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 242
Cys Gly Ser Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Asn Trp Val Cys Asp Gly Asp Asp Asp Cys Asp Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Thr Ser Ala Ala Pro Thr
        35   40

<210> 243
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 243
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp

```
            20                  25                  30

Glu Lys Ser Cys Thr Thr Pro Ala Pro Thr
        35                  40


<210> 244
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 244
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15

Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30

Glu Thr Gly Cys Lys Ala Pro Thr
        35                  40


<210> 245
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 245
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15

Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30

Glu Thr Gly Cys Ala Lys Pro Thr
        35                  40


<210> 246
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 246
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```
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 247
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 247
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala Pro Thr
        35                  40


<210> 248
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 248
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35                  40                  45


<210> 249
<211> 51
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 249
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 250
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 250
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 251
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 251
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15
```

```
Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Asp Ser His Ile Leu Pro Phe Gly Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 252
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 252
Cys Glu Ser Asn Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
        35                  40


<210> 253
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 253
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Val Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 254
```

<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 254
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Val Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35   40   45

Pro Ser Thr
    50

<210> 255
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 255
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35   40   45

Pro Ser Thr
    50

<210> 256
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 256

Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35   40   45

Pro Ser Thr
    50

<210> 257
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 257
Cys Pro Ala Gly Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35   40   45

Pro Ser Thr
    50

<210> 258
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (51)..(51)
<223> Variable amino acid

<400> 258
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

```
Ala Asn Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Xaa
    50


<210> 259
<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 259
Cys Glu Pro Ser Gln Phe Thr Cys Arg Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Ala Leu Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr
        35                  40                  45


Leu Gly Pro Ser Thr
    50


<210> 260
<211> 53
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 260
Cys Leu Ser Ser Glu Phe Thr Cys Lys Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Ala Leu Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr
        35                  40                  45
```

Pro Gly Pro Ser Thr
50

<210> 261
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (2)..(3)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Variable amino acid

<400> 261
Cys Xaa Xaa Ser Gln Phe Xaa Cys Arg Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

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

Pro Ser Thr
50

<210> 262
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 262
Cys Gln Ala Asp Gln Phe Gln Cys Arg Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Ala Pro Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Ser Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
35 40 45

Pro Ser Thr
50

<210> 263
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 263
Cys Arg Ala Asp Gln Phe Gln Cys Arg Ser Thr Asn Arg Cys Leu Pro
1 5 10 15

Gly Pro Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
35 40 45

Pro Ser Thr
50

<210> 264
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 264
Cys Gln Thr Gly Glu Phe Arg Cys Arg Ser Thr Asp Arg Cys Ile Pro
1 5 10 15

Ala Glu Trp Val Cys Asp Gly Asp Ser Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
35 40 45

Pro Ser Thr
50

<210> 265
<211> 51
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 265
```
Cys Ala Ser Asn Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Asn Thr Pro Gly
        35                  40                  45


Pro Ile Thr
    50
```

<210> 266
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 266
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Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro
        35                  40                  45


Gly Pro Ser Thr
    50
```

<210> 267
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 267
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Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15
```

Pro Ala Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro
        35   40   45

Gly Pro Ser Thr
    50

<210> 268
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 268
Cys His Pro Thr Ala Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro
        35   40   45

Gly Pro Ser Thr
    50

<210> 269
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 269
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20   25   30

Asp Glu Lys Asp Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro
        35   40   45

```
Gly Pro Ser Thr
    50


<210> 270
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<400> 270
Cys Xaa Pro Ser Glu Phe Thr Cys Lys Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Pro His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 271
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 271
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Pro His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50
```

```
<210> 272
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 272
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Gly Leu Glu Ala Ser
        35                  40                  45


<210> 273
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 273
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser
    50


<210> 274
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 274
Cys Ala Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
```

```
1               5                   10                  15


Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser
    50


<210> 275
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 275
Cys Ala Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser
    50


<210> 276
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 276
Cys Arg Ser Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Pro Ala Ile Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr
        35                  40                  45
```

Pro Gly Leu Glu Ala Ser
50

<210> 277
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 277
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Arg Ser Cys Lys Pro Pro Thr
35 40

<210> 278
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 278
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Leu Glu Ala
35 40 45

Ser

<210> 279
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

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      polypeptide

<400> 279
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
        35                  40


<210> 280
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 280
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
        35                  40


<210> 281
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 281
Cys Gly Ser Asp Glu Phe Gln Cys Lys Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Asp Ser Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Gly Arg Pro Gly Leu Glu Ala Ser Gly Gly Ser
        35                  40                  45


<210> 282
<211> 40
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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 282
Cys Gln Ser Asn Glu Phe Thr Cys Gln Ser Thr Asn Arg Cys Leu Pro
1               5                   10                  15


Leu Pro Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Gly Gln Arg Thr
        35                  40


<210> 283
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 283
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
        35                  40


<210> 284
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 284
Cys Glu Ala Asp Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Ala Pro Gly Pro Thr
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35 40

<210> 285
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 285
Cys Ala Ala Asp Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Asn Cys Thr Pro Pro Thr
35 40

<210> 286
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 286
Cys Ala Pro Asn Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Gln Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Asn Cys Ala Lys His Thr
35 40

<210> 287
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 287
Cys Ala Pro Asn Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

```
Gln Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Ala Lys His Thr
        35                  40


<210> 288
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 288
Cys Val Ser Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Ala Lys His Thr
        35                  40


<210> 289
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 289
Cys Ala Pro Ser Glu Phe Gln Cys Gln Ser Thr Lys Arg Cys Ile Pro
1               5                   10                  15


Glu Gly Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Glu Ala Pro Val Arg Thr
        35                  40


<210> 290
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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<400> 290
Cys Ala Pro Ser Glu Phe Gln Cys Gln Ser Thr Lys Arg Cys Ile Pro
1   5   10   15

Glu Gly Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Gly Cys Glu Ala Pro Val Arg Thr
        35   40

<210> 291
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 291
Cys Val Pro Ser Glu Phe Gln Cys Gln Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asp Cys Lys Ala Pro Gly His Thr
        35   40

<210> 292
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 292
Cys Pro Ser Asp Gln Phe Gln Cys Ser Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Arg Ser Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asp Cys Ala Ala Pro Thr
        35   40

<210> 293
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 293
Cys Pro Ser Asp Gln Phe Gln Cys Ser Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Arg Ser Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Asp Cys Ala Ala Pro Thr
35 40

<210> 294
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 294
Cys Glu Ser Asn Gln Phe Gln Cys His Ser Thr Gly Arg Cys Val Pro
1 5 10 15

Gln Ser Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Thr Asp Cys Ala Pro Pro Thr
35 40

<210> 295
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 295
Cys Leu Ser Asn Gln Phe Gln Cys Asn Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Gln His Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Gly Cys Ala Ala Thr Gly His Thr
35 40

<210> 296
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 296
Cys Gly Ala Asp Gln Phe Gln Cys Gln Ser Thr Asn Arg Cys Val Pro
1   5   10   15

Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asp Cys Lys Ala Thr Ala Arg Thr
        35   40

<210> 297
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (3)..(3)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (21)..(22)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Variable amino acid

<400> 297
Cys Pro Xaa Asn Glu Phe Arg Cys Gly Asn Gly Arg Cys Leu Pro Leu
1   5   10   15

Arg Leu Arg Cys Xaa Xaa Glu Asn Asp Cys Gly Asp Xaa Ser Asp Glu
            20   25   30

Glu Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40

<210> 298
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 298
Cys Pro Ala Gly Glu Phe Gln Cys Lys Asn Gly Arg Cys Leu Pro Pro
1   5   10   15

Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Thr Gly Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40

<210> 299
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (20)..(20)
<223> Variable amino acid

<400> 299
Cys Gln Ala Asp Gln Phe Pro Cys Ser Asn Gly His Cys Val Pro Gln
1   5   10   15

Thr Leu Val Xaa Asp Gly Val Pro Asp Cys Gln Asp Asp Ser Asp Glu
            20   25   30

Thr Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40

<210> 300
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 300
Cys Leu Ala Asp Glu Phe Pro Cys His Ser Thr Gly Arg Cys Ile Pro

1   5   10   15

Ala Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 301
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 301
Cys Ala Ala Asp Glu Phe Gln Cys Gln Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Val Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 302
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 302
Cys Leu Ala Asn Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Arg Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 303
<211> 47
<212> PRT
<213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 303
Cys Ala Ala Asp Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Pro Leu Ala Leu Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 304
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 304
Cys Asn Thr Thr Gln Phe Ser Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Asp Trp Gln Cys Asp Gly Val Thr Asp Cys Glu Asp Asn Ser Asp
            20                  25                  30


Glu Ala Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 305
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 305
Cys Leu Pro Ser Glu Phe Gln Cys Lys Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Leu Tyr Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 306
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<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 306
Cys Leu Pro Ser Glu Phe Gln Cys Lys Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Leu Tyr Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 307
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (34)..(34)
<223> Variable amino acid

<400> 307
Cys Leu Pro Ser Gln Phe Gln Cys Asn Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Leu Tyr Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Xaa Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 308
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
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<222> (2)..(2)
<223> Variable amino acid

<400> 308
Cys Xaa Pro Ser Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp
            20                  25                  30


Glu Thr Gly Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 309
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 309
Cys Glu Pro Asn Gln Phe Thr Cys His Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Gln Pro Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Leu Ala Thr Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 310
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 310
Cys Glu Pro Asn Gln Phe Thr Cys His Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Gln Pro Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Leu Ala Thr Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 311
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<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 311
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 312
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 312
Cys Gly Ser Asp Glu Phe Gln Cys Lys Ser Thr Arg Arg Cys Ile Pro
1   5   10   15

Leu Asn Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Pro Pro Ala Thr Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 313
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 313
Cys Gly Ser Asp Glu Phe Gln Cys Lys Ser Thr Arg Arg Cys Ile Pro
1   5   10   15

Leu Asn Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Pro Pro Ala Thr Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 314
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 314
Cys Gly Ser Asp Glu Phe Gln Cys Lys Ser Thr Arg Arg Cys Ile Pro
1 5 10 15

Leu Asn Trp Leu Cys Asp Gly Val Pro Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Pro Pro Ala Thr Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 315
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 315
Cys Pro Ser Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Ser
1 5 10 15

Leu Thr Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 316
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 316
Cys Pro Ser Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Ser
1 5 10 15

Leu Thr Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 317
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 317
Cys Pro Ser Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Leu Thr Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Arg Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 318
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 318
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Pro Ala Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 319
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 319
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Pro Ala Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 320
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 320
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 321
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 321
Cys His Pro Thr Ala Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Val Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 322
<211> 48
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 322
Cys Asp Pro Ile Ala Glu Phe Lys Cys His Ser Thr Gly Arg Cys Ile
1   5   10   15

Pro Leu Asp Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser
            20   25   30

Asp Glu Ser Pro Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 323
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 323
Cys Pro Ser Asp Glu Phe Lys Cys His Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Val Glu Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 324
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 324
Cys Pro Pro Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Arg Asp Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Asp Leu Cys Gly Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 325
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 325
Cys Val Ala Ser Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Glu Ser Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Pro Asp Leu Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 326
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 326
Cys Gly Ala Ser Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Gln His Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Asp Cys Ser Ala Pro Ala Ser Glu Ser Pro Gly
        35   40   45

<210> 327
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 327
Cys Gln Ala Ser Glu Phe Thr Cys His Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp

```
            20                  25                  30


Glu Glu Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 328
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 328
Cys Glu Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gly Gly Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Thr Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 329
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 329
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Pro Asp Leu Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 330
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 330
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Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 331
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 331
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 332
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 332
Cys Ser Ser Asp Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Arg Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asp Cys Gly Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 333
<211> 45
<212> PRT
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (21)..(22)
<223> Variable amino acid

<400> 333
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Gly Trp Val Xaa Xaa Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Asn Cys Ser Ala Ser Ala Ser Glu Pro Pro Cys
        35                  40                  45


<210> 334
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (3)..(3)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (22)..(22)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (24)..(24)
<223> Variable amino acid

<400> 334
Cys Leu Xaa Asn Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Xaa Gly Xaa Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45
```

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<210> 335
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 335
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Gly Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 336
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 336
Cys Leu Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Leu Pro
1               5                   10                  15


Arg Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 337
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 337
Cys Gly Ser Asn Gln Phe Thr Cys Arg Ser Thr Lys Arg Cys Ile Thr
1               5                   10                  15


Ala Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
```

```
Glu Thr Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 338
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 338
Cys Gln Ala Asn Glu Phe Thr Cys Arg Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Ala Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 339
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 339
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Gly Arg Cys Ile Ser
1               5                   10                  15


Arg Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 340
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 340
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15
```

Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Pro Glu His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 341
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 341
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Arg Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 342
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 342
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
35 40 45

<210> 343
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

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      polypeptide

<400> 343
Cys Arg Ser Asn Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Gly Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Ser Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 344
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (36)..(36)
<223> Variable amino acid

<400> 344
Cys Xaa Ser Phe Thr Glu Phe Glu Cys Arg Ser Thr Gly Xaa Cys Ile
1               5                   10                  15


Pro Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Glu Xaa Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35                  40                  45


<210> 345
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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<400> 345
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 346
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 346
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Val Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Ser Asp Ile Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 347
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 347
Cys Val Pro Ser Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 348
<211> 45
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 348
Cys Val Ser Gly Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Val Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asp Cys Gly Ala Pro Ala Ser Glu Pro Pro Gly
        35   40   45

<210> 349
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 349
Cys Glu Pro Ser Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Lys Ser Cys Ser Ala Pro Ala Pro Glu Pro Pro Gly
        35   40   45

<210> 350
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 350
Cys Glu Pro Ser Gln Phe Pro Cys His Ser Thr Asn Arg Cys Leu Pro
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Asn Cys Ser Ala Pro Ala Ser Glu Pro Ser Gly
        35   40   45

```
<210> 351
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 351
Cys Glu Ser Ser Gln Phe Thr Cys Asn Ser Thr Lys Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Glu Ala Pro Ala His Thr
        35                  40


<210> 352
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 352
Cys Gln Pro Ser Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 353
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 353
Cys Gln Pro Ser Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
```

20 25 30

Glu Lys Asn Cys Lys Ala His Thr
35 40

<210> 354
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 354
Cys Leu Pro Ser Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1 5 10 15

Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Asn Cys Lys Ala His Thr
35 40

<210> 355
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 355
Cys Gln Pro Asp Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1 5 10 15

Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Asn Cys Lys Ala His Thr
35 40

<210> 356
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 356

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Cys Pro Pro Asn Gln Phe Thr Cys His Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 357
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (39)..(39)
<223> Variable amino acid

<400> 357
Cys Gln Pro Ser Gln Phe Thr Cys Xaa Arg Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala Xaa Thr
        35                  40


<210> 358
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 358
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
```

Glu Ala Gly Cys Ala Thr Ser Gly Pro Thr
35 40

<210> 359
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 359
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Gly Cys Ala Thr Ser Gly Pro Thr
35 40

<210> 360
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 360
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ala Gly Cys Ala Thr Ser Gly Pro Thr
35 40

<210> 361
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 361
Cys Ala Ala Asp Gln Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro

1   5   10   15

Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Ala Thr Ser Gly Pro Thr
        35   40

<210> 362
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 362
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Asp Cys Ala Pro His Thr
        35   40

<210> 363
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 363
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Pro Ala Leu Cys Lys Ala Pro Thr
        35   40

<210> 364
<211> 42
<212> PRT
<213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 364
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Pro Ala Leu Cys Lys Ala Pro Thr
        35                  40


<210> 365
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 365
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Ser Cys Glu Thr Pro Thr
        35                  40


<210> 366
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (20)..(20)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (38)..(38)
<223> Variable amino acid

<400> 366
Cys Ala Ala Ser Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15
```

Val Glu Trp Xaa Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Thr Gly Cys Lys Xaa Pro Thr
35 40

<210> 367
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 367
Cys Glu Ser Asp Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Asp Cys Lys Gln His Thr
35 40

<210> 368
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 368
Cys Glu Ser Asp Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Asp Cys Lys Gln His Thr
35 40

<210> 369
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

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      polypeptide


<220>
<221> MOD_RES
<222> (38)..(39)
<223> Variable amino acid

<400> 369
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Xaa Xaa Thr
        35                  40


<210> 370
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 370
Cys Val Ser Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Glu Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 371
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 371
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
```

```
Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 372
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 372
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 373
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 373
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 374
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 374
Cys Glu Ala Ser Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15
```

```
Arg Gln Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 375
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 375
Cys Ala Ala Ser Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Leu Ala Thr Cys Gln Gln His Thr
        35                  40


<210> 376
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 376
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 377
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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```
<400> 377
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 378
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 378
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys His Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 379
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 379
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Lys His Thr
        35                  40


<210> 380
<211> 40
<212> PRT
```

```
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 380
Cys Pro Pro Asp Glu Phe Arg Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys His Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Pro His Thr
        35                  40


<210> 381
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 381
Cys Leu Ala Asn Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 382
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 382
Cys Gln Thr Gly Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40
```

<210> 383
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 383
```
Cys Arg Ala Asp Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gly Ala Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40
```

<210> 384
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 384
```
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40
```

<210> 385
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 385
```
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
```

```
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40


<210> 386
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 386
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 387
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (15)..(15)
<223> Variable amino acid

<400> 387
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Xaa Pro
1               5                   10                  15


Ala Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Lys Ala His Thr
        35                  40


<210> 388
<211> 40
<212> PRT
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 388
```
Cys Ala Pro Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Gln His Thr
        35                  40
```

<210> 389
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 389
```
Cys Gln Pro Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Pro Ala Asn Cys Ala Thr Pro Thr His Thr
        35                  40
```

<210> 390
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 390
```
Cys Val Pro Asn Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Ser Ala Leu Cys Ser Glu Pro Thr
        35                  40
```

<210> 391
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 391
Cys Glu Pro Asp Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Gly Cys Ala Lys Pro Thr
        35   40

<210> 392
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 392
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Leu Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Asn Cys Gln Pro Pro Thr
        35   40

<210> 393
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 393
Cys Ala Ala Gly Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

```
Glu Glu Gly Cys Gly Ala Ala Glu Pro Thr
        35                  40


<210> 394
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 394
Cys Gln Leu Asp Gln Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Gly Cys Gly Ala Ala Glu Pro Thr
        35                  40


<210> 395
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 395
Cys Pro Ala Asp Gln Phe Thr Cys Arg Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Gly Asp Trp Val Cys Asp Ala Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asn Cys Leu Glu Arg Thr
        35                  40


<210> 396
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 396
Cys Pro Ala Asp Gln Phe Thr Cys Arg Ser Thr Asp Arg Cys Ile Pro
```

```
1               5                   10                  15


Gly Asp Trp Val Cys Asp Ala Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asn Cys Leu Glu Arg Thr
        35                  40


<210> 397
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 397
Cys Gly Ser Asp Gln Phe Gln Cys Arg Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asp Cys Thr Arg Ser Val Pro Thr
        35                  40


<210> 398
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<400> 398
Cys Gln Ser Gly Gln Phe Gln Cys Xaa Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Gln Pro Pro Thr
        35                  40
```

<210> 399
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<400> 399

```
Cys Gln Ser Gly Gln Phe Gln Cys Xaa Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Gln Pro Pro Thr
        35                  40
```

<210> 400
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 400

```
Cys Ala Ser Asp Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln His Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asn Cys Gly Pro Pro Gly Pro Ser Ala Ile Ser Thr Ala Ala
        35                  40                  45


Gly
```

<210> 401
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 401
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Gln Leu Cys Thr Ala His Thr
35 40

<210> 402
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 402
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Gln Leu Cys Thr Ala His Thr
35 40

<210> 403
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 403
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Gln Leu Cys Thr Ala His Thr
35 40

<210> 404
<211> 41

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 404
```
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40
```

<210> 405
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 405
```
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40
```

<210> 406
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 406
```
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
```

35 40

<210> 407
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 407
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Gln Leu Cys Thr Ala His Thr
35 40

<210> 408
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 408
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ser Gln Leu Cys Thr Ala His Thr
35 40

<210> 409
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 409
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Gln Leu Cys Thr Ala His Thr
        35   40

<210> 410
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 410
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Gln Leu Cys Thr Ala His Thr
        35   40

<210> 411
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 411
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Gln Leu Cys Thr Ala His Thr
        35   40

<210> 412
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

```
<400> 412
Cys Leu Ala Asn Gln Phe Pro Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser His Leu Cys Thr Ala His Thr
        35                  40


<210> 413
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 413
Cys Arg Ala Asn Glu Phe Pro Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser His Leu Cys Thr Ala His Thr
        35                  40


<210> 414
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 414
Cys Leu Ser Asn Glu Phe Pro Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40


<210> 415
<211> 41
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 415
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40


<210> 416
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 416
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40


<210> 417
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 417
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40
```

```
<210> 418
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 418
Cys Glu Pro Ser Gly Gln Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40


<210> 419
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 419
Cys Leu Ala Asp Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr
        35                  40


<210> 420
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 420
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Val His Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30
```

Glu Ala Gln Val Cys Thr Glu His Thr
        35   40

<210> 421
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 421
Cys Leu Ala Asp Glu Phe Arg Cys Ser Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Gln Val Cys Thr Glu His Thr
        35   40

<210> 422
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 422
Cys Pro Ala Gly Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ser Gln His Cys Pro Pro His Thr
        35   40

<210> 423
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 423
Cys Pro Ala Gly Gln Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro

1 5 10 15

Leu Gln Trp Val Cys His Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Ser Gln His Cys Pro Pro His Thr
35 40

<210> 424
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 424
Cys Ala Ser Asp Glu Phe Thr Cys His Ser Thr Arg Arg Cys Ile Pro
1 5 10 15

Gln Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Asp Cys Pro Pro His Thr
35 40

<210> 425
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 425
Cys Pro Ser Ser Gln Phe Thr Cys His Ser Thr Arg Arg Cys Ile Pro
1 5 10 15

Gln Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Asp Cys Pro Pro His Thr
35 40

<210> 426
<211> 40
<212> PRT
<213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 426
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Gly Cys Pro Lys His Thr
        35                  40


<210> 427
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 427
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Gly Cys Pro Lys His Thr
        35                  40


<210> 428
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 428
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1               5                   10                  15


Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Gly Cys Pro Lys His Thr
        35                  40


<210> 429
```

<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 429
Cys Val Ser Asn Glu Phe Thr Cys Arg Ser Thr Lys Arg Cys Val Pro
1   5   10   15

Gln Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Gly Cys Pro Lys His Thr
        35   40

<210> 430
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 430
Cys Gln Ala Asn Gln Phe Lys Cys Arg Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Gly Cys Lys Pro His Thr
        35   40

<210> 431
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 431
Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Leu Pro Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

```
Glu Ala Pro Ala Ile Cys Glu Lys His Thr
        35                  40


<210> 432
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 432
Cys Ala Ser Ser Glu Phe Gln Cys Lys Ser Thr Glu Arg Cys Leu Pro
1               5                   10                  15


Leu Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Pro Ala Ile Cys Thr Thr Pro Gly Pro Thr
        35                  40


<210> 433
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 433
Cys Pro Pro Ser Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu His Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Pro Pro Glu Pro Cys Thr Ala Thr Val Pro Thr
        35                  40


<210> 434
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 434
Cys Gln Pro Asn Gln Phe Gln Cys His Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15
```

Leu Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Ser Ala Pro Cys Glu Thr Thr Gly Pro Thr
        35   40

<210> 435
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 435
Cys Glu Ser Ser Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Pro Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Gly Cys Gln Pro His Arg
        35   40

<210> 436
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 436
Cys Glu Ala Ser Glu Phe Gln Cys Arg Ser Thr Lys Arg Cys Leu Pro
1   5   10   15

Arg His Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Lys Ser Cys Pro Ala His Thr
        35   40

<210> 437
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

```
<400> 437
Cys Glu Ala Ser Glu Phe Gln Cys Arg Ser Thr Lys Arg Cys Leu Pro
1               5                   10                  15


Arg His Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Pro Ala His Thr
        35                  40


<210> 438
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (28)..(28)
<223> Variable amino acid

<400> 438
Cys Glu Ala Ser Glu Phe Gln Cys Arg Ser Thr Lys Arg Cys Leu Pro
1               5                   10                  15


Arg His Trp Val Cys Asp Gly Asp Asn Asp Cys Xaa Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Pro Leu His
        35


<210> 439
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 439
Cys Arg Ser Gly Gln Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Ser
1               5                   10                  15


Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Ser Ala Ile Cys Glu Ser Ser Glu His Thr
```

        35   40

<210> 440
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 440
Cys Pro Pro Asp Glu Phe Arg Cys Asn Ser Thr Asn Arg Cys Ile Ser
1   5   10   15

Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Ser Ala Ile Cys Glu Ser Ser Glu His Thr
        35   40

<210> 441
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 441
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35   40

<210> 442
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 442
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35   40

<210> 443
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 443
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35   40

<210> 444
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 444
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35   40

<210> 445
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

```
<400> 445
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 446
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 446
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 447
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 447
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 448
<211> 42
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 448
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 449
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<400> 449
Cys Glu Ser Asn Glu Phe Gln Cys Xaa Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 450
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 450
Cys Glu Ser Asn Glu Phe Gln Cys His Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Arg Val Asn Asp Cys Glu Asp Gly Ser Asp
```

```
            20                  25                  30

Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40


<210> 451
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (25)..(25)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (35)..(35)
<223> Variable amino acid

<400> 451
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly Val Xaa Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Xaa Cys Thr Ala Ala Val His Thr
        35                  40


<210> 452
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 452
Cys Glu Pro Ser Gln Phe Thr Cys Arg Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Thr Ala Ala Val His Thr
        35                  40
```

<210> 453
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 453
Cys Ser Ser Asp Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Arg Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Leu Ala Pro Cys Thr Ser Thr Ala His Thr
        35   40

<210> 454
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (33)..(33)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (37)..(37)
<223> Variable amino acid

<400> 454
Cys Ser Ser Xaa Glu Phe Gln Cys Ser Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Arg Glu Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Xaa Ala Leu Ala Xaa Cys Thr Ser Thr Ala His Thr
        35   40

```
<210> 455
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 455
Cys Val Ser Gly Glu Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Asp Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Pro Ser Ala Pro Cys Thr Thr Ala Ala His Thr
        35                  40


<210> 456
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 456
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 457
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 457
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30
```

```
Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 458
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 458
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 459
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 459
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 460
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 460
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15
```

```
Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 461
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 461
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 462
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 462
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 463
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
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polypeptide

<400> 463
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr
        35   40

<210> 464
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 464
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr
        35   40

<210> 465
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 465
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr
        35   40

<210> 466
<211> 40

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 466
```
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40
```

<210> 467
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 467
```
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40
```

<210> 468
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 468
```
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
```

```
        35                  40


<210> 469
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 469
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 470
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 470
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 471
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 471
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15
```

```
Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 472
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 472
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 473
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 473
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 474
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

```
<400> 474
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 475
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 475
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 476
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 476
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 477
<211> 40
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 477
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 478
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 478
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 479
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 479
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40
```

```
<210> 480
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (10)..(10)
<223> Variable amino acid

<400> 480
Cys Pro Ser Gly Glu Phe Gln Cys Arg Xaa Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 481
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (34)..(34)
<223> Variable amino acid

<400> 481
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Xaa Ser Cys Thr Pro Pro Thr
        35                  40


<210> 482
<211> 40
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 482
Cys Pro Pro Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 483
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (17)..(17)
<223> Variable amino acid

<400> 483
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 484
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 484
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Lys Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
```

            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr
        35   40

<210> 485
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (38)..(39)
<223> Variable amino acid

<400> 485
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Xaa Xaa Thr
        35   40

<210> 486
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (17)..(17)
<223> Variable amino acid

<220>

<221> MOD_RES
<222> (32)..(32)
<223> Variable amino acid

<400> 486
Cys Pro Ser Gly Glu Phe Arg Cys Arg Xaa Thr Xaa Arg Cys Ile Pro
1   5   10   15

Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Xaa
            20   25   30

Glu Glu Ser Cys Thr Pro Pro Thr
        35   40

<210> 487
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 487
Cys Pro Ser Ser Gln Phe Gln Cys Pro Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Lys Ser Cys Thr Pro Pro Thr
        35   40

<210> 488
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 488
Cys Gln Ala Ser Gln Phe Thr Cys Gly Ser Gly Asn Cys Val Pro Pro
1   5   10   15

Pro Trp Gly Cys Asp Gly Asp Asp Asp Cys Glu Asp Gly Ser Asp Glu
            20   25   30

Glu Ser Cys Thr Pro Pro Thr
        35

<210> 489
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 489
```
Cys Pro Ala Asn Gln Phe Gln Cys Arg Ser Thr Asn Arg Cys Val Pro
1               5                   10                  15


Gly Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Ala Thr Pro Thr
        35                  40
```

<210> 490
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 490
```
Cys Val Ala Gly Gln Phe Met Cys Arg Ser Thr Gly Arg Cys Val Ser
1               5                   10                  15


Ala Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Thr Ala Pro Thr
        35                  40
```

<210> 491
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 491
```
Cys Leu Ser Asp Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Phe Pro
1               5                   10                  15


Val Asn Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30
```

```
Glu Glu Ser Cys Pro Gln Pro Thr
        35                  40


<210> 492
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<400> 492
Cys Gln Ser Asp Glu Phe Thr Cys Xaa Asn Gly Gln Cys Ile Pro Gln
1               5                   10                  15


Asp Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser Ser Asp Glu
            20                  25                  30


Ala Pro Ala His Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 493
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 493
Cys Gln Pro Asp Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Pro Asp Trp Val Cys Asp Gly Val Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Gly Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 494
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
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```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 494
Cys Val Ser Ser Gln Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Ala Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Gly Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 495
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 495
Cys Gln Ser Ser Glu Phe Thr Cys Lys Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Asn Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 496
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 496
Cys Glu Ser Asp Glu Phe Thr Cys Lys Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Glu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 497
```

<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 497
```
Cys Leu Ala Asp Glu Phe Gln Cys His Ser Thr Lys Arg Cys Val Pro
1               5                   10                  15


Arg His Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45
```

<210> 498
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 498
```
Cys Pro Ala Asp Gln Phe Gln Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Glu His Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45
```

<210> 499
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 499
```
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
```

```
Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35                  40


<210> 500
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 500
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35                  40


<210> 501
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 501
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35                  40


<210> 502
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 502
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1               5                   10                  15
```

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35   40

<210> 503
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 503
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1   5   10   15

Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35   40

<210> 504
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 504
Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro
1   5   10   15

Leu Ala Trp Val Cys His Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35   40

<210> 505
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 505
Cys Ala Pro Ser Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Pro Ala Leu Cys Thr Thr Pro Val Pro Ala
        35   40

<210> 506
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 506
Cys Pro Ala Ser Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35   40

<210> 507
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 507
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Gly Cys Thr Thr Pro Glu Pro Thr
        35   40

<210> 508
<211> 41
<212> PRT

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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (4)..(4)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (23)..(24)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (37)..(37)
<223> Variable amino acid

<400> 508
Cys Ala Ser Xaa Glu Phe Lys Cys Ser Ser Gly Arg Cys Leu Pro Pro
1               5                   10                  15


Ser Trp Leu Cys Asp Gly Xaa Xaa Asp Cys Glu Asp Gly Ser Asp Glu
            20                  25                  30


Ala Asn Cys Thr Xaa Pro Val Pro Thr
        35                  40


<210> 509
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 509
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30


Glu Ser Leu Ala Leu Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
    50
```

```
<210> 510
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 510
Cys Val Ser Gly Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Val Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Pro Pro Ala Leu Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
    50


<210> 511
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (47)..(47)
<223> Variable amino acid

<400> 511
Cys Glu Ser Ser Glu Phe Gln Cys Arg Ser Thr Asp Arg Cys Leu Pro
1               5                   10                  15


Val Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ser Asn Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Xaa Ala
        35                  40                  45


Ala



<210> 512
<211> 52
<212> PRT
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```
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (46)..(46)
<223> Variable amino acid

<400> 512
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Ala Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Gly Xaa Thr Ser
        35                  40                  45


Ala Pro Ala Ala
    50


<210> 513
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 513
Cys His Ala Pro Thr Gln Phe Glu Cys Arg Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


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


Ala Pro Ala Ala
    50


<210> 514
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
```

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (17)..(17)
<223> Variable amino acid

<400> 514
Cys Arg Ala Asn Gln Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Xaa Ser Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
    50


<210> 515
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 515
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asp Arg Cys Leu Pro
1               5                   10                  15


Val Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala
    50


<210> 516
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

```
<400> 516
Cys Leu Ser Asn Glu Phe Arg Cys Ser Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15


Arg Pro Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


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


Pro Ala Ala
    50


<210> 517
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 517
Cys Leu Ala Ser Glu Phe Thr Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


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


Ala



<210> 518
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 518
Cys Leu Ala Ser Glu Phe Thr Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30
```

```
Glu Asp Asn Ala His Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
    50


<210> 519
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 519
Cys Pro Pro Asn Glu Phe Thr Cys Gln Ser Thr Asp Arg Cys Leu Pro
1               5                   10                  15


Ala Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


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


Ala



<210> 520
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 520
Cys Asp Pro Ile Ala Glu Phe Lys Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Leu Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


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


Ala Ala
    50


<210> 521
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<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 521
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Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Val Asp Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


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


Ala Ala
    50
```

<210> 522
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 522
```
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Ser Cys Gly Arg Pro Gly Pro Gly Gly Thr Ser Ala Pro Ala
        35                  40                  45


Ala
```

<210> 523
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 523

```
Cys Ala Pro Asp Glu Phe Pro Cys Arg Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Leu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Ser Ala Thr Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
    50


<210> 524
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 524
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr
        35                  40


<210> 525
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 525
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Leu Glu Ile Cys Pro Gln Pro Thr
        35                  40


<210> 526
```

```
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 526
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asp Cys Lys Thr Pro Gly Pro Thr
        35                  40


<210> 527
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (45)..(45)
<223> Variable amino acid

<400> 527
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Xaa Thr Pro Gly
        35                  40                  45


Pro Ser Thr
    50


<210> 528
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> 528
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Gly Cys Ala Lys Pro Thr
        35   40

<210> 529
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 529
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Gly Cys Ala Lys Pro Thr
        35   40

<210> 530
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (40)..(40)
<223> Variable amino acid

<400> 530
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Thr Gly Cys Ala Lys Pro Xaa

```
        35                  40


<210> 531
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 531
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Gly Cys Ala Ala Ser Gly Pro Thr
        35                  40


<210> 532
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 532
Cys Glu Ala Asn Glu Phe Gln Cys Gln Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Asn Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Gly Thr Pro Gly Pro Thr
        35                  40


<210> 533
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 533
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15
```

Leu Glu Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Asn Cys Gly Ala Ala Ala Arg Thr
35 40

<210> 534
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 534
Cys Gln Ser Ser Glu Phe Thr Cys Lys Ser Thr Asn Arg Cys Ile Pro
1 5 10 15

Leu Ala Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Ala Asn Cys Thr Ser Pro Glu Arg Thr
35 40

<210> 535
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 535
Cys Arg Ser Ser Glu Phe Thr Cys Arg Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Glu Asn Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Gly Cys Gly Thr Ser Ala Pro Thr
35 40

<210> 536
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 536
Cys Arg Ser Ser Glu Phe Thr Cys Arg Ser Thr Ser Arg Cys Ile Pro
1   5   10   15

Glu Asn Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Thr Gly Cys Gly Thr Ser Ala Pro Thr
        35   40

<210> 537
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 537
Cys Gln Ala Gly Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr
        35   40

<210> 538
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 538
Cys Gln Ala Gly Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr
        35   40

<210> 539
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 539
Cys Gln Ala Gly Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr
        35   40

<210> 540
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 540
Cys Gln Ala Gly Gln Phe Glu Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr
        35   40

<210> 541
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (25)..(25)
<223> Variable amino acid

<400> 541
Cys Gln Ala Gly Gln Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1   5   10   15

Gln Asp Trp Val Cys Asp Gly Val Xaa Asp Cys Glu Asp Ser Ser Asp

```
            20                  25                  30


Glu Glu Arg Cys Thr Ser Pro Ala Arg Thr
        35                  40


<210> 542
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 542
Cys Pro Ala Gly Gln Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Asp Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Ser Pro Ala Arg Thr
        35                  40


<210> 543
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 543
Cys Glu Ala Asn Gln Phe Arg Cys Lys Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15


Gln Asn Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Asn Cys Thr Arg Thr Ala Pro Thr
        35                  40


<210> 544
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 544
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```
Cys Glu Ala Asp Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Ser
1               5                   10                  15


Val Asp Trp Arg Cys Asp Gly Val Ser Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Glu Ser Cys Glu Ser Thr Ala Pro Thr
        35                  40


<210> 545
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 545
Cys Glu Ala Gly Glu Phe Arg Cys Lys Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Ser Cys Lys Ser Ser Ala His Thr
        35                  40


<210> 546
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 546
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Arg Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ala Asn Cys Lys Lys Pro Thr
        35                  40


<210> 547
<211> 40
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 547
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ala Asn Cys Lys Lys Pro Thr
        35   40

<210> 548
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 548
Cys Glu Ala Asn Glu Phe Arg Cys Lys Ser Thr Gly Arg Cys Ile Ser
1   5   10   15

Gln Thr Trp Arg Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asn Cys Lys Pro Pro Thr
        35   40

<210> 549
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 549
Cys Leu Pro Ser Glu Phe Pro Cys Ser Asn Gly Arg Cys Val Pro Arg
1   5   10   15

Pro Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Asn Ser Asp Glu
            20   25   30

Ala Gly Cys Pro Lys Pro Thr
        35

```
<210> 550
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 550
Cys Glu Pro Gly Glu Phe Pro Cys Ser Ser Thr Gly Arg Cys Val Pro
1               5                   10                  15


Val Ala Trp His Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Gly Cys Gln Lys Arg Thr
        35                  40


<210> 551
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 551
Cys Gln Pro Asp Glu Phe Arg Cys Arg Asn Thr Asp Ile Cys Ile Pro
1               5                   10                  15


Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asp Cys Gln Gln Pro Thr
        35                  40


<210> 552
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (32)..(33)
<223> Variable amino acid

<220>
<221> MOD_RES
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<222> (36)..(36)
<223> Variable amino acid

<400> 552

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Cys Gln Ala Asp Glu Phe Arg Cys Gly Asn Gly Arg Cys Ile Pro Gln
1               5                   10                  15


Arg Trp Val Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp Xaa
            20                  25                  30


Xaa Asp Cys Xaa Thr Pro Thr
        35
```

<210> 553
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (38)..(38)
<223> Variable amino acid

<400> 553

```
Cys Leu Ala Asp Glu Phe Arg Cys Xaa Ser Asn Asn Arg Cys Leu Pro
1               5                   10                  15


Leu Asp Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asp Cys Ala Xaa Pro Thr
        35                  40
```

<210> 554
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES

<222> (24)..(24)
<223> Variable amino acid

<400> 554
Cys Pro Pro Asp Gln Phe Pro Cys Asp Asn Gly Asp Cys Leu Pro Gln
1   5   10   15

Pro Trp Val Cys Asp Gly Glu Xaa Asp Cys Pro Asp Asp Ser Asp Glu
            20   25   30

Ala Ser Cys Thr Thr Ser Val His Thr
        35   40

<210> 555
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (24)..(24)
<223> Variable amino acid

<400> 555
Cys Ala Ala Asp Gln Phe Lys Cys Asp Asn Gly Arg Cys Val Pro Gln
1   5   10   15

Asn Trp Arg Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Glu Asn Cys Thr Thr Pro Thr
        35

<210> 556
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 556
Ser Gln Pro Ile Gly Gln Phe Lys Cys Gly Asn Gly Asn Cys Val Pro
1   5   10   15

Arg Thr Trp Arg Cys Asp Gly Val Asn Asp Cys Pro Asp Asn Ser Asp
            20   25   30

Glu Thr Asp Cys Pro Thr Pro Thr
35 40

<210> 557
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (21)..(21)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (24)..(24)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Variable amino acid

<400> 557
Cys Glu Ala Gly Gln Phe Arg Cys Asn Asn Gly Asn Cys Xaa Pro Gln
1 5 10 15

His Trp Leu Cys Xaa Gly Glu Xaa Asp Cys Glu Asp Asn Ser Asp Glu
20 25 30

Ala Xaa Cys Glu Lys Pro Thr
35

<210> 558
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (5)..(5)

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<223> Variable amino acid

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Variable amino acid

<400> 558
Cys Ala Pro Asp Xaa Phe Xaa Cys Xaa Asn Gly Lys Cys Leu Pro Leu
1               5                   10                  15


Asp Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Xaa Cys Gln
        35


<210> 559
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 559
Cys Ala Ser Asn Gln Phe Thr Cys Asn Asn Gly His Cys Leu Pro Gln
1               5                   10                  15


His Trp Arg Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ala Ser Cys Gln Pro Pro Thr
        35


<210> 560
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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```
<400> 560
Cys Gln Ala Asp Glu Phe Lys Cys Gly Asn Gly Arg Cys Leu Pro Glu
1               5                   10                  15


Ala Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ala Asp Cys Gln Ala Pro Thr
        35


<210> 561
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (24)..(24)
<223> Variable amino acid

<400> 561
Cys Gln Ala Asp Glu Phe Arg Cys Gly Asn Gly Arg Cys Ile Ser Pro
1               5                   10                  15


Thr Trp Val Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asp Ser Asp Glu
            20                  25                  30


Ala Asn Cys Ala Thr Thr Glu Arg Thr
        35                  40


<210> 562
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (20)..(21)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (23)..(23)
<223> Variable amino acid
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```
<400> 562
Cys Gln Pro Gly Glu Phe Arg Cys Arg Asn Gly Lys Cys Ile Pro Gln
1               5                   10                  15


Thr Trp Leu Xaa Xaa Gly Xaa Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ala Asp Cys Ala Thr Thr Ala Pro Thr
        35                  40


<210> 563
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (24)..(24)
<223> Variable amino acid

<400> 563
Cys Pro Pro Asp Glu Phe Lys Cys Gly Asn Gly His Cys Ile Ser Gln
1               5                   10                  15


Thr Trp Leu Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Glu Ser Cys Ala Ala Pro Thr
        35


<210> 564
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (23)..(23)
<223> Variable amino acid

<400> 564
Cys Pro Ser Gly Glu Phe Arg Cys Ser Asn Gly Ser Cys Ile Pro Gln
1               5                   10                  15
```

```
Glu Trp Gly Cys Asp Gly Xaa Asn Asp Cys Gly Asp Asp Ser Asp Glu
            20                  25                  30


Lys Asn Cys Ala Ala Ala Gly Pro Thr
        35                  40


<210> 565
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 565
Cys Pro Ser Gly Glu Phe Arg Cys Gln Ser Ser Asn Thr Cys Ile Pro
1               5                   10                  15


Leu Asn Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Asp Ser Asp
            20                  25                  30


Glu Lys Asn Cys Glu Ala Ser Val Pro Thr
        35                  40


<210> 566
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 566
Cys Leu Ser Gly Glu Phe Arg Cys Ser Asn Gly Asn Cys Leu Pro Ala
1               5                   10                  15


Asp Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Ser Cys Ala Ala Ser Glu Pro Thr
        35                  40


<210> 567
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> 567
Cys Gln Pro Gly Glu Phe Thr Cys Asn Asn Gly Asn Cys Leu Pro Leu
1   5   10   15

Glu Trp Val Cys Asp Gly Glu Asn Asp Cys Gly Asp Ser Ser Asp Glu
            20   25   30

Glu Asn Cys Gly Gly Ser Glu His Thr
        35   40

<210> 568
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 568
Cys Gln Ser Asp Gln Phe Arg Cys Ser Asn Gly Arg Cys Ile Pro Val
1   5   10   15

Glu Trp Val Cys Asp Gly Glu Asp Asp Cys Leu Asp Gly Ser Asp Glu
            20   25   30

Pro Gln Val Cys Gly Thr Thr Ala Pro Thr
        35   40

<210> 569
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 569
Cys Pro Pro Asp Glu Phe Arg Cys Ser Asn Gly Arg Cys Leu Pro Gln
1   5   10   15

Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Thr Ser Cys Ala Thr Thr Ala Pro Thr
        35   40

<210> 570
<211> 41
<212> PRT
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 570
Cys Ala Ser Asn Gln Phe Arg Cys Arg Asn Gly Arg Cys Ile Pro Leu
1               5                   10                  15


Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gln Asp Asn Ser Asp Glu
            20                  25                  30


Ala Ser Cys Ala Ala Pro Ala Pro Thr
        35                  40


<210> 571
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 571
Cys Ala Ser Asn Gln Phe Arg Cys Arg Asn Gly Arg Cys Ile Pro Leu
1               5                   10                  15


Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gln Asp Asn Ser Asp Glu
            20                  25                  30


Ala Ser Cys Ala Ala Pro Ala Pro Thr
        35                  40


<210> 572
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (39)..(39)
<223> Variable amino acid

<400> 572
Cys Val Ala Asp Glu Phe Pro Cys Gly Asn Gly Asn Cys Ile Pro Leu
1               5                   10                  15


Pro Trp Arg Cys Asp Gly Asp Asp Asp Cys Gly Asp Asn Ser Asp Glu
```

20 25 30

Thr Asp Cys Glu Ser Ser Xaa Pro Thr
35 40

<210> 573
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 573
Cys Pro Pro Asp Glu Phe Pro Cys Ser Asn Ser Gly Ile Cys Ile Pro
1 5 10 15

Arg Ser Trp Arg Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp
20 25 30

Glu Glu Asp Cys Thr Ser Ala Gly His Thr
35 40

<210> 574
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 574
Cys Ala Pro Asn Glu Phe Pro Cys Gly Asn Gly Arg Cys Ile Pro Ala
1 5 10 15

Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
20 25 30

Glu Gly Cys Gly Gly Ser Ala Arg Thr
35 40

<210> 575
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 575

```
Cys Pro Pro Ser Glu Phe Pro Cys Gly Asn Gly Ser Cys Val Pro Gln
1               5                   10                  15


Ala Trp Val Cys Asp Gly Asp Pro Asp Cys Pro Asp Asn Ser Asp Glu
            20                  25                  30


Glu Gly Cys Thr Gly Thr Gly Pro Thr
        35                  40


<210> 576
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 576
Cys Pro Pro Asp Glu Phe Arg Cys Asn Asn Gly Lys Cys Ile Pro Leu
1               5                   10                  15


Ser Trp Arg Cys Asp Gly Asp Asp Asp Cys Gln Asp Ser Ser Asp Glu
            20                  25                  30


Ala Gly Cys Thr Glu Arg Thr
        35


<210> 577
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<400> 577
Cys Xaa Pro Gly Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Pro Ala
1               5                   10                  15


Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Gly Cys Thr Glu His Thr
        35
```

```
<210> 578
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<400> 578
Cys Xaa Pro Gly Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Pro Ala
1               5                   10                  15


Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Gly Cys Thr Glu His Thr
        35


<210> 579
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 579
Cys Gln Ser Asn Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Ser Val
1               5                   10                  15


Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Ser Ser Asp Glu
            20                  25                  30


Thr Asp Cys Thr Ser Ala Val Pro Thr
        35                  40


<210> 580
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 580
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```
Cys Pro Ser Ser Glu Phe Gln Cys Arg Asn Asn Lys Thr Cys Ile Pro
1               5                   10                  15


Arg Asn Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30


Glu Thr Asp Cys Thr Thr His Thr
        35                  40


<210> 581
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (19)..(19)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (22)..(22)
<223> Variable amino acid

<400> 581
Cys Val Pro Gly Glu Phe Arg Cys His Asp Ser Gly Thr Cys Val Pro
1               5                   10                  15


Leu Ala Xaa Leu Cys Xaa Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp
            20                  25                  30


Glu Ala Ser Cys Glu Ser Ser Glu Pro Thr
        35                  40


<210> 582
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 582
Cys Ala Pro Gly Gln Phe Arg Cys Lys Asn Gly Arg Cys Val Pro Leu
1               5                   10                  15


Ser Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Asp Ser Asp Glu
            20                  25                  30
```

Ala Asn Cys Glu Ser Pro Glu Pro Thr
35 40

<210> 583
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 583
Cys Ala Ala Asp Gln Phe Arg Cys Ser Ser Gly Arg Cys Val Pro Leu
1 5 10 15

Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Ala Asp Asp Ser Asp Glu
20 25 30

Lys Asp Cys Glu Ser Thr Ala His Thr
35 40

<210> 584
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 584
Cys Ala Ala Asp Glu Phe Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Val Ser Trp Val Cys Asp Gly Glu Asp Asp Cys Arg Asp Asp Ser Asp
20 25 30

Glu Glu Asn Cys Arg Ser Ser Glu Pro Thr
35 40

<210> 585
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 585
Cys Leu Ala Gly Glu Phe Arg Cys Asn Ser Gly Arg Cys Ile Pro Glu

```
1               5                   10                  15


His Trp Arg Cys Asp Gly Glu Asp Asp Cys Leu Asp Ser Ser Asp Glu
            20                  25                  30


Lys Asp Cys Thr Thr Ser Glu Pro Thr
        35                  40


<210> 586
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Variable amino acid

<400> 586
Cys Xaa Ala Xaa Gln Phe Thr Cys Asp Asn Gly Gln Cys Leu Pro Gln
1               5                   10                  15


Asn Trp Val Cys Asp Gly Glu Asn Asp Cys Pro Asp Xaa Ser Asp Glu
            20                  25                  30


Lys Asn Cys Ala Pro His Thr
        35


<210> 587
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
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<222> (2)..(2)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (17)..(17)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (33)..(34)
<223> Variable amino acid

<400> 587
Cys Xaa Ser Ser Xaa Phe Arg Cys Xaa Asn Gly Xaa Cys Leu Pro Leu
1 5 10 15

Xaa Trp Val Cys Asp Gly Glu Asn Asp Cys Gly Asp Xaa Ser Asp Glu
20 25 30

Xaa Xaa Cys
35

<210> 588
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 588
Cys Val Ala Asp Gln Phe Arg Cys Asp Asn Gly Arg Cys Leu Ser Arg
1 5 10 15

Glu Trp Val Cys Asp Gly Val Asn Asp Cys Gln Asp Gly Ser Asp Glu

```
            20                  25                  30


Thr Asn Cys Gln Glu Arg Thr
        35


<210> 589
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 589
Cys Ala Ala Gly Glu Phe Arg Cys Arg Asp Ser Gly Arg Cys Leu Pro
1               5                   10                  15


Gln His Trp Leu Cys Asp Gly Glu Asn Asp Cys Ala Asp Gly Ser Asp
            20                  25                  30


Glu Thr Asn Cys Thr Gln His Thr
        35                  40


<210> 590
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (21)..(21)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (23)..(23)
<223> Variable amino acid

<400> 590
Cys Xaa Pro Ser Glu Phe Thr Cys Ser Ser Gly Gln Cys Ile Pro Glu
1               5                   10                  15


Asp Trp Val Cys Xaa Gly Xaa Asn Asp Cys Gly Asp Asp Ser Asp Glu
            20                  25                  30
```

```
Thr Asn Cys Glu Thr Arg Thr
        35


<210> 591
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 591
Cys Val Ala Asn Glu Phe Lys Cys Gly Ser Gly Lys Cys Ile Pro Glu
1               5                   10                  15


Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ser Cys Ala Gln Pro Thr
        35


<210> 592
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 592
Cys Gly Ala Asn Glu Phe Lys Cys Ser Ser Gly Ser Cys Ile Pro Gln
1               5                   10                  15


Glu Trp Arg Cys Asp Gly Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ser Leu Ala Pro Cys Lys Glu Pro Thr
        35                  40


<210> 593
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 593
Cys Arg Ala Asp Glu Phe Lys Cys Gly Asn Gly His Cys Ile Pro Gly
```

```
1               5                   10                  15


Gln Trp Leu Cys Asp Gly Glu Asn Asp Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30


Lys Ser Cys Glu Gln Pro Thr
        35


<210> 594
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 594
Cys Leu Pro Asn Gln Phe Gln Cys Gln Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Asn Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asp Ser Asp
            20                  25                  30


Glu Thr Ser Cys Lys Ala Pro Thr
        35                  40


<210> 595
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 595
Cys Pro Ala Ser Glu Phe Gln Cys Gly Asn Gly Arg Cys Ile Ser Glu
1               5                   10                  15


His Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Ser Cys Lys Ala Pro Val Pro Thr
        35                  40


<210> 596
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
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```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 596
Cys Gln Ala Asp Glu Phe Gln Cys Arg Asn Thr Glu Lys Cys Leu Pro
1               5                   10                  15


Leu Asn Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asp Ser Asp
            20                  25                  30


Glu Thr Ser Cys Ala Thr Pro Thr
        35                  40


<210> 597
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 597
Cys Val Ala Ser Glu Phe Thr Cys Lys Asp Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Leu His Trp Val Cys Asp Gly Val Asp Asp Cys Gly Asp Asn Ser Asp
            20                  25                  30


Glu Ala Asp Cys Glu Thr Ser Val His Thr
        35                  40


<210> 598
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 598
Cys Glu Ala Asn Glu Phe Arg Cys Gln Ser Thr Asp Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Val Cys Asp Gly Val Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Thr Thr Ser Gly His Thr
        35                  40


<210> 599
```

```
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 599
Cys Glu Ala Ser Glu Phe Thr Cys Asn Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15


Leu Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Lys Ser Cys Thr Thr Ser Val Arg Thr
        35                  40


<210> 600
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 600
Cys Ala Pro Asn Glu Phe Thr Cys Ser Ser Thr Gly Arg Cys Leu Pro
1               5                   10                  15


Arg Ala Trp Val Cys Asp Gly Val Asp Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Thr Ser Cys Gly Ala Thr Val His Thr
        35                  40


<210> 601
<211> 44
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
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<400> 601
Cys Gly Ala Asn Glu Phe Thr Cys Gln Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gln Ser Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30
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Glu Ser Pro Val Leu Cys Ala Thr Thr Val His Thr
        35   40

<210> 602
<211> 42
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
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<400> 602
Cys Gln Pro Asp Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Leu Pro
1   5   10   15

Gln Glu Trp Leu Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asp Cys Gly Thr Ser Ala His Thr
        35   40

<210> 603
<211> 42
<212> PRT
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<220>
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<400> 603
Cys Ala Pro Gly Glu Phe Pro Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Gln Thr Trp Val Cys Asp Gly Val Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys Ala Thr Ala Glu His Thr
        35   40

<210> 604
<211> 35
<212> PRT
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<220>
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<223> Variable amino acid

<400> 604
Cys Xaa Xaa Xaa Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Pro Xaa
1               5                   10                  15


Xaa Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20                  25                  30


Thr Xaa Cys
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<210> 605
<211> 36
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<220>
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<223> Variable amino acid

<400> 605
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Cys Pro Pro Xaa Glu Phe Pro Cys Xaa Asn Gly Xaa Cys Ile Pro Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Asp Xaa Asp Cys Xaa Asp Asn Ser Asp Glu
            20                  25                  30


Glu Gly Cys Thr
        35
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<210> 606
<211> 38
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<223> Variable amino acid

<400> 606
Cys Xaa Ala Gly Glu Phe Arg Cys Xaa Xaa Gly Arg Cys Ile Pro Leu
1   5   10   15

Xaa Trp Xaa Cys Asp Gly Asp Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20   25   30

Xaa Asp Cys Glu Ser Ser
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<210> 607
<211> 36
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<223> Variable amino acid

<400> 607
Cys Pro Ser Gly Glu Phe Arg Cys Ser Asn Gly Xaa Cys Ile Pro Gln
1   5   10   15

Xaa Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20   25   30

Xaa Xaa Cys Ala
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<210> 608
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<223> Variable amino acid

<400> 608
Cys Xaa Ala Asp Glu Phe Lys Cys Gly Asn Gly Arg Cys Ile Pro Xaa
1               5                   10                  15


Xaa Trp Val Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asp Ser Asp Glu
            20                  25                  30


Xaa Ser Cys
        35


<210> 609
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<220>
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<223> Variable amino acid

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<222> (33)..(34)
<223> Variable amino acid

<400> 609
Cys Pro Ala Xaa Glu Phe Xaa Cys Xaa Asn Gly Arg Cys Ile Pro Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Asp Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Cys
        35


<210> 610
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<400> 610
Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Asn Gly Xaa Cys Ile Pro Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Xaa Asp Asp Cys Gly Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Cys
        35


<210> 611
<211> 99
<212> PRT
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<220>
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<400> 611
Cys Gln Ala Ser Asp Gln Phe Glu Cys Lys Ser Thr Gly Arg Cys Ile
1               5                   10                  15
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Pro Leu Ala Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser
            20                  25                  30


Asp Glu Ser Pro Ala Ile Cys Gly Arg Pro Gly Leu Glu Ala Ser Gly
        35                  40                  45


Gly Ser Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys
    50                  55                  60


Ile Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly
65                  70                  75                  80


Ser Asp Glu Ala Ser Cys Gly Arg Pro Gly Pro Gly Gly Thr Ser Ala
                85                  90                  95


Pro Ala Ala



<210> 612
<211> 109
<212> PRT
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<220>
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      polypeptide


<220>
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<400> 612
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Ala Pro Asp Leu Cys Ala Ser Ala Ala Pro Thr Ser Leu Gln Ala
        35                  40                  45


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


Glu Cys Arg Ser Thr Gly Arg Cys Ile Pro Ala Ala Trp Val Cys Asp
65                  70                  75                  80
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Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Ser Pro Ala Ile Cys
                85   90   95

Gly Arg Pro Gly Leu Gly Xaa Thr Ser Ala Pro Ala Ala
            100   105

<210> 613
<211> 82
<212> PRT
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<220>
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<220>
<221> MOD_RES
<222> (82)..(82)
<223> Variable amino acid

<400> 613
Cys Glu Ser Gly Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Gln Leu Cys Thr Ala His Thr Cys Ala Pro Gly Glu Phe Gln
        35   40   45

Cys His Ser Thr Gly Arg Cys Ile Pro Ala Ser Trp Leu Arg Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Ser Xaa Leu Cys Thr Ala
65   70   75   80

His Xaa

<210> 614
<211> 108
<212> PRT
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<220>
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      polypeptide

<400> 614
Cys Arg Ser Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20   25   30

Glu Ser Pro Ala Ile Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr
        35   40   45

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

Cys Arg Ser Thr Asn Arg Cys Ile Pro Leu Gln Trp Val Cys Asp Gly
65   70   75   80

Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Asn Cys Gly Asp Ser
                85   90   95

His Ile Leu Pro Phe Ser Thr Pro Gly Pro Ser Thr
            100   105

<210> 615
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<212> PRT
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<400> 615
Cys Leu Ala Asn Glu Phe Thr Cys Arg Ser Thr Gly Arg Cys Ile Pro
1   5   10   15

Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp

20 25 30

Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Gly Leu Glu Ala Ser
35 40 45

Xaa Gly Ser Cys Xaa Xaa Ser Gln Phe Xaa Cys Arg Ser Thr Gly Arg
50 55 60

Cys Ile Pro Ala Glu Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp
65 70 75 80

Ser Ser Asp Glu Ala Ser Cys Gly Asp Ser His Ile Leu Pro Phe Ser
85 90 95

Thr Pro Gly Pro Ser Thr
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<210> 616
<211> 106
<212> PRT
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<220>
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polypeptide

<400> 616
Cys Ala Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1 5 10 15

Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
20 25 30

Glu Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
35 40 45

Leu Glu Ala Ser Gly Gly Ser Cys Gln Thr Gly Glu Phe Arg Cys Arg
50 55 60

Ser Thr Asp Arg Cys Ile Pro Ala Glu Trp Val Cys Asp Gly Asp Ser
65 70 75 80

Asp Cys Glu Asp Gly Ser Asp Glu Thr Asn Cys Gly Asp Ser His Ile
85 90 95

Leu Pro Phe Ser Thr Pro Gly Pro Ser Thr
100 105

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<220>
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<400> 617
Cys Ala Ser Ser Glu Phe Arg Cys Arg Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser Gly Gly Ser Cys Ala Ala Asp Gln Phe Gln Cys Arg
    50                  55                  60


Ser Thr Gly Arg Cys Ile Pro Arg Thr Trp Leu Cys Asp Gly Val Asn
65                  70                  75                  80


Asp Cys Glu Asp Gly Ser Asp Glu Pro Leu Ala Leu Cys Ser Ala Pro
                85                  90                  95


Ala Ser Glu Pro Pro Gly Ser Leu
            100


<210> 618
<211> 102
<212> PRT
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      polypeptide

<400> 618
Cys Glu Ala Ser Glu Phe Thr Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Leu Gln Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Gly Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly
        35                  40                  45


Leu Glu Ala Ser Gly Gly Ser Cys Gly Ser Asn Gln Phe Thr Cys Arg
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    50                  55                  60

Ser Thr Lys Arg Cys Ile Thr Ala Thr Trp Val Cys Asp Gly Asp Asn
65                  70                  75                  80

Asp Cys Glu Asp Ser Ser Asp Glu Thr Asp Cys Ser Ala Pro Ala Ser
                85                  90                  95

Glu Pro Pro Gly Ser Leu
            100


<210> 619
<211> 87
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      polypeptide


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<400> 619
Cys Gly Ser Asp Glu Phe Gln Cys Lys Ser Thr Ser Arg Cys Ile Pro
1               5                   10                  15

Leu Thr Trp Arg Cys Asp Gly Asp Ser Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30

Glu Ala Asn Cys Gly Arg Pro Gly Leu Glu Ala Ser Gly Gly Ser Cys
        35                  40                  45

Gln Ser Gly Gln Phe Gln Cys Xaa Ser Thr Gly Arg Cys Ile Pro Arg
    50                  55                  60

Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu
65                  70                  75                  80

Lys Asn Cys Gln Pro Pro Thr
                85


<210> 620
<211> 96
<212> PRT
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<220>
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<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 620
Cys Glu Ser Asn Glu Phe Gln Cys Gln Ser Thr Ser Arg Cys Ile Pro
1 5 10 15

Leu Thr Trp Arg Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
20 25 30

Glu Lys Ser Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Leu Glu Ala
35 40 45

Ser Gly Gly Ser Cys Pro Ala Ser Glu Phe Thr Cys Arg Ser Thr Gly
50 55 60

Arg Cys Ile Ser Gln Gly Trp Val Cys Asp Gly Asp Asn Asp Cys Glu
65 70 75 80

Asp Ser Ser Asp Glu Ser Pro Ala Ile Cys Ala Thr Thr Gly Pro Thr
85 90 95

<210> 621
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Ile Pro Leu Thr Trp Arg Cys Asp Gly Asp Ser Asp Cys Glu Asp Ser
            20                  25                  30

Ser Asp Glu Ala Xaa Xaa Xaa Xaa Asn Cys Gly Xaa Xaa Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Gly Ser Cys Gln Xaa Xaa
65                  70                  75                  80

Ser Xaa Xaa Gln Phe Gln Cys Xaa Ser Thr Gly Arg Cys Ile Pro Arg
                85                  90                  95

Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu
            100                 105                 110

Lys Xaa Xaa Xaa Xaa Cys Gln Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa
145
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<211> 79
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<400> 627
Cys Xaa Ala Xaa Gln Phe Thr Cys Asp Asn Gly Gln Cys Leu Pro Gln
1   5   10   15

Asn Trp Val Cys Asp Gly Glu Asn Asp Cys Pro Asp Xaa Ser Asp Glu
            20   25   30

Lys Asn Cys Ala Pro His Thr Cys Pro Ser Gly Glu Phe Gln Cys Arg
        35   40   45

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65   70   75

<210> 628
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

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Cys Gln Pro Gly Glu Phe Thr Cys Asn Asn Gly Asn Cys Leu Pro Leu
1   5   10   15

Glu Trp Val Cys Asp Gly Glu Asn Asp Cys Gly Asp Ser Ser Asp Glu
            20   25   30

Glu Asn Cys Gly Gly Ser Glu His Thr Cys Pro Ser Gly Glu Phe Gln
        35   40   45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65   70   75   80

Thr

<210> 629
<211> 81
<212> PRT
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      polypeptide

<400> 629
Cys Leu Ala Gly Glu Phe Arg Cys Asn Ser Gly Arg Cys Ile Pro Glu
1               5                   10                  15


His Trp Arg Cys Asp Gly Glu Asp Asp Cys Leu Asp Ser Ser Asp Glu
            20                  25                  30


Lys Asp Cys Thr Thr Ser Glu Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35                  40                  45


Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50                  55                  60


Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65                  70                  75                  80


Thr




<210> 630
<211> 81
<212> PRT
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<220>
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      polypeptide


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<400> 630
Cys Pro Ser Gly Glu Phe Arg Cys Ser Asn Gly Ser Cys Ile Pro Gln
1               5                   10                  15


Glu Trp Gly Cys Asp Gly Xaa Asn Asp Cys Gly Asp Asp Ser Asp Glu
            20                  25                  30


Lys Asn Cys Ala Ala Ala Gly Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35                  40                  45


Cys Arg Ser Thr Asn Arg Cys Ile Pro Lys Thr Trp Leu Cys Asp Gly
    50                  55                  60


Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
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65   70   75   80

Thr

<210> 631
<211> 82
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 631
Cys Pro Ser Gly Glu Phe Arg Cys Gln Ser Ser Asn Thr Cys Ile Pro
1   5   10   15

Leu Asn Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Asp Ser Asp
            20   25   30

Glu Lys Asn Cys Glu Ala Ser Val Pro Thr Cys Pro Ser Gly Glu Phe
        35   40   45

Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp
    50   55   60

Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro
65   70   75   80

Pro Thr

<210> 632
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 632
Cys Ala Ser Asn Gln Phe Arg Cys Arg Asn Gly Arg Cys Ile Pro Leu
1   5   10   15

Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gln Asp Asn Ser Asp Glu
            20   25   30

Ala Ser Cys Ala Ala Pro Ala Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35   40   45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65   70   75   80

Thr

<210> 633
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
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      polypeptide

<400> 633
Cys Ala Ser Asn Gln Phe Arg Cys Arg Asn Gly Arg Cys Ile Pro Leu
1   5   10   15

Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gln Asp Asn Ser Asp Glu
            20   25   30

Ala Ser Cys Ala Ala Pro Ala Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35   40   45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65   70   75   80

Thr

<210> 634
<211> 79
<212> PRT
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<220>
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      polypeptide

<220>
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<223> Variable amino acid

<400> 634
Cys Ala Ser Asn Gln Phe Thr Cys Asn Asn Gly His Cys Leu Pro Gln
1   5   10   15

His Trp Arg Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

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

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Xaa Xaa Thr
65   70   75

<210> 635
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<212> PRT
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<220>
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      polypeptide

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<223> Variable amino acid

<400> 635
Cys Gln Ala Asp Glu Phe Arg Cys Gly Asn Gly Arg Cys Ile Ser Pro
1   5   10   15

Thr Trp Val Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asp Ser Asp Glu
            20   25   30

Ala Asn Cys Ala Thr Thr Glu Arg Thr Cys Pro Ser Gly Glu Phe Gln
        35   40   45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65   70   75   80

Thr

<210> 636
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<220>
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<400> 636
Cys Pro Pro Asp Glu Phe Lys Cys Gly Asn Gly His Cys Ile Ser Gln
1   5   10   15

Thr Trp Leu Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

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

Xaa Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65   70   75

<210> 637
<211> 81
<212> PRT
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<220>
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      polypeptide

<400> 637
Cys Pro Pro Asp Glu Phe Arg Cys Ser Asn Gly Arg Cys Leu Pro Gln
1   5   10   15

Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Thr Ser Cys Ala Thr Thr Ala Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35   40   45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50   55   60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65   70   75   80

Thr

<210> 638
<211> 79
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

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Cys Val Ala Asn Glu Phe Lys Cys Gly Ser Gly Lys Cys Ile Pro Glu
1   5   10   15

Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

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

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65   70   75

<210> 639
<211> 81
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 639
Cys Gly Ala Asn Glu Phe Lys Cys Ser Ser Gly Ser Cys Ile Pro Gln
1   5   10   15

Glu Trp Arg Cys Asp Gly Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu

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            20                  25                  30

Ser Leu Ala Pro Cys Lys Glu Pro Thr Cys Pro Ser Gly Glu Phe Gln
        35                  40                  45

Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly
    50                  55                  60

Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro
65                  70                  75                  80

Thr



<210> 640
<211> 79
<212> PRT
<213> Artificial Sequence

<220>
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      polypeptide

<400> 640
Cys Arg Ala Asp Glu Phe Lys Cys Gly Asn Gly His Cys Ile Pro Gly
1               5                   10                  15

Gln Trp Leu Cys Asp Gly Glu Asn Asp Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30

Lys Ser Cys Glu Gln Pro Thr Cys Pro Ser Gly Glu Phe Gln Cys Arg
        35                  40                  45

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50                  55                  60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65                  70                  75


<210> 641
<211> 82
<212> PRT
<213> Artificial Sequence

<220>
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      polypeptide


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<222> (19)..(19)
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<220>
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<223> Variable amino acid

<400> 641

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1               5                   10                  15


Leu Ala Xaa Leu Cys Xaa Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp
            20                  25                  30


Glu Ala Ser Cys Glu Ser Ser Glu Pro Thr Cys Pro Ser Gly Glu Phe
        35                  40                  45


Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp
    50                  55                  60


Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro
65                  70                  75                  80


Pro Thr
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<210> 642
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<212> PRT
<213> Artificial Sequence

<220>
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<223> Asp or Glu

<220>
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<400> 642

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1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Gly Xaa Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60
```

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80


Xaa Xaa Xaa Xaa Xaa Xaa Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 643
<211> 94
<212> PRT
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<220>
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      polypeptide


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<222> (17)..(17)
<223> Ile, Leu or Val

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            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Xaa
    50   55   60

Thr Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp
65   70   75   80

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Xaa Xaa Thr
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            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Xaa
    50   55   60

Thr Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp
65   70   75   80

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Xaa Xaa Thr
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Xaa Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa
            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Xaa
    50   55   60

Thr Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp
65   70   75   80

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Xaa
    50                  55                  60


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Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45
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Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
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        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
    50                  55                  60

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65                  70                  75                  80

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Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Gly Xaa Cys
1               5                   10                  15
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Xaa Pro Xaa Xaa Trp Xaa Cys Asp Gly Glu Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
    50                  55                  60

Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
65                  70                  75                  80

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
                85                  90
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<210> 650
<211> 94
<212> PRT
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<220>
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polypeptide

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<220>
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<223> Variable amino acid that may or may not be present

<400> 650

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1               5                   10                  15


Xaa Pro Xaa Xaa Trp Xaa Cys Asp Gly Glu Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
    50                  55                  60


Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
65                  70                  75                  80


Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
                85                  90


<210> 651
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
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<222> (11)..(11)
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<220>
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<223> Variable amino acid that may or may not be present

<400> 651
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Asn Gly Xaa Cys
1               5                   10                  15
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Xaa Pro Xaa Xaa Trp Val Cys Asp Gly Glu Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
    50                  55                  60

Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
65                  70                  75                  80

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
                85                  90
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<210> 652
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
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<222> (4)..(4)
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<220>
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<222> (5)..(5)
<223> Glu or Gln

<220>
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<222> (7)..(7)
<223> Lys or Arg

<220>
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<222> (9)..(9)
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<223> Ile, Leu or Val

<220>
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<223> Ile, Leu or Val

<220>
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<223> Asp or Asn

<220>
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<400> 652
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Asn Gly Xaa Cys
1               5                   10                  15


Xaa Pro Xaa Xaa Trp Xaa Cys Asp Gly Glu Xaa Asp Cys Xaa Asp Xaa
            20                  25                  30


Ser Asp Glu Xaa Ser Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser
    50                  55                  60


Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
65                  70                  75                  80


Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
                85                  90


<210> 653
<211> 90
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 653
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30


Glu Ser Leu Ala Leu Cys Gly Arg Pro Gly Pro Ala Thr Ser Ala Pro
        35                  40                  45


Ala Ala Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys
    50                  55                  60


Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly
65                  70                  75                  80
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Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
                85                  90


<210> 654
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 654
Cys Pro Ser Gly Glu Phe Gln Cys Arg Ser Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Ser Cys Thr Pro Pro Thr Cys Pro Pro Gly Phe Gln Cys Arg
        35                  40                  45


Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50                  55                  60


Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65                  70                  75                  80


<210> 655
<211> 83
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


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<220>
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<400> 655
Cys Gln Ser Phe Thr Glu Phe Glu Cys His Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Pro Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser
            20                  25                  30


Asp Glu Glu Gly Cys Glu Ala Ala Ala Pro Thr Cys Pro Ser Gly Phe
        35                  40                  45


Arg Cys Arg Xaa Thr Xaa Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp
    50                  55                  60


Gly Asp Asn Asp Cys Glu Asp Gly Ser Xaa Glu Glu Ser Cys Thr Pro
65                  70                  75                  80


Pro Thr Glu



<210> 656
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 656
Cys Arg Ala Asn Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Ser Trp Leu Cys Asp Gly Asp Asn Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Ser Gln Leu Cys Thr Ala His Thr Cys Pro Ser Gly Phe Gln Cys
        35                  40                  45


Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp
    50                  55                  60


Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Glu
65                  70                  75                  80


<210> 657
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<211> 79
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
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<222> (2)..(2)
<223> Variable amino acid

<400> 657
Cys Xaa Pro Gly Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Pro Ala
1   5   10   15

Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Thr Gly Cys Thr Glu His Thr Cys Pro Ser Gly Phe Gln Cys Arg Ser
        35   40   45

Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
    50   55   60

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65   70   75

<210> 658
<211> 79
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (2)..(2)
<223> Variable amino acid

<400> 658
Cys Xaa Pro Gly Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Pro Ala
1   5   10   15

Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Thr Gly Cys Thr Glu His Thr Cys Pro Ser Gly Phe Gln Cys Arg Ser
        35   40   45

```
Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp
    50                  55                  60


Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65                  70                  75


<210> 659
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 659
Cys Gln Ser Asn Glu Phe Gln Cys Asn Asn Gly Arg Cys Ile Ser Val
1               5                   10                  15


Thr Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Ser Ser Asp Glu
            20                  25                  30


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


Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp
    50                  55                  60


Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65                  70                  75                  80


Glu




<210> 660
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 660
Cys Pro Ser Ser Glu Phe Gln Cys Arg Asn Asn Lys Thr Cys Ile Pro
1               5                   10                  15


Arg Asn Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30
```

Glu Thr Asp Cys Thr Thr His Thr Cys Pro Ser Gly Phe Gln Cys Arg
        35   40   45

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65   70   75   80

<210> 661
<211> 79
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
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<222> (55)..(55)
<223> Variable amino acid

<400> 661
Cys Leu Pro Ser Glu Phe Pro Cys Ser Asn Gly Arg Cys Val Pro Arg
1   5   10   15

Pro Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Asn Ser Asp Glu
            20   25   30

Ala Gly Cys Pro Lys Pro Thr Cys Pro Ser Gly Phe Gln Cys Arg Ser
        35   40   45

Thr Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp
    50   55   60

Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65   70   75

<210> 662
<211> 81
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 662
Cys Pro Pro Ser Glu Phe Pro Cys Gly Asn Gly Ser Cys Val Pro Gln
1   5   10   15

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Ala Trp Val Cys Asp Gly Asp Pro Asp Cys Pro Asp Asn Ser Asp Glu
            20                  25                  30


Glu Gly Cys Thr Gly Thr Gly Pro Thr Cys Pro Ser Gly Phe Gln Cys
        35                  40                  45


Arg Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp
    50                  55                  60


Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65                  70                  75                  80


Glu




<210> 663
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 663
Cys Leu Pro Asn Gln Phe Gln Cys Gln Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Asn Trp Leu Cys Asp Gly Asp Asp Asp Cys Gly Asp Asp Ser Asp
            20                  25                  30


Glu Thr Ser Cys Lys Ala Pro Thr Cys Pro Ser Gly Phe Gln Cys Arg
        35                  40                  45


Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50                  55                  60


Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65                  70                  75                  80


<210> 664
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
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<400> 664
Cys Gln Ala Asp Glu Phe Gln Cys Arg Asn Thr Glu Lys Cys Leu Pro
1   5   10   15

Leu Asn Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asp Ser Asp
            20   25   30

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

Ser Thr Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn
    50   55   60

Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr Glu
65   70   75   80

<210> 665
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 665
Cys Gln Pro Asp Glu Phe Arg Cys Arg Asn Thr Asp Ile Cys Ile Pro
1   5   10   15

Gln Arg Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp
            20   25   30

Glu Ala Asp Cys Gln Gln Pro Thr Cys Arg Ala Asn Glu Phe Gln Cys
        35   40   45

His Ser Thr Gly Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp
    50   55   60

Asn Asp Cys Glu Asp Gly Ser Asp Glu Glu Ser Cys Thr Pro Pro Thr
65   70   75   80

<210> 666
<211> 119
<212> PRT
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<220>
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      polypeptide

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<223> Variable amino acid that may or may not be present

<220>
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<223> Glu or Gln

<220>
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<223> Variable amino acid

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<223> Variable amino acid

<220>
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<223> Variable amino acid that may or may not be present

<220>
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<220>
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<220>
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<223> Ile, Leu or Val

<220>
<221> MOD_RES
<222> (20)..(22)
<223> Variable amino acid

<220>
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<222> (24)..(24)
<223> Ile, Leu or Val

<220>
<221> MOD_RES
<222> (28)..(28)
<223> Asp or Glu

<220>

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<223> Variable amino acid that may or may not be present

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Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Xaa Cys Arg Xaa Thr
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Xaa Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Gln Cys Arg Ser Thr
65                  70                  75                  80


Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
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Asn Arg Cys Ile Pro Xaa Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
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Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Gln Cys Arg Ser Thr
65                  70                  75                  80


Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Gln Cys Arg Ser Thr
65                  70                  75                  80

Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
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            20                  25                  30


Xaa Asp Cys Gly Asp Xaa Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60


Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Gln Cys Arg Ser Thr
65                  70                  75                  80


Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
                85                  90                  95


Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Asp Asp Cys Gly Asp Xaa Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60


Xaa Xaa Thr Cys Pro Xaa Xaa Xaa Xaa Gly Phe Gln Cys Arg Ser Thr
65                  70                  75                  80


Asn Arg Cys Ile Pro Glu Thr Trp Leu Cys Asp Gly Asp Asn Asp Cys
                85                  90                  95


Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            100                 105                 110


Xaa Thr Pro Pro Thr Xaa Xaa
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            20                  25                  30


Glu Ser Pro Ala Asn Cys Ala Thr Pro Thr His Thr Cys Pro Ala Ser
        35                  40                  45


Glu Phe Gln Cys His Ser Thr Gly Arg Cys Ile Pro Ala Ser Trp Leu
    50                  55                  60


Cys Asp Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys
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Thr Thr Pro Glu Pro Thr
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Cys Ala Pro Gly Gln Phe Arg Cys Lys Asn Gly Arg Cys Val Pro Leu
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            20                  25                  30


Ala Asn Cys Glu Ser Pro Glu Pro Thr Cys Glu Ser Gly Glu Phe Gln
        35                  40                  45


Cys His Ser Thr Gly Arg Cys Ile Pro Ala Ser Trp Leu Cys Asp Gly
    50                  55                  60


Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Thr Thr Pro
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Glu Pro Thr



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            20                  25                  30


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


Gln Cys Asn Ser Thr Gly Arg Cys Ile Pro Val Ser Trp Val Cys Asp
    50                  55                  60
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Gly Val Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Ala Thr
65                  70                  75                  80


Ser Gly Pro Thr



<210> 680
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            20                  25                  30


Ala Asp Cys Gln Ala Pro Thr Cys Ala Ala Asp Glu Phe Gln Cys Asn
        35                  40                  45


Ser Thr Gly Arg Cys Ile Pro Val Ser Trp Val Cys Asp Gly Xaa Asn
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Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Ala Thr Ser Gly Pro
65                  70                  75                  80


Thr



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1               5                   10                  15
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            20                  25                  30


Glu Glu Asp Cys Thr Ser Ala Gly His Thr Cys Ala Pro Ser Glu Phe
        35                  40                  45


Thr Cys Asn Ser Thr Gly Arg Cys Ile Pro Gln Glu Trp Val Cys Asp
    50                  55                  60


Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Pro Asp Leu Cys
65                  70                  75                  80


Ala Ser Ala Ala Pro Thr
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Thr Trp Leu Xaa Xaa Gly Xaa Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ala Asp Cys Ala Thr Thr Ala Pro Thr Cys Pro Pro Asp Glu Phe Thr
        35                  40                  45


Cys Arg Ser Thr Glu Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly
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Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Thr Thr Pro
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Asp Trp Leu Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Thr Ser Cys Ala Ala Ser Glu Pro Thr Cys Pro Pro Asp Glu Phe Thr
        35                  40                  45


Cys Arg Ser Thr Glu Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly
    50                  55                  60


Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Thr Thr Pro
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Glu Pro Thr



<210> 684
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Glu Asn Trp Val Cys Asp Gly Asp Asp Asp Cys Glu Asp Ser Ser Asp
            20                  25                  30


Glu Lys Ser Cys Thr Ser Ala Ala Pro Thr Cys Pro Pro Asp Glu Phe
        35                  40                  45
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Thr Cys Arg Ser Thr Glu Arg Cys Ile Pro Leu Ala Trp Val Cys Asp
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Gly Asp Asn Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Thr Thr
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Pro Glu Pro Thr

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Asn Trp Arg Cys Asp Gly Glu Xaa Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Glu Asn Cys Thr Thr Pro Thr Cys Pro Pro Asp Glu Phe Thr Cys Arg
        35   40   45

Ser Thr Glu Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly Asp Asn
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Asp Cys Glu Asp Ser Ser Asp Glu Ala Gly Cys Thr Thr Pro Glu Pro
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<210> 686
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            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Thr Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Ser Thr Xaa
    50   55   60

Arg Cys Ile Pro Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu
65   70   75   80

Asp Ser Ser Asp Glu Ala Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
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Pro Thr

<210> 687
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Thr Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Ser Thr Xaa
    50                  55                  60


Arg Cys Ile Pro Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu
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Pro Thr
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Thr Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Ser Thr Xaa
    50                  55                  60


Arg Cys Ile Pro Xaa Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Glu
65                  70                  75                  80


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Pro Thr
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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Thr Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Ser Thr Xaa
    50                  55                  60


Arg Cys Ile Pro Xaa Xaa Trp Xaa Cys Asp Gly Asp Asn Asp Cys Glu
65                  70                  75                  80


Asp Ser Ser Asp Glu Ala Gly Xaa Xaa Xaa Xaa Cys Thr Thr Pro Glu
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Pro Thr




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            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Thr Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Ser Thr Xaa
    50   55   60

Arg Cys Ile Pro Xaa Xaa Trp Xaa Cys Asp Gly Asp Asn Asp Cys Glu
65   70   75   80

Asp Ser Ser Asp Glu Ala Gly Xaa Xaa Xaa Xaa Cys Thr Thr Pro Glu
                85   90   95

Pro Thr

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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Pro Thr Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu
    50                  55                  60


Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu
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Asp Ser Ser Asp Glu Ala Gly Xaa Xaa Xaa Xaa Cys Thr Thr Pro Glu
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                85                  90                  95

Pro Thr



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1               5                   10                  15


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            20                  25                  30


Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Pro Thr Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu
    50                  55                  60


Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu
65                  70                  75                  80


Asp Ser Ser Asp Glu Ala Gly Xaa Xaa Xaa Xaa Cys Thr Thr Pro Glu
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Pro Thr
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Xaa Pro Xaa Asn Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa
            20   25   30

Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Thr Xaa Xaa Xaa
        35   40   45

Xaa Xaa Pro Thr Cys Pro Pro Asp Glu Phe Thr Cys Arg Ser Thr Glu
    50   55   60

Arg Cys Ile Pro Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu
65   70   75   80

Asp Ser Ser Asp Glu Ala Gly Xaa Xaa Xaa Xaa Cys Thr Thr Pro Glu
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Pro Thr

<210> 694
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<212> PRT
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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
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Met Trp Trp Arg Cys Asp Gly Val Pro Asp Cys Pro Asp Asn Ser Asp
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Glu Lys Ser Cys Glu Pro Pro Thr
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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Pro Asp Cys Val Asp Asn Ser Asp
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Glu Thr Ser Cys Thr Ser Thr Val His Thr
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1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Pro Asp Cys Ala Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asp Cys Gln Gln His Thr
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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Asn Asp Cys Gly Asp Gly Ser Asp
            20                  25                  30


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


Ala




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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Pro Asp Cys Leu Asp Ser Ser Asp
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Glu Lys Ser Cys Asn Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35                  40                  45


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1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Pro Asp Cys Arg Asp Gly Ser Asp
            20                  25                  30


Glu Ala Pro Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser
        35                  40                  45


Leu



<210> 700
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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
1               5                   10                  15


Gln Trp Trp Val Cys Asp Gly Val Pro Asp Cys Arg Asp Gly Ser Asp
            20                  25                  30


Glu Pro Glu Gln Cys Thr Pro Pro Thr
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Cys Leu Ser Ser Gln Phe Arg Cys Arg Asp Thr Gly Ile Cys Val Pro
1               5                   10                  15


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Glu Lys Gly Cys Gly Arg Thr Gly His Thr
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Gln Trp Trp Val Cys Asp Gly Val Pro Asp Cys Arg Asp Gly Ser Asp
            20                  25                  30


Glu Ala Ala Val Cys Gly Arg Pro Gly His Thr
        35                  40


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            20                  25                  30


Glu Ala Pro Ala His Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser
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Leu



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Xaa Trp Trp Xaa Cys Asp Gly Val Xaa Asp Cys Xaa Asp Xaa Ser Asp
            20   25   30

Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa
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<211> 67
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1               5                   10                  15


Xaa Trp Trp Xaa Cys Asp Gly Val Pro Asp Cys Xaa Asp Xaa Ser Asp
            20                  25                  30


Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa
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            20                  25                  30


Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45
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Xaa Xaa Xaa
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<210> 707
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<400> 707
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Cys Ala Ser Gly Gln Phe Gln Cys Arg Ser Thr Ser Ile Cys Val Pro
1               5                   10                  15


Met Trp Trp Arg Cys Asp Gly Val Xaa Asp Cys Xaa Asp Xaa Ser Asp
            20                  25                  30
```

```
Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60


Xaa Xaa Xaa
65


<210> 708
<211> 47
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 708
Cys Gly Ala Ser Glu Phe Thr Cys Arg Ser Ser Ser Arg Cys Ile Pro
1               5                   10                  15


Gln Ala Trp Val Cys Asp Gly Glu Asn Asp Cys Arg Asp Asn Ser Asp
            20                  25                  30


Glu Ala Asp Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35                  40                  45


<210> 709
<211> 47
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 709
Cys Arg Ser Asn Glu Phe Thr Cys Arg Ser Ser Glu Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Arg Asp Asp Ser Asp
            20                  25                  30


Glu Ala Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35                  40                  45


<210> 710
<211> 49
<212> PRT
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<220>
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polypeptide

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Cys Val Ser Asn Glu Phe Gln Cys Arg Gly Thr Arg Arg Cys Ile Pro
1   5   10   15

Arg Thr Trp Leu Cys Asp Gly Leu Pro Asp Cys Gly Asp Asn Ser Asp
            20   25   30

Glu Ala Pro Ala Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser
        35   40   45

Leu

<210> 711
<211> 48
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 711
Cys His Pro Thr Gly Gln Phe Arg Cys Arg Ser Ser Gly Arg Cys Val
1   5   10   15

Ser Pro Thr Trp Val Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser
            20   25   30

Asp Glu Glu Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
        35   40   45

<210> 712
<211> 46
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 712
Cys Gln Ala Gly Glu Phe Gln Cys Gly Asn Gly Arg Cys Ile Ser Pro
1   5   10   15

Ala Trp Val Cys Asp Gly Glu Asn Asp Cys Arg Asp Gly Ser Asp Glu
            20   25   30

Ala Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro Gly Ser Leu
35 40 45

<210> 713
<211> 54
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Cys Xaa Xaa Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Xaa Xaa Xaa Arg
1               5                   10                  15


Cys Xaa Xaa Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp
            20                  25                  30
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```
Xaa Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Ser Ala Pro Ala Ser
        35                  40                  45


Glu Pro Pro Gly Ser Leu
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<210> 714
<211> 54
<212> PRT
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<223> Ile or Val

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<400> 714
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1               5                   10                  15


Cys Xaa Xaa Xaa Xaa Trp Val Cys Asp Gly Xaa Asn Asp Cys Xaa Asp
            20                  25                  30
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```
Xaa Ser Asp Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Ser Ala Pro Ala Ser
        35                  40                  45


Glu Pro Pro Gly Ser Leu
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<400> 715
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Cys Ile Xaa Xaa Ala Trp Val Cys Asp Gly Xaa Asn Asp Cys Arg Asp
            20   25   30

Xaa Ser Asp Glu Xaa Xaa Xaa Xaa Ala Xaa Cys Ser Ala Pro Ala Ser
        35   40   45

Glu Pro Pro Gly Ser Leu
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<210> 716
<211> 29
<212> PRT
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<400> 716
Xaa Phe Xaa Cys Arg Xaa Xaa Xaa Arg Cys Xaa Xaa Xaa Xaa Trp Xaa

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1               5                   10                  15


Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20                  25


<210> 717
<211> 49
<212> PRT
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<220>
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      polypeptide

<400> 717
Cys Pro Pro Ser Gln Phe Thr Cys Lys Ser Asn Asp Lys Cys Ile Pro
1               5                   10                  15


Val His Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30


Glu Ala Asn Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Pro Ala
        35                  40                  45


Ala



<210> 718
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<220>
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Cys Pro Ser Gly Glu Phe Pro Cys Arg Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Arg Asp Asn Ser Asp
            20                  25                  30


Glu Pro Pro Ala Leu Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala
        35                  40                  45


Pro Ala Ala
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<210> 719
<211> 43
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<212> PRT
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<223> Description of Artificial Sequence: Synthetic
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Cys Ala Pro Ser Glu Phe Gln Cys Arg Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Pro Trp Val Cys Asp Gly Glu Asp Asp Cys Arg Asp Gly Ser Asp
            20                  25                  30


Glu Ser Ala Val Cys Gly Ala Pro Ala Pro Thr
        35                  40


<210> 720
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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
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Cys Gln Ala Ser Glu Phe Thr Cys Lys Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Gln Glu Trp Leu Cys Asp Gly Glu Asp Asp Cys Arg Asp Ser Ser Asp
            20                  25                  30


Glu Lys Asn Cys Gln Gln Pro Thr
        35                  40


<210> 721
<211> 40
<212> PRT
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<220>
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      polypeptide

<400> 721
Cys Leu Ser Ser Glu Phe Gln Cys Gln Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Leu Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Arg Asp Asp Ser Asp
            20                  25                  30


Glu Lys Ser Cys Lys Pro Arg Thr
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        35                  40


<210> 722
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<212> PRT
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<220>
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<223> Ile, Leu or Val

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<223> Asp or Glu

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<223> Asp or Asn

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Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp
            20   25   30

Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50   55   60

<210> 723
<211> 62
<212> PRT
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<220>
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1   5   10   15

Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Arg Asp Xaa Ser Asp
            20   25   30

Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50   55   60

<210> 724
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<220>
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<223> Asp or Glu

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<400> 724
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Cys Xaa Xaa Ser Glu Phe Xaa Cys Xaa Ser Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Xaa Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Arg Asp Xaa Ser Asp
            20                  25                  30


Glu Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60
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<210> 725
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 725
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Cys Pro Ala Asn Glu Phe Gln Cys Ser Asn Gly Arg Cys Ile Ser Pro
1               5                   10                  15


Ala Trp Leu Cys Asp Gly Glu Asn Asp Cys Val Asp Gly Ser Asp Glu
            20                  25                  30


Lys Gly Cys Thr Pro Arg Thr
        35
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<210> 726
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 726
Cys Pro Pro Ser Glu Phe Gln Cys Gly Asn Gly Arg Cys Ile Ser Pro
1   5   10   15

Ala Trp Leu Cys Asp Gly Asp Asn Asp Cys Val Asp Gly Ser Asp Glu
            20   25   30

Thr Asn Cys Thr Thr Ser Gly Pro Thr
        35   40

<210> 727
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 727
Cys Pro Pro Gly Glu Phe Gln Cys Gly Asn Gly Arg Cys Ile Ser Ala
1   5   10   15

Gly Trp Val Cys Asp Gly Glu Asn Asp Cys Val Asp Asp Ser Asp Glu
            20   25   30

Lys Asp Cys Pro Ala Arg Thr
        35

<210> 728
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 728
Cys Gly Ser Gly Glu Phe Gln Cys Ser Asn Gly Arg Cys Ile Ser Leu
1   5   10   15

Gly Trp Val Cys Asp Gly Glu Asp Asp Cys Pro Asp Gly Ser Asp Glu
            20   25   30

Thr Asn Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr Pro Gly Pro
        35   40   45

Ser Thr
    50

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<210> 729
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 729
Cys Pro Ala Asp Glu Phe Thr Cys Gly Asn Gly Arg Cys Ile Ser Pro
1               5                   10                  15


Ala Trp Val Cys Asp Gly Glu Pro Asp Cys Arg Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ala Val Cys Glu Thr His Thr
        35                  40


<210> 730
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 730
Cys Pro Ser Asn Glu Phe Thr Cys Gly Asn Gly Arg Cys Ile Ser Leu
1               5                   10                  15


Ala Trp Leu Cys Asp Gly Glu Pro Asp Cys Arg Asp Ser Ser Asp Glu
            20                  25                  30


Ser Leu Ala Ile Cys Ser Gln Asp Pro Glu Phe His Lys Val
        35                  40                  45


<210> 731
<211> 43
<212> PRT
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<220>
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      polypeptide


<220>
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<223> Ile, Leu or Val

<220>
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<223> Asp or Glu

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<223> Variable amino acid that may or may not be present

<220>
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<223> Variable amino acid

<220>
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<222> (40)..(43)
<223> Variable amino acid

<400> 731
Cys Xaa Xaa Xaa Glu Phe Xaa Cys Xaa Asn Gly Arg Cys Ile Ser Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40


<210> 732
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
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<223> Variable amino acid

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<223> Variable amino acid

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<221> MOD_RES
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<223> Variable amino acid

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<222> (19)..(19)
<223> Ile, Leu or Val

<220>
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<222> (23)..(23)
<223> Asp or Glu

<220>
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<223> Variable amino acid

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<223> Variable amino acid that may or may not be present

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<223> Variable amino acid

<400> 732

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Cys Pro Xaa Xaa Glu Phe Xaa Cys Xaa Asn Gly Arg Cys Ile Ser Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40
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<210> 733
<211> 43
<212> PRT
<213> Artificial Sequence

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<220>
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<220>
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<223> Variable amino acid

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<223> Ile, Leu or Val

<220>
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<222> (23)..(23)
<223> Asp or Glu

<220>
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<223> Variable amino acid

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<220>
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<220>
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<223> Variable amino acid

<400> 733

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Cys Pro Xaa Xaa Glu Phe Xaa Cys Gly Asn Gly Arg Cys Ile Ser Xaa
1               5                   10                  15


Xaa Trp Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35                  40
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<210> 734
<211> 43
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polypeptide

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<220>
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<222> (19)..(19)
<223> Ile, Leu or Val

<220>
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<223> Asp or Glu

<220>
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<400> 734
Cys Pro Xaa Xaa Glu Phe Gln Cys Xaa Asn Gly Arg Cys Ile Ser Xaa
1   5   10   15

Xaa Trp Xaa Cys Asp Gly Xaa Asn Asp Cys Val Asp Xaa Ser Asp Glu
            20   25   30

Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
        35   40

<210> 735
<211> 35
<212> PRT
<213> Homo sapiens

<400> 735
Cys Glu Pro Tyr Gln Phe Arg Cys Lys Asn Asn Arg Cys Val Pro Gly
1   5   10   15

Arg Trp Gln Cys Asp Tyr Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu

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            20                  25                  30


Glu Ser Cys
        35


<210> 736
<211> 36
<212> PRT
<213> Homo sapiens

<400> 736
Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn Cys Gly Asp Gly Glu Asp
            20                  25                  30


Glu Arg Asp Cys
        35


<210> 737
<211> 35
<212> PRT
<213> Homo sapiens

<400> 737
Cys Ser Gln Asp Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg
1               5                   10                  15


Gln Phe Val Cys Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ser Cys
        35


<210> 738
<211> 35
<212> PRT
<213> Homo sapiens

<400> 738
Cys Ser Ser Ser Ala Phe Thr Cys Gly His Gly Glu Cys Ile Pro Ala
1               5                   10                  15


His Trp Arg Cys Asp Lys Arg Asn Asp Cys Val Asp Gly Ser Asp Glu
            20                  25                  30


His Asn Cys
        35
```

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<210> 739
<211> 36
<212> PRT
<213> Homo sapiens

<400> 739
Cys Ser Ser Ser Glu Phe Gln Cys Ala Ser Gly Arg Cys Ile Pro Gln
1               5                   10                  15


His Trp Tyr Cys Asp Gln Glu Thr Asp Cys Phe Asp Ala Ser Asp Glu
            20                  25                  30


Pro Ala Ser Cys
        35


<210> 740
<211> 36
<212> PRT
<213> Homo sapiens

<400> 740
Cys His Ser Gln Gly Leu Val Glu Cys Arg Asn Gly Gln Cys Ile Pro
1               5                   10                  15


Ser Thr Phe Gln Cys Asp Gly Asp Glu Asp Cys Lys Asp Gly Ser Asp
            20                  25                  30


Glu Glu Asn Cys
        35


<210> 741
<211> 35
<212> PRT
<213> Homo sapiens

<400> 741
Cys Pro Ala Gln Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys
1               5                   10                  15


Ser Gln Gln Cys Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ser Cys
        35


<210> 742
<211> 34
<212> PRT
<213> Homo sapiens

<400> 742
Cys Glu Gly Phe Val Cys Ala Gln Thr Gly Arg Cys Val Asn Arg Arg
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1               5                   10                  15


Leu Leu Cys Asn Gly Asp Asn Asp Cys Gly Asp Gln Ser Asp Glu Ala
            20                  25                  30


Asn Cys



<210> 743
<211> 36
<212> PRT
<213> Homo sapiens

<400> 743
Cys Thr Lys His Thr Tyr Arg Cys Leu Asn Gly Leu Cys Leu Ser Lys
1               5                   10                  15


Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp Cys Ser Asp Gly Ser Asp
            20                  25                  30


Glu Lys Asp Cys
        35


<210> 744
<211> 38
<212> PRT
<213> Homo sapiens

<400> 744
Cys Leu Gly Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp
1               5                   10                  15


Ile Ser Lys Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp
            20                  25                  30


Glu Pro Leu Lys Glu Cys
        35


<210> 745
<211> 37
<212> PRT
<213> Homo sapiens

<400> 745
Cys Pro Ala Glu Lys Leu Ser Cys Gly Pro Thr Ser His Lys Cys Val
1               5                   10                  15


Pro Ala Ser Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Gly Gly Ala
            20                  25                  30
```

Asp Glu Ala Gly Cys
        35

<210> 746
<211> 41
<212> PRT
<213> Homo sapiens

<400> 746
Cys Thr His Phe Met Asp Phe Val Cys Lys Asn Arg Gln Gln Cys Leu
1   5   10   15

Phe His Ser Met Val Cys Asp Gly Ile Ile Gln Cys Arg Asp Gly Ser
            20   25   30

Asp Glu Asp Ala Ala Phe Ala Gly Cys
        35   40

<210> 747
<211> 40
<212> PRT
<213> Homo sapiens

<400> 747
Cys Ala Tyr Asn Gln Phe Gln Cys Leu Ser Arg Phe Thr Lys Val Tyr
1   5   10   15

Thr Cys Leu Pro Glu Ser Leu Lys Cys Asp Gly Asn Ile Asp Cys Leu
            20   25   30

Asp Leu Gly Asp Glu Ile Asp Cys
        35   40

<210> 748
<211> 35
<212> PRT
<213> Homo sapiens

<220>
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<223> Variable amino acid

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<223> Variable amino acid

<220>
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<222> (29)..(29)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (33)..(34)
<223> Variable amino acid

<400> 748
Cys Xaa Xaa Xaa Xaa Phe Xaa Cys Xaa Xaa Gly Xaa Cys Ile Xaa Xaa
1   5   10   15

Xaa Xaa Xaa Cys Asp Gly Xaa Xaa Asp Cys Xaa Asp Xaa Ser Asp Glu
            20   25   30

Xaa Xaa Cys
        35

<210> 749
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

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<223> Variable amino acid

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<223> Hydrophobic amino acid

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<222> (7)..(7)
<223> Variable amino acid

<220>
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<222> (9)..(12)
<223> Variable amino acid

<220>
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<222> (14)..(14)
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<220>
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<223> Variable amino acid

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<223> Variable amino acid

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<223> Variable amino acid

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<222> (25)..(25)
<223> Negatively charged amino acid

<220>
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<222> (27)..(30)
<223> Variable amino acid

<220>
<221> MOD_RES
<222> (31)..(32)
<223> Negatively charged amino acid

<220>
<221> MOD_RES
<222> (33)..(34)
<223> Variable amino acid

<400> 749
Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1   5   10   15

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Cys
        35

<210> 750
<211> 37
<212> PRT
<213> Homo sapiens

<400> 750
Cys Asn Pro Gly Gln Phe Ala Cys Arg Ser Gly Thr Ile Gln Cys Ile
1   5   10   15

Pro Leu Pro Trp Gln Cys Asp Gly Trp Ala Thr Cys Glu Asp Glu Ser
            20   25   30

Asp Glu Ala Asn Cys
        35

<210> 751
<211> 35
<212> PRT
<213> Homo sapiens

<400> 751
Cys Gln Ala Asp Glu Phe Arg Cys Asp Asn Gly Lys Cys Leu Pro Gly
1   5   10   15

Pro Trp Gln Cys Asn Thr Val Asp Glu Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Gly Asn Cys
        35

<210> 752
<211> 38
<212> PRT
<213> Homo sapiens

<400> 752
Cys Pro Gly Gly Thr Phe Pro Cys Ser Gly Ala Arg Ser Thr Arg Cys
1   5   10   15

Leu Pro Val Glu Arg Arg Cys Asp Gly Leu Gln Asp Cys Gly Asp Gly

            20   25   30

Ser Asp Glu Ala Gly Cys
        35

<210> 753
<211> 46
<212> PRT
<213> Homo sapiens

<400> 753
Cys Leu Pro Trp Glu Gln Pro Cys Gly Ser Ser Ser Asp Ser Asp Gly
1   5   10   15

Gly Ser Leu Gly Asp Gln Gly Cys Phe Ser Glu Pro Gln Arg Cys Asp
            20   25   30

Gly Trp Trp His Cys Ala Ser Gly Arg Asp Glu Gln Gly Cys
        35   40   45

<210> 754
<211> 37
<212> PRT
<213> Homo sapiens

<400> 754
Cys Pro Pro Asp Gln Tyr Pro Cys Glu Gly Gly Ser Gly Leu Cys Tyr
1   5   10   15

Thr Pro Ala Asp Arg Cys Asn Asn Gln Lys Ser Cys Pro Asp Gly Ala
            20   25   30

Asp Glu Lys Asn Cys
        35

<210> 755
<211> 35
<212> PRT
<213> Homo sapiens

<400> 755
Cys Gln Pro Gly Thr Phe His Cys Gly Thr Asn Leu Cys Ile Phe Glu
1   5   10   15

Thr Trp Arg Cys Asp Gly Gln Glu Asp Cys Gln Asp Gly Ser Asp Glu
            20   25   30

His Gly Cys
        35

<210> 756
<211> 37
<212> PRT
<213> Homo sapiens

<400> 756
Cys Ser Pro Asp Gln Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile
1   5   10   15

Pro Gly Ala Trp Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser
            20   25   30

Asp Glu Glu Gly Cys
        35

<210> 757
<211> 35
<212> PRT
<213> Homo sapiens

<400> 757
Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly Gln Cys Val Asp Leu
1   5   10   15

Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln Asp Arg Ser Asp Glu
            20   25   30

Val Asp Cys
        35

<210> 758
<211> 35
<212> PRT
<213> Homo sapiens

<400> 758
Cys Leu Pro Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile
1   5   10   15

Lys Gln Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu
            20   25   30

Leu Met Cys
        35

<210> 759
<211> 37
<212> PRT
<213> Homo sapiens

<400> 759
Cys Ser Pro Gln Gln Phe Thr Cys Phe Thr Gly Glu Ile Asp Cys Ile

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1               5                   10                  15


Pro Val Ala Trp Arg Cys Asp Gly Phe Thr Glu Cys Glu Asp His Ser
            20                  25                  30


Asp Glu Leu Asn Cys
        35


<210> 760
<211> 35
<212> PRT
<213> Homo sapiens

<400> 760
Cys Ser Glu Ser Gln Phe Gln Cys Ala Ser Gly Gln Cys Ile Asp Gly
1               5                   10                  15


Ala Leu Arg Cys Asn Gly Asp Ala Asn Cys Gln Asp Lys Ser Asp Glu
            20                  25                  30


Lys Asn Cys
        35


<210> 761
<211> 35
<212> PRT
<213> Homo sapiens

<400> 761
Cys Leu Ile Asp Gln Phe Arg Cys Ala Asn Gly Gln Cys Ile Gly Lys
1               5                   10                  15


His Lys Lys Cys Asp His Asn Val Asp Cys Ser Asp Lys Ser Asp Glu
            20                  25                  30


Leu Asp Cys
        35


<210> 762
<211> 35
<212> PRT
<213> Homo sapiens

<400> 762
Cys Ala Cys Asp Gln Phe Arg Cys Gly Asn Gly Lys Cys Ile Pro Glu
1               5                   10                  15


Ala Trp Lys Cys Asn Asn Met Asp Glu Cys Gly Asp Ser Ser Asp Glu
            20                  25                  30
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Glu Ile Cys
        35


<210> 763
<211> 40
<212> PRT
<213> Homo sapiens

<400> 763
Cys Ala Tyr Asn Gln Phe Gln Cys Leu Ser Arg Phe Thr Lys Val Tyr
1               5                   10                  15


Thr Cys Leu Pro Glu Ser Leu Lys Cys Asp Gly Asn Ile Asp Cys Leu
            20                  25                  30


Asp Leu Gly Asp Glu Ile Asp Cys
        35                  40


<210> 764
<211> 36
<212> PRT
<213> Homo sapiens

<400> 764
Cys Leu Pro Trp Glu Ile Pro Cys Gly Gly Asn Trp Gly Cys Tyr Thr
1               5                   10                  15


Glu Gln Gln Arg Cys Asp Gly Tyr Trp His Cys Pro Asn Gly Arg Asp
            20                  25                  30


Glu Thr Asn Cys
        35


<210> 765
<211> 36
<212> PRT
<213> Homo sapiens

<400> 765
Cys Gln Lys Glu Glu Phe Pro Cys Ser Arg Asn Gly Val Cys Tyr Pro
1               5                   10                  15


Arg Ser Asp Arg Cys Asn Tyr Gln Asn His Cys Pro Asn Gly Ser Asp
            20                  25                  30


Glu Lys Asn Cys
        35


<210> 766
<211> 35
<212> PRT
```

<213> Homo sapiens

<400> 766

```
Cys Gln Pro Gly Asn Phe His Cys Lys Asn Asn Arg Cys Val Phe Glu
1               5                   10                  15


Ser Trp Val Cys Asp Ser Gln Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Glu Asn Cys
        35
```

<210> 767
<211> 36
<212> PRT
<213> Homo sapiens

<400> 767

```
Cys Gly Arg Gly Glu Asn Phe Leu Cys Ala Ser Gly Ile Cys Ile Pro
1               5                   10                  15


Gly Lys Leu Gln Cys Asn Gly Tyr Asn Asp Cys Asp Asp Trp Ser Asp
            20                  25                  30


Glu Ala His Cys
        35
```

<210> 768
<211> 35
<212> PRT
<213> Homo sapiens

<400> 768

```
Cys Ser Glu Asn Leu Phe His Cys His Thr Gly Lys Cys Leu Asn Tyr
1               5                   10                  15


Ser Leu Val Cys Asp Gly Tyr Asp Asp Cys Gly Asp Leu Ser Asp Glu
            20                  25                  30


Gln Asn Cys
        35
```

<210> 769
<211> 36
<212> PRT
<213> Homo sapiens

<400> 769

```
Cys Asn Pro Thr Thr Glu His Arg Cys Gly Asp Gly Arg Cys Ile Ala
1               5                   10                  15
```

```
Met Glu Trp Val Cys Asp Gly Asp His Asp Cys Val Asp Lys Ser Asp
            20                  25                  30


Glu Val Asn Cys
        35


<210> 770
<211> 36
<212> PRT
<213> Homo sapiens

<400> 770
Cys His Ser Gln Gly Leu Val Glu Cys Arg Asn Gly Gln Cys Ile Pro
1               5                   10                  15


Ser Thr Phe Gln Cys Asp Gly Asp Glu Asp Cys Lys Asp Gly Ser Asp
            20                  25                  30


Glu Glu Asn Cys
        35


<210> 771
<211> 35
<212> PRT
<213> Homo sapiens

<400> 771
Cys Ser Pro Ser His Phe Lys Cys Arg Ser Gly Gln Cys Val Leu Ala
1               5                   10                  15


Ser Arg Arg Cys Asp Gly Gln Ala Asp Cys Asp Asp Asp Ser Asp Glu
            20                  25                  30


Glu Asn Cys
        35


<210> 772
<211> 37
<212> PRT
<213> Homo sapiens

<400> 772
Cys Lys Glu Arg Asp Leu Trp Glu Cys Pro Ser Asn Lys Gln Cys Leu
1               5                   10                  15


Lys His Thr Val Ile Cys Asp Gly Phe Pro Asp Cys Pro Asp Tyr Met
            20                  25                  30


Asp Glu Lys Asn Cys
        35
```

<210> 773
<211> 35
<212> PRT
<213> Homo sapiens

<400> 773
Cys Gln Asp Asp Glu Leu Glu Cys Ala Asn His Ala Cys Val Ser Arg
1   5   10   15

Asp Leu Trp Cys Asp Gly Glu Ala Asp Cys Ser Asp Ser Ser Asp Glu
            20   25   30

Trp Asp Cys
        35

<210> 774
<211> 36
<212> PRT
<213> Homo sapiens

<400> 774
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
1   5   10   15

Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
            20   25   30

Glu Asn Arg Cys
        35

<210> 775
<211> 35
<212> PRT
<213> Homo sapiens

<400> 775
Cys Ser Gly Lys Tyr Arg Cys Arg Ser Ser Phe Lys Cys Ile Glu Leu
1   5   10   15

Ile Ala Arg Cys Asp Gly Val Ser Asp Cys Lys Asp Gly Glu Asp Glu
            20   25   30

Tyr Arg Cys
        35

<210> 776
<211> 34
<212> PRT
<213> Homo sapiens

<400> 776

```
Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys Ile Arg Lys Glu
1               5                   10                  15


Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His Ser Asp Glu Leu
            20                  25                  30


Asn Cys




<210> 777
<211> 36
<212> PRT
<213> Homo sapiens

<400> 777
Cys Asp Ala Gly His Gln Phe Thr Cys Lys Asn Lys Phe Cys Lys Pro
1               5                   10                  15


Leu Phe Trp Val Cys Asp Ser Val Asn Asp Cys Gly Asp Asn Ser Asp
            20                  25                  30


Glu Gln Gly Cys
        35


<210> 778
<211> 35
<212> PRT
<213> Homo sapiens

<400> 778
Cys Pro Ala Gln Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys
1               5                   10                  15


Ser Gln Gln Cys Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ser Cys
        35


<210> 779
<211> 36
<212> PRT
<213> Homo sapiens

<400> 779
Cys Thr Lys His Thr Tyr Arg Cys Leu Asn Gly Leu Cys Leu Ser Lys
1               5                   10                  15


Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp Cys Ser Asp Gly Ser Asp
            20                  25                  30
```

```
Glu Lys Asp Cys
        35


<210> 780
<211> 38
<212> PRT
<213> Homo sapiens

<400> 780
Cys Leu Pro Gly Ser Ser Pro Cys Thr Asp Ala Leu Thr Cys Ile Lys
1               5                   10                  15


Ala Asp Leu Phe Cys Asp Gly Glu Val Asn Cys Pro Asp Gly Ser Asp
            20                  25                  30


Glu Asp Asn Lys Met Cys
        35


<210> 781
<211> 35
<212> PRT
<213> Homo sapiens

<400> 781
Cys Lys Ala Asp His Phe Gln Cys Lys Asn Gly Glu Cys Val Pro Leu
1               5                   10                  15


Val Asn Leu Cys Asp Gly His Leu His Cys Glu Asp Gly Ser Asp Glu
            20                  25                  30


Ala Asp Cys
        35


<210> 782
<211> 35
<212> PRT
<213> Homo sapiens

<400> 782
Cys Gln Pro Thr Gln Phe Arg Cys Ser Asn Gly Cys Cys Ile Asp Ser
1               5                   10                  15


Phe Leu Glu Cys Asp Asp Thr Pro Asn Cys Pro Asp Ala Ser Asp Glu
            20                  25                  30


Ala Ala Cys
        35


<210> 783
<211> 42
```

<212> PRT
<213> Homo sapiens

<400> 783
Cys Tyr Thr Gln Lys Ala Asp Ser Pro Met Asp Asp Phe Phe Gln Cys
1   5   10   15

Val Asn Gly Lys Tyr Ile Ser Gln Met Lys Ala Cys Asp Gly Ile Asn
            20   25   30

Asp Cys Gly Asp Gln Ser Asp Glu Leu Cys
        35   40

<210> 784
<211> 35
<212> PRT
<213> Homo sapiens

<400> 784
Cys Gln Gly Lys Gly Phe His Cys Lys Ser Gly Val Cys Ile Pro Ser
1   5   10   15

Gln Tyr Gln Cys Asn Gly Glu Val Asp Cys Ile Thr Gly Glu Asp Glu
            20   25   30

Val Gly Cys
        35

<210> 785
<211> 34
<212> PRT
<213> Homo sapiens

<400> 785
Cys Lys Asn Lys Phe Arg Cys Asp Ser Gly Arg Cys Ile Ala Arg Lys
1   5   10   15

Leu Glu Cys Asn Gly Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu Arg
            20   25   30

Asp Cys

<210> 786
<211> 35
<212> PRT
<213> Homo sapiens

<400> 786
Cys Gly Glu Arg Phe Arg Cys Phe Ser Gly Gln Cys Ile Ser Lys Ser
1   5   10   15

```
Leu Val Cys Asn Gly Asp Ser Asp Cys Asp Glu Asp Ser Ala Asp Glu
            20                  25                  30


Asp Arg Cys
        35


<210> 787
<211> 35
<212> PRT
<213> Homo sapiens

<400> 787
Cys Gly Gln Asp Phe Gln Cys Lys Glu Thr Gly Arg Cys Leu Lys Arg
1               5                   10                  15


His Leu Val Cys Asn Gly Asp Gln Asp Cys Leu Asp Gly Ser Asp Glu
            20                  25                  30


Asp Asp Cys
        35


<210> 788
<211> 34
<212> PRT
<213> Homo sapiens

<400> 788
Cys Glu Gly Phe Val Cys Ala Gln Thr Gly Arg Cys Val Asn Arg Arg
1               5                   10                  15


Leu Leu Cys Asn Gly Asp Asn Asp Cys Gly Asp Gln Ser Asp Glu Ala
            20                  25                  30


Asn Cys



<210> 789
<211> 34
<212> PRT
<213> Homo sapiens

<400> 789
Cys Gly Asn Asp Phe Gln Cys Ser Thr Gly Arg Cys Ile Lys Met Arg
1               5                   10                  15


Leu Arg Cys Asn Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu Asp
            20                  25                  30


Asp Cys
```

<210> 790
<211> 36
<212> PRT
<213> Homo sapiens

<400> 790
Cys Thr Glu Ala Glu Phe Ala Cys His Ser Tyr Asn Glu Cys Val Ala
1   5   10   15

Leu Glu Tyr Arg Cys Asp Arg Arg Pro Asp Cys Arg Asp Met Ser Asp
            20   25   30

Glu Leu Asn Cys
        35

<210> 791
<211> 35
<212> PRT
<213> Homo sapiens

<400> 791
Cys Gly Pro Gln Glu Ala Ala Cys Arg Asn Gly His Cys Ile Pro Arg
1   5   10   15

Asp Tyr Leu Cys Asp Gly Gln Glu Asp Cys Glu Asp Gly Ser Asp Glu
            20   25   30

Leu Asp Cys
        35

<210> 792
<211> 35
<212> PRT
<213> Homo sapiens

<400> 792
Cys Glu Pro Asn Glu Phe Pro Cys Gly Asn Gly His Cys Ala Leu Lys
1   5   10   15

Leu Trp Arg Cys Asp Gly Asp Phe Asp Cys Glu Asp Arg Thr Asp Glu
            20   25   30

Ala Asn Cys
        35

<210> 793
<211> 36
<212> PRT
<213> Homo sapiens

<400> 793
Cys Gly Pro Thr Gln Phe Arg Cys Val Ser Thr Asn Met Cys Ile Pro
1   5   10   15

Ala Ser Phe His Cys Asp Glu Glu Ser Asp Cys Pro Asp Arg Ser Asp
            20   25   30

Glu Phe Gly Cys
        35

<210> 794
<211> 35
<212> PRT
<213> Homo sapiens

<400> 794
Cys Leu Arg Asn Gln Tyr Arg Cys Ser Asn Gly Asn Cys Ile Asn Ser
1   5   10   15

Ile Trp Trp Cys Asp Phe Asp Asn Asp Cys Gly Asp Met Ser Asp Glu
            20   25   30

Arg Asn Cys
        35

<210> 795
<211> 37
<212> PRT
<213> Homo sapiens

<400> 795
Cys Asp Leu Asp Thr Gln Phe Arg Cys Gln Glu Ser Gly Thr Cys Ile
1   5   10   15

Pro Leu Ser Tyr Lys Cys Asp Leu Glu Asp Asp Cys Gly Asp Asn Ser
            20   25   30

Asp Glu Ser His Cys
        35

<210> 796
<211> 35
<212> PRT
<213> Homo sapiens

<400> 796
Cys Arg Ser Asp Glu Tyr Asn Cys Ser Ser Gly Met Cys Ile Arg Ser
1   5   10   15

Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Arg Asp Trp Ser Asp Glu
            20   25   30

```
Ala Asn Cys
        35


<210> 797
<211> 37
<212> PRT
<213> Homo sapiens

<400> 797
Cys Glu Ala Ser Asn Phe Gln Cys Arg Asn Gly His Cys Ile Pro Gln
1               5                   10                  15


Arg Trp Ala Cys Asp Gly Asp Thr Asp Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30


Asp Pro Val Asn Cys
        35


<210> 798
<211> 33
<212> PRT
<213> Homo sapiens

<400> 798
Cys Asn Gly Phe Arg Cys Pro Asn Gly Thr Cys Ile Pro Ser Ser Lys
1               5                   10                  15


His Cys Asp Gly Leu Arg Asp Cys Ser Asp Gly Ser Asp Glu Gln His
            20                  25                  30


Cys



<210> 799
<211> 41
<212> PRT
<213> Homo sapiens

<400> 799
Cys Thr His Phe Met Asp Phe Val Cys Lys Asn Arg Gln Gln Cys Leu
1               5                   10                  15


Phe His Ser Met Val Cys Asp Gly Ile Ile Gln Cys Arg Asp Gly Ser
            20                  25                  30


Asp Glu Asp Ala Ala Phe Ala Gly Cys
        35                  40


<210> 800
```

```
<211> 35
<212> PRT
<213> Homo sapiens

<400> 800
Cys Asp Glu Phe Gly Phe Gln Cys Gln Asn Gly Val Cys Ile Ser Leu
1               5                   10                  15


Ile Trp Lys Cys Asp Gly Met Asp Asp Cys Gly Asp Tyr Ser Asp Glu
            20                  25                  30


Ala Asn Cys
        35


<210> 801
<211> 36
<212> PRT
<213> Homo sapiens

<400> 801
Cys Ser Arg Tyr Phe Gln Phe Arg Cys Glu Asn Gly His Cys Ile Pro
1               5                   10                  15


Asn Arg Trp Lys Cys Asp Arg Glu Asn Asp Cys Gly Asp Trp Ser Asp
            20                  25                  30


Glu Lys Asp Cys
        35


<210> 802
<211> 35
<212> PRT
<213> Homo sapiens

<400> 802
Cys Leu Pro Asn Tyr Tyr Arg Cys Ser Ser Gly Thr Cys Val Met Asp
1               5                   10                  15


Thr Trp Val Cys Asp Gly Tyr Arg Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Glu Ala Cys
        35


<210> 803
<211> 36
<212> PRT
<213> Homo sapiens

<400> 803
Cys Asp Arg Phe Glu Phe Glu Cys His Gln Pro Lys Thr Cys Ile Pro
1               5                   10                  15
```

```
Asn Trp Lys Arg Cys Asp Gly His Gln Asp Cys Gln Asp Gly Arg Asp
            20                  25                  30


Glu Ala Asn Cys
        35


<210> 804
<211> 36
<212> PRT
<213> Homo sapiens

<400> 804
Cys Met Ser Arg Glu Phe Gln Cys Glu Asp Gly Glu Ala Cys Ile Val
1               5                   10                  15


Leu Ser Glu Arg Cys Asp Gly Phe Leu Asp Cys Ser Asp Glu Ser Asp
            20                  25                  30


Glu Lys Ala Cys
        35


<210> 805
<211> 35
<212> PRT
<213> Homo sapiens

<400> 805
Cys Glu Lys Asp Gln Phe Gln Cys Arg Asn Glu Arg Cys Ile Pro Ser
1               5                   10                  15


Val Trp Arg Cys Asp Glu Asp Asp Asp Cys Leu Asp His Ser Asp Glu
            20                  25                  30


Asp Asp Cys
        35


<210> 806
<211> 37
<212> PRT
<213> Homo sapiens

<400> 806
Cys Ala Asp Ser Asp Phe Thr Cys Asp Asn Gly His Cys Ile His Glu
1               5                   10                  15


Arg Trp Lys Cys Asp Gly Glu Glu Glu Cys Pro Asp Gly Ser Asp Glu
            20                  25                  30


Ser Glu Ala Thr Cys
```

35

<210> 807
<211> 37
<212> PRT
<213> Homo sapiens

<400> 807
Cys Pro Ala Glu Lys Leu Ser Cys Gly Pro Thr Ser His Lys Cys Val
1   5   10   15

Pro Ala Ser Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Gly Gly Ala
            20   25   30

Asp Glu Ala Gly Cys
        35

<210> 808
<211> 35
<212> PRT
<213> Homo sapiens

<400> 808
Cys Ala Pro His Glu Phe Gln Cys Gly Asn Arg Ser Cys Leu Ala Ala
1   5   10   15

Val Phe Val Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Arg Gly Cys
        35

<210> 809
<211> 40
<212> PRT
<213> Homo sapiens

<400> 809
Cys Gly Pro Arg Glu Phe Arg Cys Gly Gly Asp Gly Gly Gly Ala Cys
1   5   10   15

Ile Pro Glu Arg Trp Val Cys Asp Arg Gln Phe Asp Cys Glu Asp Arg
            20   25   30

Ser Asp Glu Ala Ala Glu Leu Cys
        35   40

<210> 810
<211> 36
<212> PRT
<213> Homo sapiens

```
<400> 810
Cys Ala Thr Val Ser Gln Phe Ala Cys Arg Ser Gly Glu Cys Val His
1               5                   10                  15


Leu Gly Trp Arg Cys Asp Gly Asp Arg Asp Cys Lys Asp Lys Ser Asp
            20                  25                  30


Glu Ala Asp Cys
        35


<210> 811
<211> 35
<212> PRT
<213> Homo sapiens

<400> 811
Cys Arg Gly Asp Glu Phe Gln Cys Gly Asp Gly Thr Cys Val Leu Ala
1               5                   10                  15


Ile Lys His Cys Asn Gln Glu Gln Asp Cys Pro Asp Gly Ser Asp Glu
            20                  25                  30


Ala Gly Cys
        35


<210> 812
<211> 37
<212> PRT
<213> Homo sapiens

<400> 812
Cys Glu Arg Asn Glu Phe Gln Cys Gln Asp Gly Lys Cys Ile Ser Tyr
1               5                   10                  15


Lys Trp Val Cys Asp Gly Ser Ala Glu Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30


Ser Gln Glu Thr Cys
        35


<210> 813
<211> 37
<212> PRT
<213> Homo sapiens

<400> 813
Cys Lys Ser Gly Asp Phe Ser Cys Gly Gly Arg Val Asn Arg Cys Ile
1               5                   10                  15


Pro Gln Phe Trp Arg Cys Asp Gly Gln Val Asp Cys Asp Asn Gly Ser
```

            20   25   30

Asp Glu Gln Gly Cys
        35

<210> 814
<211> 35
<212> PRT
<213> Homo sapiens

<400> 814
Cys Ser Gln Asp Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg
1   5   10   15

Gln Phe Val Cys Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu
            20   25   30

Ala Ser Cys
        35

<210> 815
<211> 37
<212> PRT
<213> Homo sapiens

<400> 815
Cys Gly Pro Ala Ser Phe Gln Cys Asn Ser Ser Thr Cys Ile Pro Gln
1   5   10   15

Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly Ser Asp Glu
            20   25   30

Trp Pro Gln Arg Cys
        35

<210> 816
<211> 35
<212> PRT
<213> Homo sapiens

<400> 816
Cys Ser Ala Phe Glu Phe His Cys Leu Ser Gly Glu Cys Ile His Ser
1   5   10   15

Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp Lys Ser Asp Glu
            20   25   30

Glu Asn Cys
        35

<210> 817
<211> 35
<212> PRT
<213> Homo sapiens

<400> 817
Cys Arg Pro Asp Glu Phe Gln Cys Ser Asp Gly Asn Cys Ile His Gly
1   5   10   15

Ser Arg Gln Cys Asp Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu
            20   25   30

Val Gly Cys
        35

<210> 818
<211> 38
<212> PRT
<213> Homo sapiens

<400> 818
Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu Cys Ile Thr
1   5   10   15

Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp Trp Ser Asp
            20   25   30

Glu Pro Ile Lys Glu Cys
        35

<210> 819
<211> 35
<212> PRT
<213> Homo sapiens

<400> 819
Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
1   5   10   15

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu
            20   25   30

Lys Asn Cys
        35

<210> 820
<211> 37
<212> PRT
<213> Homo sapiens

<400> 820
Cys Ala Glu Ser Asp Phe Val Cys Asn Asn Gly Gln Cys Val Pro Ser

```
1               5                   10                  15


Arg Trp Lys Cys Asp Gly Asp Pro Asp Cys Glu Asp Gly Ser Asp Glu
            20                  25                  30


Ser Pro Glu Gln Cys
        35


<210> 821
<211> 37
<212> PRT
<213> Homo sapiens

<400> 821
Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile
1               5                   10                  15


Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu
            20                  25                  30


Asp Glu Glu Asn Cys
        35


<210> 822
<211> 35
<212> PRT
<213> Homo sapiens

<400> 822
Cys Ser Pro Asp Glu Phe Thr Cys Ser Ser Gly Arg Cys Ile Ser Arg
1               5                   10                  15


Asn Phe Val Cys Asn Gly Gln Asp Asp Cys Ser Asp Gly Ser Asp Glu
            20                  25                  30


Leu Asp Cys
        35


<210> 823
<211> 37
<212> PRT
<213> Homo sapiens

<400> 823
Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile
1               5                   10                  15


Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
            20                  25                  30
```

```
Ser Leu Glu Gln Cys
        35


<210> 824
<211> 35
<212> PRT
<213> Homo sapiens

<400> 824
Cys Pro Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys
1               5                   10                  15


Lys Trp Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu
            20                  25                  30


Val Asn Cys
        35


<210> 825
<211> 35
<212> PRT
<213> Homo sapiens

<400> 825
Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly Ser Cys Ile His Gly
1               5                   10                  15


Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val Asp Gly Ser Asp Glu
            20                  25                  30


Val Asn Cys
        35


<210> 826
<211> 38
<212> PRT
<213> Homo sapiens

<400> 826
Cys Leu Gly Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp
1               5                   10                  15


Ile Ser Lys Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp
            20                  25                  30


Glu Pro Leu Lys Glu Cys
        35


<210> 827
<211> 38
<212> PRT
```

```
<213> Homo sapiens

<400> 827
Cys Ser Pro Lys Gln Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser
1               5                   10                  15


Lys Gly Trp Arg Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp
            20                  25                  30


Glu Ala Pro Glu Ile Cys
        35


<210> 828
<211> 37
<212> PRT
<213> Homo sapiens

<400> 828
Cys Gln Pro Asn Glu His Asn Cys Leu Gly Thr Glu Leu Cys Val Pro
1               5                   10                  15


Met Ser Arg Leu Cys Asn Gly Val Gln Asp Cys Met Asp Gly Ser Asp
            20                  25                  30


Glu Gly Pro His Cys
        35


<210> 829
<211> 37
<212> PRT
<213> Homo sapiens

<400> 829
Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln Glu
1               5                   10                  15


Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp Glu
            20                  25                  30


Ala Pro Ala Leu Cys
        35


<210> 830
<211> 37
<212> PRT
<213> Homo sapiens

<400> 830
Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
1               5                   10                  15
```

Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
            20   25   30

Ser Asn Ala Thr Cys
        35

<210> 831
<211> 36
<212> PRT
<213> Homo sapiens

<400> 831
Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro Ile
1   5   10   15

Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp Glu
            20   25   30

Ser Ala Ser Cys
        35

<210> 832
<211> 36
<212> PRT
<213> Homo sapiens

<400> 832
Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn
1   5   10   15

Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp
            20   25   30

Glu Ala Gly Cys
        35

<210> 833
<211> 37
<212> PRT
<213> Homo sapiens

<400> 833
Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro Glu
1   5   10   15

His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp Glu
            20   25   30

Thr His Ala Asn Cys
        35

<210> 834
<211> 36
<212> PRT
<213> Homo sapiens

<400> 834
Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro
1   5   10   15

Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp
            20   25   30

Glu Lys Ser Cys
        35

<210> 835
<211> 37
<212> PRT
<213> Homo sapiens

<400> 835
Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile
1   5   10   15

Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser
            20   25   30

Asp Glu Glu Asn Cys
        35

<210> 836
<211> 38
<212> PRT
<213> Homo sapiens

<400> 836
Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val Cys Leu
1   5   10   15

Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly Asp Gly Ser
            20   25   30

Asp Glu Gly Glu Leu Cys
        35

<210> 837
<211> 38
<212> PRT
<213> Homo sapiens

<400> 837

Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys Ile Asn
1   5   10   15

Phe Ser Leu Thr Cys Asp Gly Val Pro His Cys Lys Asp Lys Ser Asp
            20   25   30

Glu Lys Pro Ser Tyr Cys
        35

<210> 838
<211> 35
<212> PRT
<213> Homo sapiens

<400> 838
Cys Lys Lys Thr Phe Arg Gln Cys Ser Asn Gly Arg Cys Val Ser Asn
1   5   10   15

Met Leu Trp Cys Asn Gly Ala Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Ile Pro Cys
        35

<210> 839
<211> 35
<212> PRT
<213> Homo sapiens

<400> 839
Cys Gly Val Gly Glu Phe Arg Cys Arg Asp Gly Thr Cys Ile Gly Asn
1   5   10   15

Ser Ser Arg Cys Asn Gln Phe Val Asp Cys Glu Asp Ala Ser Asp Glu
            20   25   30

Met Asn Cys
        35

<210> 840
<211> 45
<212> PRT
<213> Homo sapiens

<400> 840
Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu Phe Gln Pro
1   5   10   15

Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val Cys Asp Gly
            20   25   30

```
Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp Cys
        35                  40                  45


<210> 841
<211> 35
<212> PRT
<213> Homo sapiens

<400> 841
Cys Pro Leu Asn Tyr Phe Ala Cys Pro Ser Gly Arg Cys Ile Pro Met
1               5                   10                  15


Ser Trp Thr Cys Asp Lys Glu Asp Asp Cys Glu His Gly Glu Asp Glu
            20                  25                  30


Thr His Cys
        35


<210> 842
<211> 36
<212> PRT
<213> Homo sapiens

<400> 842
Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile Ser Lys
1               5                   10                  15


Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Ala Ala His Cys
        35


<210> 843
<211> 39
<212> PRT
<213> Homo sapiens

<400> 843
Cys Gly Pro Ser Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro
1               5                   10                  15


Glu Arg Trp Leu Cys Asp Gly Asp Lys Asp Cys Ala Asp Gly Ala Asp
            20                  25                  30


Glu Ser Ile Ala Ala Gly Cys
        35


<210> 844
<211> 36
```

```
<212> PRT
<213> Homo sapiens

<400> 844
Cys Asp Asp Arg Glu Phe Met Cys Gln Asn Arg Gln Cys Ile Pro Lys
1               5                   10                  15


His Phe Val Cys Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Ser Pro Glu Cys
        35


<210> 845
<211> 40
<212> PRT
<213> Homo sapiens

<400> 845
Cys Gly Pro Ser Glu Phe Arg Cys Ala Asn Gly Arg Cys Leu Ser Ser
1               5                   10                  15


Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp Cys His Asp Gln Ser Asp
            20                  25                  30


Glu Ala Pro Lys Asn Pro His Cys
        35                  40


<210> 846
<211> 36
<212> PRT
<213> Homo sapiens

<400> 846
Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser Ser Gly Arg Cys Val Ala
1               5                   10                  15


Glu Ala Leu Leu Cys Asn Gly Gln Asp Asp Cys Gly Asp Ser Ser Asp
            20                  25                  30


Glu Arg Gly Cys
        35


<210> 847
<211> 36
<212> PRT
<213> Homo sapiens

<400> 847
Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile Pro Phe
1               5                   10                  15
```

```
Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His Ser Asp Glu
            20                  25                  30


Pro Pro Asp Cys
        35


<210> 848
<211> 35
<212> PRT
<213> Homo sapiens

<400> 848
Cys Arg Pro Gly Gln Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro
1               5                   10                  15


Ala Phe Ile Cys Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu
            20                  25                  30


Ala Asn Cys
        35


<210> 849
<211> 36
<212> PRT
<213> Homo sapiens

<400> 849
Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr Asn Arg Cys Ile Pro
1               5                   10                  15


Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn Cys Gly Asp Gly Glu Asp
            20                  25                  30


Glu Arg Asp Cys
        35


<210> 850
<211> 37
<212> PRT
<213> Homo sapiens

<400> 850
Cys Ala Pro Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile Pro
1               5                   10                  15


Arg Val Trp Val Cys Asp Arg Asp Asn Asp Cys Val Asp Gly Ser Asp
            20                  25                  30


Glu Pro Ala Asn Cys
        35
```

```
<210> 851
<211> 38
<212> PRT
<213> Homo sapiens

<400> 851
Cys Gly Val Asp Glu Phe Arg Cys Lys Asp Ser Gly Arg Cys Ile Pro
1               5                   10                  15


Ala Arg Trp Lys Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp
            20                  25                  30


Glu Pro Lys Glu Glu Cys
        35


<210> 852
<211> 35
<212> PRT
<213> Homo sapiens

<400> 852
Cys Glu Pro Tyr Gln Phe Arg Cys Lys Asn Asn Arg Cys Val Pro Gly
1               5                   10                  15


Arg Trp Gln Cys Asp Tyr Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Glu Ser Cys
        35


<210> 853
<211> 35
<212> PRT
<213> Homo sapiens

<400> 853
Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys Ile Ala Gly
1               5                   10                  15


Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Lys Asp Cys
        35


<210> 854
<211> 35
<212> PRT
<213> Homo sapiens
```

<400> 854
Cys Asp Met Asp Gln Phe Gln Cys Lys Ser Gly His Cys Ile Pro Leu
1   5   10   15

Arg Trp Arg Cys Asp Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu
            20   25   30

Glu Ala Cys
        35

<210> 855
<211> 37
<212> PRT
<213> Homo sapiens

<400> 855
Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn Thr Leu Cys Lys Pro Leu
1   5   10   15

Ala Trp Lys Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Asn Pro Glu Glu Cys
        35

<210> 856
<211> 37
<212> PRT
<213> Homo sapiens

<400> 856
Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg Val Cys Leu
1   5   10   15

Trp Ile Gly Arg Gln Cys Asp Gly Thr Asp Asn Cys Gly Asp Gly Thr
            20   25   30

Asp Glu Glu Asp Cys
        35

<210> 857
<211> 36
<212> PRT
<213> Homo sapiens

<400> 857
Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg Cys Leu Ser
1   5   10   15

Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys Gly Asp Gly Ser Asp
            20   25   30

```
Glu Glu Asp Cys
        35


<210> 858
<211> 35
<212> PRT
<213> Homo sapiens

<400> 858
Cys Asp Ser Ala His Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala
1               5                   10                  15


Asp Trp Arg Cys Asp Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu
            20                  25                  30


Ile Gly Cys
        35


<210> 859
<211> 37
<212> PRT
<213> Homo sapiens

<400> 859
Cys Gln Gln Gly Tyr Phe Lys Cys Gln Ser Glu Gly Gln Cys Ile Pro
1               5                   10                  15


Ser Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly Ser Asp
            20                  25                  30


Glu Arg Gln Asp Cys
        35


<210> 860
<211> 35
<212> PRT
<213> Homo sapiens

<400> 860
Cys Ser Ser His Gln Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser
1               5                   10                  15


Glu Tyr Arg Cys Asp His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu
            20                  25                  30


Asn Asp Cys
        35


<210> 861
```

```
<211> 33
<212> PRT
<213> Homo sapiens

<400> 861
Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr Ser Gln
1               5                   10                  15


Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu Ile Asn
            20                  25                  30


Cys




<210> 862
<211> 35
<212> PRT
<213> Homo sapiens

<400> 862
Cys Leu His Asn Glu Phe Ser Cys Gly Asn Gly Glu Cys Ile Pro Arg
1               5                   10                  15


Ala Tyr Val Cys Asp His Asp Asn Asp Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30


His Ala Cys
        35


<210> 863
<211> 35
<212> PRT
<213> Homo sapiens

<400> 863
Cys Gly Gly Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln
1               5                   10                  15


Asn Trp Val Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu
            20                  25                  30


Asp Gly Cys
        35


<210> 864
<211> 42
<212> PRT
<213> Homo sapiens

<400> 864
Cys Ser Pro Arg Glu Trp Ser Cys Pro Glu Ser Gly Arg Cys Ile Ser
1               5                   10                  15
```

```
Ile Tyr Lys Val Cys Asp Gly Ile Leu Asp Cys Pro Gly Arg Glu Asp
            20                  25                  30


Glu Asn Asn Thr Ser Thr Gly Lys Tyr Cys
        35                  40


<210> 865
<211> 35
<212> PRT
<213> Homo sapiens

<400> 865
Cys Gly Leu Phe Ser Phe Pro Cys Lys Asn Gly Arg Cys Val Pro Asn
1               5                   10                  15


Tyr Tyr Leu Cys Asp Gly Val Asp Asp Cys His Asp Asn Ser Asp Glu
            20                  25                  30


Gln Leu Cys
        35


<210> 866
<211> 35
<212> PRT
<213> Homo sapiens

<400> 866
Cys Ser Ser Ser Ala Phe Thr Cys Gly His Gly Glu Cys Ile Pro Ala
1               5                   10                  15


His Trp Arg Cys Asp Lys Arg Asn Asp Cys Val Asp Gly Ser Asp Glu
            20                  25                  30


His Asn Cys
        35


<210> 867
<211> 35
<212> PRT
<213> Homo sapiens

<400> 867
Cys Leu Asp Thr Gln Tyr Thr Cys Asp Asn His Gln Cys Ile Ser Lys
1               5                   10                  15


Asn Trp Val Cys Asp Thr Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Lys Asn Cys
```

```
        35


<210> 868
<211> 35
<212> PRT
<213> Homo sapiens

<400> 868
Cys Gln Pro Ser Gln Phe Asn Cys Pro Asn His Arg Cys Ile Asp Leu
1               5                   10                  15


Ser Phe Val Cys Asp Gly Asp Lys Asp Cys Val Asp Gly Ser Asp Glu
            20                  25                  30


Val Gly Cys
        35


<210> 869
<211> 36
<212> PRT
<213> Homo sapiens

<400> 869
Cys Thr Ala Ser Gln Phe Lys Cys Ala Ser Gly Asp Lys Cys Ile Gly
1               5                   10                  15


Val Thr Asn Arg Cys Asp Gly Val Phe Asp Cys Ser Asp Asn Ser Asp
            20                  25                  30


Glu Ala Gly Cys
        35


<210> 870
<211> 37
<212> PRT
<213> Homo sapiens

<400> 870
Cys His Ser Asp Glu Phe Gln Cys Gln Glu Asp Gly Ile Cys Ile Pro
1               5                   10                  15


Asn Phe Trp Glu Cys Asp Gly His Pro Asp Cys Leu Tyr Gly Ser Asp
            20                  25                  30


Glu His Asn Ala Cys
        35


<210> 871
<211> 35
<212> PRT
<213> Homo sapiens
```

<400> 871
Cys Pro Ser Ser Tyr Phe His Cys Asp Asn Gly Asn Cys Ile His Arg
1   5   10   15

Ala Trp Leu Cys Asp Arg Asp Asn Asp Cys Gly Asp Met Ser Asp Glu
            20   25   30

Lys Asp Cys
        35

<210> 872
<211> 37
<212> PRT
<213> Homo sapiens

<400> 872
Cys Pro Ser Trp Gln Trp Gln Cys Leu Gly His Asn Ile Cys Val Asn
1   5   10   15

Leu Ser Val Val Cys Asp Gly Ile Phe Asp Cys Pro Asn Gly Thr Asp
            20   25   30

Glu Ser Pro Leu Cys
        35

<210> 873
<211> 37
<212> PRT
<213> Homo sapiens

<400> 873
Cys Gly Ala Ser Ser Phe Thr Cys Ser Asn Gly Arg Cys Ile Ser Glu
1   5   10   15

Glu Trp Lys Cys Asp Asn Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Met Glu Ser Val Cys
        35

<210> 874
<211> 35
<212> PRT
<213> Homo sapiens

<400> 874
Cys Ser Pro Thr Ala Phe Thr Cys Ala Asn Gly Arg Cys Val Gln Tyr
1   5   10   15

Ser Tyr Arg Cys Asp Tyr Tyr Asn Asp Cys Gly Asp Gly Ser Asp Glu

```
            20                  25                  30


Ala Gly Cys
        35


<210> 875
<211> 38
<212> PRT
<213> Homo sapiens

<400> 875
Cys Asn Ala Thr Thr Glu Phe Met Cys Asn Asn Arg Arg Cys Ile Pro
1               5                   10                  15


Arg Glu Phe Ile Cys Asn Gly Val Asp Asn Cys His Asp Asn Asn Thr
            20                  25                  30


Ser Asp Glu Lys Asn Cys
        35


<210> 876
<211> 38
<212> PRT
<213> Homo sapiens

<400> 876
Cys Gln Ser Gly Tyr Thr Lys Cys His Asn Ser Asn Ile Cys Ile Pro
1               5                   10                  15


Arg Val Tyr Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp
            20                  25                  30


Glu Asn Pro Thr Tyr Cys
        35


<210> 877
<211> 36
<212> PRT
<213> Homo sapiens

<400> 877
Cys Ser Ser Ser Glu Phe Gln Cys Ala Ser Gly Arg Cys Ile Pro Gln
1               5                   10                  15


His Trp Tyr Cys Asp Gln Glu Thr Asp Cys Phe Asp Ala Ser Asp Glu
            20                  25                  30


Pro Ala Ser Cys
        35
```

```
<210> 878
<211> 38
<212> PRT
<213> Homo sapiens

<400> 878
Cys Leu Ala Asp Glu Phe Lys Cys Asp Gly Gly Arg Cys Ile Pro Ser
1               5                   10                  15


Glu Trp Ile Cys Asp Gly Asp Asn Asp Cys Gly Asp Met Ser Asp Glu
            20                  25                  30


Asp Lys Arg His Gln Cys
        35


<210> 879
<211> 41
<212> PRT
<213> Homo sapiens

<400> 879
Cys Ser Asp Ser Glu Phe Leu Cys Val Asn Asp Arg Pro Pro Asp Arg
1               5                   10                  15


Arg Cys Ile Pro Gln Ser Trp Val Cys Asp Gly Asp Val Asp Cys Thr
            20                  25                  30


Asp Gly Tyr Asp Glu Asn Gln Asn Cys
        35                  40


<210> 880
<211> 35
<212> PRT
<213> Homo sapiens

<400> 880
Cys Ser Glu Asn Glu Phe Thr Cys Gly Tyr Gly Leu Cys Ile Pro Lys
1               5                   10                  15


Ile Phe Arg Cys Asp Arg His Asn Asp Cys Gly Asp Tyr Ser Asp Glu
            20                  25                  30


Arg Gly Cys
        35


<210> 881
<211> 37
<212> PRT
<213> Homo sapiens

<400> 881
Cys Gln Gln Asn Gln Phe Thr Cys Gln Asn Gly Arg Cys Ile Ser Lys
```

1   5   10   15

Thr Phe Val Cys Asp Glu Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Leu Met His Leu Cys
        35

<210> 882
<211> 35
<212> PRT
<213> Homo sapiens

<400> 882
Cys Pro Pro His Glu Phe Lys Cys Asp Asn Gly Arg Cys Ile Glu Met
1   5   10   15

Met Lys Leu Cys Asn His Leu Asp Asp Cys Leu Asp Asn Ser Asp Glu
            20   25   30

Lys Gly Cys
        35

<210> 883
<211> 37
<212> PRT
<213> Homo sapiens

<400> 883
Cys Ser Ser Thr Gln Phe Leu Cys Ala Asn Asn Glu Lys Cys Ile Pro
1   5   10   15

Ile Trp Trp Lys Cys Asp Gly Gln Lys Asp Cys Ser Asp Gly Ser Asp
            20   25   30

Glu Leu Ala Leu Cys
        35

<210> 884
<211> 37
<212> PRT
<213> Homo sapiens

<400> 884
Cys Arg Leu Gly Gln Phe Gln Cys Ser Asp Gly Asn Cys Thr Ser Pro
1   5   10   15

Gln Thr Leu Cys Asn Ala His Gln Asn Cys Pro Asp Gly Ser Asp Glu
            20   25   30

```
Asp Arg Leu Leu Cys
        35


<210> 885
<211> 37
<212> PRT
<213> Homo sapiens

<400> 885
Cys Asp Ser Asn Glu Trp Gln Cys Ala Asn Lys Arg Cys Ile Pro Glu
1               5                   10                  15


Ser Trp Gln Cys Asp Thr Phe Asn Asp Cys Glu Asp Asn Ser Asp Glu
            20                  25                  30


Asp Ser Ser His Cys
        35


<210> 886
<211> 37
<212> PRT
<213> Homo sapiens

<400> 886
Cys Arg Pro Gly Gln Phe Arg Cys Ala Asn Gly Arg Cys Ile Pro Gln
1               5                   10                  15


Ala Trp Lys Cys Asp Val Asp Asn Asp Cys Gly Asp His Ser Asp Glu
            20                  25                  30


Pro Ile Glu Glu Cys
        35


<210> 887
<211> 37
<212> PRT
<213> Homo sapiens

<400> 887
Cys Asp Asn Phe Thr Glu Phe Ser Cys Lys Thr Asn Tyr Arg Cys Ile
1               5                   10                  15


Pro Lys Trp Ala Val Cys Asn Gly Val Asp Asp Cys Arg Asp Asn Ser
            20                  25                  30


Asp Glu Gln Gly Cys
        35


<210> 888
<211> 36
<212> PRT
```

<213> Homo sapiens

<400> 888
Cys His Pro Val Gly Asp Phe Arg Cys Lys Asn His His Cys Ile Pro
1   5   10   15

Leu Arg Trp Gln Cys Asp Gly Gln Asn Asp Cys Gly Asp Asn Ser Asp
            20   25   30

Glu Glu Asn Cys
        35

<210> 889
<211> 35
<212> PRT
<213> Homo sapiens

<400> 889
Cys Thr Glu Ser Glu Phe Arg Cys Val Asn Gln Gln Cys Ile Pro Ser
1   5   10   15

Arg Trp Ile Cys Asp His Tyr Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Arg Asp Cys
        35

<210> 890
<211> 35
<212> PRT
<213> Homo sapiens

<400> 890
Cys His Pro Glu Tyr Phe Gln Cys Thr Ser Gly His Cys Val His Ser
1   5   10   15

Glu Leu Lys Cys Asp Gly Ser Ala Asp Cys Leu Asp Ala Ser Asp Glu
            20   25   30

Ala Asp Cys
        35

<210> 891
<211> 37
<212> PRT
<213> Homo sapiens

<400> 891
Cys Gln Ala Thr Met Phe Glu Cys Lys Asn His Val Cys Ile Pro Pro
1   5   10   15

Tyr Trp Lys Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Glu Leu His Leu Cys
        35

<210> 892
<211> 38
<212> PRT
<213> Homo sapiens

<400> 892
Cys Asn Ser Pro Asn Arg Phe Arg Cys Asp Asn Asn Arg Cys Ile Tyr
1   5   10   15

Ser His Glu Val Cys Asn Gly Val Asp Asp Cys Gly Asp Gly Thr Asp
            20   25   30

Glu Thr Glu Glu His Cys
        35

<210> 893
<211> 35
<212> PRT
<213> Homo sapiens

<400> 893
Cys Thr Glu Tyr Glu Tyr Lys Cys Gly Asn Gly His Cys Ile Pro His
1   5   10   15

Asp Asn Val Cys Asp Asp Ala Asp Asp Cys Gly Asp Trp Ser Asp Glu
            20   25   30

Leu Gly Cys
        35

<210> 894
<211> 38
<212> PRT
<213> Homo sapiens

<400> 894
Cys Asp Pro Gly Glu Phe Leu Cys His Asp His Val Thr Cys Val Ser
1   5   10   15

Gln Ser Trp Leu Cys Asp Gly Asp Pro Asp Cys Pro Asp Asp Ser Asp
            20   25   30

Glu Ser Leu Asp Thr Cys
        35

<210> 895
<211> 37
<212> PRT
<213> Homo sapiens

<400> 895
Cys Pro Leu Asn His Ile Ala Cys Leu Gly Thr Asn Lys Cys Val His
1   5   10   15

Leu Ser Gln Leu Cys Asn Gly Val Leu Asp Cys Pro Asp Gly Tyr Asp
            20   25   30

Glu Gly Val His Cys
        35

<210> 896
<211> 37
<212> PRT
<213> Homo sapiens

<400> 896
Cys Lys Ala Gly Glu Phe Arg Cys Lys Asn Arg His Cys Ile Gln Ala
1   5   10   15

Arg Trp Lys Cys Asp Gly Asp Asp Asp Cys Leu Asp Gly Ser Asp Glu
            20   25   30

Asp Ser Val Asn Cys
        35

<210> 897
<211> 37
<212> PRT
<213> Homo sapiens

<400> 897
Cys Pro Asp Asp Gln Phe Lys Cys Gln Asn Asn Arg Cys Ile Pro Lys
1   5   10   15

Arg Trp Leu Cys Asp Gly Ala Asn Asp Cys Gly Ser Asn Glu Asp Glu
            20   25   30

Ser Asn Gln Thr Cys
        35

<210> 898
<211> 36
<212> PRT
<213> Homo sapiens

<400> 898

```
Cys Gln Val Asp Gln Phe Ser Cys Gly Asn Gly Arg Cys Ile Pro Arg
1               5                   10                  15


Ala Trp Leu Cys Asp Arg Glu Asp Asp Cys Gly Asp Gln Thr Asp Glu
            20                  25                  30


Met Ala Ser Cys
        35


<210> 899
<211> 36
<212> PRT
<213> Homo sapiens

<400> 899
Cys Glu Pro Leu Thr Gln Phe Val Cys Lys Ser Gly Arg Cys Ile Ser
1               5                   10                  15


Ser Lys Trp His Cys Asp Ser Asp Asp Asp Cys Gly Asp Gly Ser Asp
            20                  25                  30


Glu Val Gly Cys
        35


<210> 900
<211> 37
<212> PRT
<213> Homo sapiens

<400> 900
Cys Phe Asp Asn Gln Phe Arg Cys Ser Ser Gly Arg Cys Ile Pro Gly
1               5                   10                  15


His Trp Ala Cys Asp Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu
            20                  25                  30


Ala Gln Ile Asn Cys
        35


<210> 901
<211> 36
<212> PRT
<213> Homo sapiens

<400> 901
Cys Asn Gly Asn Glu Phe Gln Cys His Pro Asp Gly Asn Cys Val Pro
1               5                   10                  15


Asp Leu Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30
```

```
Glu Lys Gly Cys
        35


<210> 902
<211> 37
<212> PRT
<213> Homo sapiens

<400> 902
Cys Asp His Lys Thr Lys Phe Ser Cys Trp Ser Thr Gly Arg Cys Ile
1               5                   10                  15


Asn Lys Ala Trp Val Cys Asp Gly Asp Ile Asp Cys Glu Asp Gln Ser
            20                  25                  30


Asp Glu Asp Asp Cys
        35


<210> 903
<211> 38
<212> PRT
<213> Homo sapiens

<400> 903
Cys Gly Pro Pro Lys His Pro Cys Ala Asn Asp Thr Ser Val Cys Leu
1               5                   10                  15


Gln Pro Glu Lys Leu Cys Asn Gly Lys Lys Asp Cys Pro Asp Gly Ser
            20                  25                  30


Asp Glu Gly Tyr Leu Cys
        35


<210> 904
<211> 38
<212> PRT
<213> Homo sapiens

<400> 904
Cys Asn Ala Tyr Ser Glu Phe Glu Cys Gly Asn Gly Glu Cys Ile Asp
1               5                   10                  15


Tyr Gln Leu Thr Cys Asp Gly Ile Pro His Cys Lys Asp Lys Ser Asp
            20                  25                  30


Glu Lys Leu Leu Tyr Cys
        35


<210> 905
<211> 35
```

<212> PRT
<213> Homo sapiens

<400> 905
Cys Arg Arg Gly Phe Lys Pro Cys Tyr Asn Arg Arg Cys Ile Pro His
1   5   10   15

Gly Lys Leu Cys Asp Gly Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Leu Asp Cys
        35

<210> 906
<211> 35
<212> PRT
<213> Homo sapiens

<400> 906
Cys Ala Thr Val Glu Phe Arg Cys Ala Asp Gly Thr Cys Ile Pro Arg
1   5   10   15

Ser Ala Arg Cys Asn Gln Asn Ile Asp Cys Ala Asp Ala Ser Asp Glu
            20   25   30

Lys Asn Cys
        35

<210> 907
<211> 45
<212> PRT
<213> Homo sapiens

<400> 907
Cys Thr His Phe Tyr Lys Leu Gly Val Lys Thr Thr Gly Phe Ile Arg
1   5   10   15

Cys Asn Ser Thr Ser Leu Cys Val Leu Pro Thr Trp Ile Cys Asp Gly
            20   25   30

Ser Asn Asp Cys Gly Asp Tyr Ser Asp Glu Leu Lys Cys
        35   40   45

<210> 908
<211> 35
<212> PRT
<213> Homo sapiens

<400> 908
Cys Glu Glu Asn Tyr Phe Ser Cys Pro Ser Gly Arg Cys Ile Leu Asn
1   5   10   15

```
Thr Trp Ile Cys Asp Gly Gln Lys Asp Cys Glu Asp Gly Arg Asp Glu
            20                  25                  30


Phe His Cys
        35


<210> 909
<211> 37
<212> PRT
<213> Homo sapiens

<400> 909
Cys Ser Trp Asn Gln Phe Ala Cys Ser Ala Gln Lys Cys Ile Ser Lys
1               5                   10                  15


His Trp Ile Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Leu Asp Glu
            20                  25                  30


Ser Asp Ser Ile Cys
        35


<210> 910
<211> 39
<212> PRT
<213> Homo sapiens

<400> 910
Cys Ala Ala Asp Met Phe Ser Cys Gln Gly Ser Arg Ala Cys Val Pro
1               5                   10                  15


Arg His Trp Leu Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp
            20                  25                  30


Glu Leu Ser Thr Ala Gly Cys
        35


<210> 911
<211> 36
<212> PRT
<213> Homo sapiens

<400> 911
Cys Asp Glu Asn Ala Phe Met Cys His Asn Lys Val Cys Ile Pro Lys
1               5                   10                  15


Gln Phe Val Cys Asp His Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Ser Pro Gln Cys
        35
```

<210> 912
<211> 40
<212> PRT
<213> Homo sapiens

<400> 912
Cys Gly Thr Glu Glu Phe Ser Cys Ala Asp Gly Arg Cys Leu Leu Asn
1   5   10   15

Thr Gln Trp Gln Cys Asp Gly Asp Phe Asp Cys Pro Asp His Ser Asp
            20   25   30

Glu Ala Pro Leu Asn Pro Lys Cys
        35   40

<210> 913
<211> 35
<212> PRT
<213> Homo sapiens

<400> 913
Cys Asn Ser Ser Phe Phe Met Cys Lys Asn Gly Arg Cys Ile Pro Ser
1   5   10   15

Gly Gly Leu Cys Asp Asn Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Arg Asn Cys
        35

<210> 914
<211> 36
<212> PRT
<213> Homo sapiens

<400> 914
Cys Thr Ala Ser Gln Phe Arg Cys Lys Thr Asp Lys Cys Ile Pro Phe
1   5   10   15

Trp Trp Lys Cys Asp Thr Val Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Pro Asp Asp Cys
        35

<210> 915
<211> 35
<212> PRT
<213> Homo sapiens

<400> 915
Cys Gln Pro Gly Arg Phe Gln Cys Gly Thr Gly Leu Cys Ala Leu Pro
1   5   10   15

Ala Phe Ile Cys Asp Gly Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20   25   30

Leu Asn Cys
        35

<210> 916
<211> 36
<212> PRT
<213> Homo sapiens

<400> 916
Cys Leu Ser Gly Gln Phe Lys Cys Thr Lys Asn Gln Lys Cys Ile Pro
1   5   10   15

Val Asn Leu Arg Cys Asn Gly Gln Asp Asp Cys Gly Asp Glu Glu Asp
            20   25   30

Glu Arg Asp Cys
        35

<210> 917
<211> 36
<212> PRT
<213> Homo sapiens

<400> 917
Cys Ser Pro Asp Tyr Phe Gln Cys Lys Thr Thr Lys His Cys Ile Ser
1   5   10   15

Lys Leu Trp Val Cys Asp Glu Asp Pro Asp Cys Ala Asp Ala Ser Asp
            20   25   30

Glu Ala Asn Cys
        35

<210> 918
<211> 35
<212> PRT
<213> Homo sapiens

<400> 918
Cys Gly Pro His Glu Phe Gln Cys Lys Asn Asn Asn Cys Ile Pro Asp
1   5   10   15

His Trp Arg Cys Asp Ser Gln Asn Asp Cys Ser Asp Asn Ser Asp Glu
            20   25   30

```
Glu Asn Cys
        35


<210> 919
<211> 35
<212> PRT
<213> Homo sapiens

<400> 919
Cys Thr Leu Lys Asp Phe Leu Cys Ala Asn Gly Asp Cys Val Ser Ser
1               5                   10                  15


Arg Phe Trp Cys Asp Gly Asp Phe Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Arg Asn Cys
        35


<210> 920
<211> 35
<212> PRT
<213> Homo sapiens

<400> 920
Cys Ser Lys Asp Gln Phe Arg Cys Ser Asn Gly Gln Cys Ile Pro Ala
1               5                   10                  15


Lys Trp Lys Cys Asp Gly His Glu Asp Cys Lys Tyr Gly Glu Asp Glu
            20                  25                  30


Lys Ser Cys
        35


<210> 921
<211> 35
<212> PRT
<213> Homo sapiens

<400> 921
Cys Ser Ser Arg Glu Tyr Ile Cys Ala Ser Asp Gly Cys Ile Ser Ala
1               5                   10                  15


Ser Leu Lys Cys Asn Gly Glu Tyr Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Met Asp Cys
        35


<210> 922
```

```
<211> 36
<212> PRT
<213> Homo sapiens

<400> 922
Cys Lys Glu Asp Gln Phe Arg Cys Lys Asn Lys Ala His Cys Ile Pro
1               5                   10                  15


Ile Arg Trp Leu Cys Asp Gly Ile His Asp Cys Val Asp Gly Ser Asp
            20                  25                  30


Glu Glu Asn Cys
        35


<210> 923
<211> 37
<212> PRT
<213> Homo sapiens

<400> 923
Cys Arg Ala Asp Glu Phe Leu Cys Asn Asn Ser Leu Cys Lys Leu His
1               5                   10                  15


Phe Trp Val Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ala Pro Asp Met Cys
        35


<210> 924
<211> 37
<212> PRT
<213> Homo sapiens

<400> 924
Cys Pro Ser Thr Arg Pro His Arg Cys Arg Asn Asn Arg Ile Cys Leu
1               5                   10                  15


Gln Ser Glu Gln Met Cys Asn Gly Ile Asp Glu Cys Gly Asp Asn Ser
            20                  25                  30


Asp Glu Asp His Cys
        35


<210> 925
<211> 35
<212> PRT
<213> Homo sapiens

<400> 925
Cys Lys Lys Asp Glu Phe Ala Cys Ser Asn Lys Lys Cys Ile Pro Met
1               5                   10                  15
```

```
Asp Leu Gln Cys Asp Arg Leu Asp Asp Cys Gly Asp Gly Ser Asp Glu
            20                  25                  30


Gln Gly Cys
        35


<210> 926
<211> 37
<212> PRT
<213> Homo sapiens

<400> 926
Cys Ala Glu Gly Glu Ala Leu Cys Gln Glu Asn Gly His Cys Val Pro
1               5                   10                  15


His Gly Trp Leu Cys Asp Asn Gln Asp Asp Cys Gly Asp Gly Ser Asp
            20                  25                  30


Glu Glu Gly Glu Cys
        35


<210> 927
<211> 37
<212> PRT
<213> Homo sapiens

<400> 927
Cys Gly Glu Gly Gln Met Thr Cys Ser Ser Gly His Cys Leu Pro Leu
1               5                   10                  15


Ala Leu Leu Cys Asp Arg Gln Asp Asp Cys Gly Asp Gly Thr Asp Glu
            20                  25                  30


Pro Ser Tyr Pro Cys
        35


<210> 928
<211> 35
<212> PRT
<213> Homo sapiens

<400> 928
Cys Pro Gln Gly Leu Leu Ala Cys Ala Asp Gly Arg Cys Leu Pro Pro
1               5                   10                  15


Ala Leu Leu Cys Asp Gly His Pro Asp Cys Leu Asp Ala Ala Asp Glu
            20                  25                  30


Glu Ser Cys
```

```
        35


<210> 929
<211> 37
<212> PRT
<213> Homo sapiens

<400> 929
Cys Val Pro Gly Glu Val Ser Cys Val Asp Gly Thr Cys Leu Gly Ala
1               5                   10                  15


Ile Gln Leu Cys Asp Gly Val Trp Asp Cys Pro Asp Gly Ala Asp Glu
            20                  25                  30


Gly Pro Gly His Cys
        35


<210> 930
<211> 35
<212> PRT
<213> Homo sapiens

<400> 930
Cys Gly Pro Phe Glu Phe Arg Cys Gly Ser Gly Glu Cys Thr Pro Arg
1               5                   10                  15


Gly Trp Arg Cys Asp Gln Glu Glu Asp Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Arg Gly Cys
        35


<210> 931
<211> 38
<212> PRT
<213> Homo sapiens

<400> 931
Cys Ala Pro His His Ala Pro Cys Ala Arg Gly Pro His Cys Val Ser
1               5                   10                  15


Pro Glu Gln Leu Cys Asp Gly Val Arg Gln Cys Pro Asp Gly Ser Asp
            20                  25                  30


Glu Gly Pro Asp Ala Cys
        35


<210> 932
<211> 36
<212> PRT
<213> Homo sapiens
```

```
<400> 932
Cys Pro Gly Leu Phe Pro Cys Gly Val Ala Pro Gly Leu Cys Leu Thr
1               5                   10                  15


Pro Glu Gln Leu Cys Asp Gly Ile Pro Asp Cys Pro Gln Gly Glu Asp
            20                  25                  30


Glu Leu Asp Cys
        35


<210> 933
<211> 39
<212> PRT
<213> Homo sapiens

<400> 933
Cys Pro Glu Tyr Thr Cys Pro Asn Gly Thr Cys Ile Gly Phe Gln Leu
1               5                   10                  15


Val Cys Asp Gly Gln Pro Asp Cys Gly Arg Pro Gly Gln Val Gly Pro
            20                  25                  30


Ser Pro Glu Glu Gln Gly Cys
        35


<210> 934
<211> 36
<212> PRT
<213> Homo sapiens

<400> 934
Cys Glu Pro Gly Val Gly Leu Arg Cys Ala Ser Gly Glu Cys Val Leu
1               5                   10                  15


Arg Gly Gly Pro Cys Asp Gly Val Leu Asp Cys Glu Asp Gly Ser Asp
            20                  25                  30


Glu Glu Gly Cys
        35


<210> 935
<211> 35
<212> PRT
<213> Homo sapiens

<400> 935
Cys Gly Pro Gly Gln Thr Pro Cys Glu Val Leu Gly Cys Val Glu Gln
1               5                   10                  15


Ala Gln Val Cys Asp Gly Arg Glu Asp Cys Leu Asp Gly Ser Asp Glu
```

```
            20                  25                  30

Arg His Cys
        35


<210> 936
<211> 35
<212> PRT
<213> Homo sapiens

<400> 936
Cys Ser Pro Ser Gln Leu Ser Cys Gly Ser Gly Glu Cys Leu Ser Ala
1               5                   10                  15


Glu Arg Arg Cys Asp Leu Arg Pro Asp Cys Gln Asp Gly Ser Asp Glu
            20                  25                  30


Asp Gly Cys
        35


<210> 937
<211> 33
<212> PRT
<213> Homo sapiens

<400> 937
Cys Lys Phe Thr Cys Thr Ser Gly Lys Cys Leu Tyr Leu Gly Ser Leu
1               5                   10                  15


Val Cys Asn Gln Gln Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu Asn
            20                  25                  30


Cys



<210> 938
<211> 36
<212> PRT
<213> Homo sapiens

<400> 938
Cys Pro Pro Thr Lys Phe Gln Cys Arg Thr Ser Gly Leu Cys Val Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Arg Asp Leu Asp Cys Ser Asp Gly Ser Asp
            20                  25                  30


Glu Glu Glu Cys
        35
```

```
<210> 939
<211> 36
<212> PRT
<213> Homo sapiens

<400> 939
Cys Leu Ala Gly Glu Leu Arg Cys Thr Leu Ser Asp Asp Cys Ile Pro
1               5                   10                  15


Leu Thr Trp Arg Cys Asp Gly His Pro Asp Cys Pro Asp Ser Ser Asp
            20                  25                  30


Glu Leu Gly Cys
        35


<210> 940
<211> 36
<212> PRT
<213> Homo sapiens

<400> 940
Cys Ser Leu Gly Tyr Phe Pro Cys Gly Asn Ile Thr Lys Cys Leu Pro
1               5                   10                  15


Gln Leu Leu His Cys Asn Gly Val Asp Asp Cys Gly Asn Gln Ala Asp
            20                  25                  30


Glu Asp Asn Cys
        35


<210> 941
<211> 35
<212> PRT
<213> Homo sapiens

<400> 941
Cys Ala His Asp Glu Phe Arg Cys Asp Gln Leu Ile Cys Leu Leu Pro
1               5                   10                  15


Asp Ser Val Cys Asp Gly Phe Ala Asn Cys Ala Asp Gly Ser Asp Glu
            20                  25                  30


Thr Asn Cys
        35


<210> 942
<211> 34
<212> PRT
<213> Homo sapiens

<400> 942
Cys Gly Pro Ser Glu Leu Ser Cys Gln Ala Gly Gly Cys Lys Gly Val
```

1   5   10   15

Gln Trp Met Cys Asp Met Trp Arg Asp Cys Thr Asp Gly Ser Asp Asp
            20   25   30

Asn Cys

<210> 943
<211> 35
<212> PRT
<213> Homo sapiens

<400> 943
Cys Ser Arg Tyr His Phe Phe Cys Asp Asp Gly Cys Cys Ile Asp Ile
1   5   10   15

Thr Leu Ala Cys Asp Gly Val Gln Gln Cys Pro Asp Gly Ser Asp Glu
            20   25   30

Asp Phe Cys
        35

<210> 944
<211> 32
<212> PRT
<213> Homo sapiens

<400> 944
Cys Pro Gly Glu Phe Leu Cys Ser Val Asn Gly Leu Cys Val Pro Ala
1   5   10   15

Cys Asp Gly Val Lys Asp Cys Pro Asn Gly Leu Asp Glu Arg Asn Cys
            20   25   30

<210> 945
<211> 35
<212> PRT
<213> Homo sapiens

<400> 945
Cys Arg Ala Thr Phe Gln Cys Lys Glu Asp Ser Thr Cys Ile Ser Leu
1   5   10   15

Pro Lys Val Cys Asp Gly Gln Pro Asp Cys Leu Asn Gly Ser Asp Glu
            20   25   30

Glu Gln Cys
        35

<210> 946
<211> 36
<212> PRT
<213> Homo sapiens

<400> 946
```
Cys Gly Thr Phe Thr Phe Gln Cys Glu Asp Arg Ser Cys Val Lys Lys
1               5                   10                  15


Pro Asn Pro Gln Cys Asp Gly Arg Pro Asp Cys Arg Asp Gly Ser Asp
            20                  25                  30


Glu Glu His Cys
        35
```

<210> 947
<211> 36
<212> PRT
<213> Homo sapiens

<400> 947
```
Cys Gln Lys Gly Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro
1               5                   10                  15


Arg Ala Phe His Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp
            20                  25                  30


Glu Glu Asn Cys
        35
```

<210> 948
<211> 35
<212> PRT
<213> Homo sapiens

<400> 948
```
Cys Ser Thr Ala Arg Tyr His Cys Lys Asn Gly Leu Cys Ile Asp Lys
1               5                   10                  15


Ser Phe Ile Cys Asp Gly Gln Asn Asn Cys Gln Asp Asn Ser Asp Glu
            20                  25                  30


Glu Ser Cys
        35
```

<210> 949
<211> 36
<212> PRT
<213> Homo sapiens

<400> 949
```
Cys Gly Pro Thr Phe Phe Pro Cys Ala Ser Gly Ile His Cys Ile Ile
```

```
1               5                   10                  15


Gly Arg Phe Arg Cys Asn Gly Phe Glu Asp Cys Pro Asp Gly Ser Asp
            20                  25                  30


Glu Glu Asn Cys
        35


<210> 950
<211> 36
<212> PRT
<213> Homo sapiens

<400> 950
Cys Asn Ile Pro Gly Asn Phe Met Cys Ser Asn Gly Arg Cys Ile Pro
1               5                   10                  15


Gly Ala Trp Gln Cys Asp Gly Leu Pro Asp Cys Phe Asp Lys Ser Asp
            20                  25                  30


Glu Lys Glu Cys
        35


<210> 951
<211> 38
<212> PRT
<213> Homo sapiens

<400> 951
Cys Ala Leu Asp Gln Phe Leu Cys Trp Asn Gly Arg Cys Ile Gly Gln
1               5                   10                  15


Arg Lys Leu Cys Asn Gly Val Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30


Ser Pro Gln Gln Asn Cys
        35


<210> 952
<211> 34
<212> PRT
<213> Homo sapiens

<400> 952
Cys Glu Glu Asp Glu Phe Pro Cys Gln Asn Gly Tyr Cys Ile Arg Ser
1               5                   10                  15


Leu Trp His Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
            20                  25                  30
```

```
Gln Cys



<210> 953
<211> 35
<212> PRT
<213> Homo sapiens

<400> 953
Cys Arg Ser Gly Glu Phe Met Cys Asp Ser Gly Leu Cys Ile Asn Ala
1               5                   10                  15


Gly Trp Arg Cys Asp Gly Asp Ala Asp Cys Asp Asp Gln Ser Asp Glu
            20                  25                  30


Arg Asn Cys
        35


<210> 954
<211> 35
<212> PRT
<213> Homo sapiens

<400> 954
Cys Thr Ala Glu Gln Phe Arg Cys His Ser Gly Arg Cys Val Arg Leu
1               5                   10                  15


Ser Trp Arg Cys Asp Gly Glu Asp Asp Cys Ala Asp Asn Ser Asp Glu
            20                  25                  30


Glu Asn Cys
        35


<210> 955
<211> 35
<212> PRT
<213> Homo sapiens

<400> 955
Cys Ser Pro Leu Asp Phe His Cys Asp Asn Gly Lys Cys Ile Arg Arg
1               5                   10                  15


Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asp Ser Asp Glu
            20                  25                  30


Gln Asp Cys
        35


<210> 956
<211> 35
<212> PRT
```

```
<213> Homo sapiens

<400> 956
Cys Asn Leu Glu Glu Phe Gln Cys Ala Tyr Gly Arg Cys Ile Leu Asp
1               5                   10                  15


Ile Tyr His Cys Asp Gly Asp Asp Asp Cys Gly Asp Trp Ser Asp Glu
            20                  25                  30


Ser Asp Cys
        35


<210> 957
<211> 35
<212> PRT
<213> Homo sapiens

<400> 957
Cys Ser Asp Lys Glu Phe Arg Cys Ser Asp Gly Ser Cys Ile Ala Glu
1               5                   10                  15


His Trp Tyr Cys Asp Gly Asp Thr Asp Cys Lys Asp Gly Ser Asp Glu
            20                  25                  30


Glu Asn Cys
        35


<210> 958
<211> 40
<212> PRT
<213> Homo sapiens

<400> 958
Cys Gly Arg Ser His Phe Thr Cys Ala Val Ser Ala Leu Gly Glu Cys
1               5                   10                  15


Thr Cys Ile Pro Ala Gln Trp Gln Cys Asp Gly Asp Asn Asp Cys Gly
            20                  25                  30


Asp His Ser Asp Glu Asp Gly Cys
        35                  40


<210> 959
<211> 35
<212> PRT
<213> Homo sapiens

<400> 959
Cys Leu Gln Glu Glu Phe Gln Cys Leu Asn His Arg Cys Val Ser Ala
1               5                   10                  15
```

Val Gln Arg Cys Asp Gly Val Asp Ala Cys Gly Asp Gly Ser Asp Glu
            20   25   30

Ala Gly Cys
        35

<210> 960
<211> 41
<212> PRT
<213> Homo sapiens

<400> 960
Cys Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly Thr Ser Gly Ala
1   5   10   15

Thr Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr Gln Thr Phe Cys
            20   25   30

Ala Asp Gly Ala Asp Glu Arg Arg Cys
        35   40

<210> 961
<211> 35
<212> PRT
<213> Homo sapiens

<400> 961
Cys Gln Pro Gly Asn Phe Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu
1   5   10   15

Thr Trp Val Cys Asp Gly Gln Pro Asp Cys Ala Asp Gly Ser Asp Glu
            20   25   30

Trp Asp Cys
        35

<210> 962
<211> 36
<212> PRT
<213> Homo sapiens

<400> 962
Cys Pro Glu Ile Thr Asp Phe Leu Cys Arg Asp Lys Lys Cys Ile Ala
1   5   10   15

Ser His Leu Leu Cys Asp Tyr Lys Pro Asp Cys Ser Asp Arg Ser Asp
            20   25   30

Glu Ala His Cys
        35

<210> 963
<211> 36
<212> PRT
<213> Homo sapiens

<400> 963
Cys Asn Asn Arg Thr Phe Lys Cys Gly Asn Asp Ile Cys Phe Arg Lys
1   5   10   15

Gln Asn Ala Lys Cys Asp Gly Thr Val Asp Cys Pro Asp Gly Ser Asp
            20   25   30

Glu Glu Gly Cys
        35

<210> 964
<211> 37
<212> PRT
<213> Homo sapiens

<400> 964
Cys Pro Pro Gly His His His Cys Gln Asn Lys Val Cys Val Glu Pro
1   5   10   15

Gln Gln Leu Cys Asp Gly Glu Asp Asn Cys Gly Asp Leu Ser Asp Glu
            20   25   30

Asn Pro Leu Thr Cys
        35

<210> 965
<211> 34
<212> PRT
<213> Homo sapiens

<400> 965
Cys Lys Gln Gly His Leu Ala Cys Gly Asp Leu Cys Val Pro Pro Glu
1   5   10   15

Gln Leu Cys Asp Phe Glu Glu Gln Cys Ala Gly Gly Glu Asp Glu Gln
            20   25   30

Ala Cys

<210> 966
<211> 36
<212> PRT
<213> Homo sapiens

<400> 966

```
Cys Pro Gly Asn Ser Phe Ser Cys Gly Asn Ser Gln Cys Val Thr Lys
1               5                   10                  15


Val Asn Pro Glu Cys Asp Asp Gln Glu Asp Cys Ser Asp Gly Ser Asp
            20                  25                  30


Glu Ala His Cys
        35


<210> 967
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      6xHis tag

<400> 967
His His His His His His
1               5
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