Claims

1. An isolated peptide comprising or consisting of the amino acid sequence of:
$K^1K^2R^3Y^4Xaa_1Xaa_2Xaa_3Xaa_4L^9L^{10}Xaa_5Xaa_6Xaa_7Xaa_8Xaa_9$ (SEQ ID NO: 21)

wherein:

Xaa_1 is selected from the group consisting of S (serine), aminoisobutyric acid and an unnatural amino acid;

Xaa_2 is selected from the group consisting of R (arginine), aminoisobutyric acid and an unnatural amino acid;

Xaa_3 is selected from the group consisting of E (glutamic acid), aminoisobutyric acid and an unnatural amino acid;

Xaa_4 is selected from the group consisting of F (phenylalanine), Q (glutamine), A (alanine), aminoisobutyric acid and an unnatural amino acid;

Xaa_5 is selected from the group consisting of G (glycine), aminoisobutyric acid and an unnatural amino acid;

Xaa_6 is selected from the group consisting of F (phenylalanine), L (leucine), aminoisobutyric acid, 2-aminobutyric acid and an unnatural amino acid;

Xaa_7 is absent or selected from the group consisting of Q (glutamine), aminoisobutyric acid and an unnatural amino acid;

Xaa_8 is absent or selected from the group consisting of F (phenylalanine), aminoisobutyric acid and an unnatural amino acid;

Xaa_9 is absent or selected from the group consisting of aminoisobutyric acid and an unnatural amino acid;

wherein the peptide comprises at least one peptide-cross linker linking Xaa_1, Xaa_2, Xaa_3 or Xaa_4 with Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9.

2. The peptide of claim 1 comprising at least two peptide cross linkers.

3. The peptide of claim 2, wherein the unnatural amino acid is in the position Xaa_1, Xaa_2, Xaa_3 or Xaa_4 and cross-links to position Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9.

4. The peptide of any one of the preceding claims wherein the cross-linker is a hydrocarbon linkage.

5. The peptide of any one of the preceding claims, wherein the unnatural amino acid at position Xaa_1, Xaa_2, Xaa_3 or Xaa_4 that cross-links the unnatural amino acid to position Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9 are both olefin-bearing unnatural amino acids.

6. The peptide of claim 5, wherein the olefin-bearing unnatural amino acid is selected from the group consisting of (*S*)-2-(4′-pentenyl)alanine, (*R*)-2-(4′-pentenyl)alanine, (S)-2-(7′-octenyl)alanine, (R)-2-(7′-octenyl)alanine and any one of the aforementioned amino acids with varied length.

7. The peptide of any one of claims 1 to 3, wherein the cross-linker is a cysteine bridge or a Lys-Asn (Lysine-Asparagine) linker.

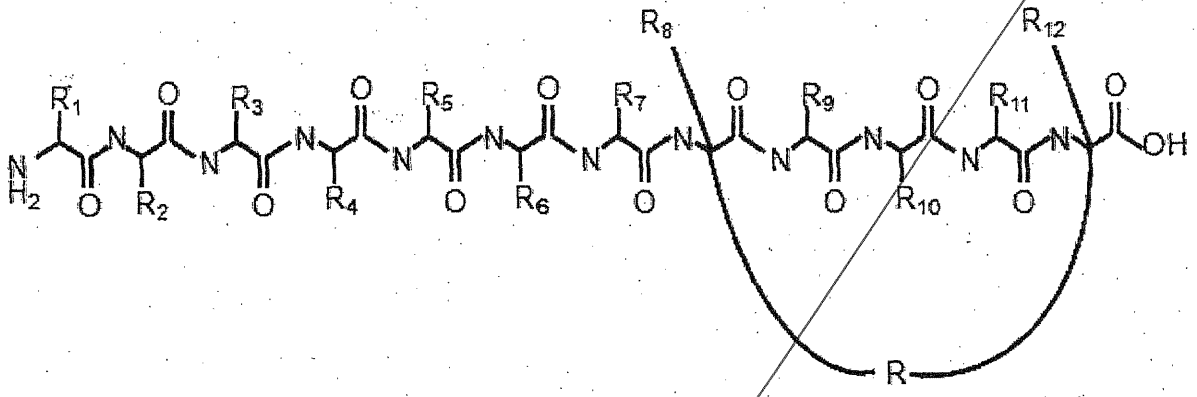
8. The peptide of any one of the preceding claims, wherein the C-terminus of the peptide is amidated.

9. The peptide of any one of the preceding claims, wherein the N-terminus of the peptide is acetylated.

10. The peptide of any one of the preceding claims, characterized in that the peptide is capable of inhibiting eIF4E and eIF4G interaction.

11. The peptide of any one of the preceding claims, wherein the peptide is modified to include one or more ligands selected from the group consisting of: hydroxyl, phosphate, amine, amide, sulphate, sulphide, a biotin moiety, a carbohydrate moiety, a fatty acid-derived acid group, a fluorescent moiety, a chromophore moiety, a radioisotope, a PEG linker, an affinity label, a targeting moiety, an antibody, a cell penetrating peptide and a combination of the aforementioned ligands.

12. The peptide of any one of the preceding claims, wherein the peptide comprises formula I:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{12} are independently H , a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl,or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

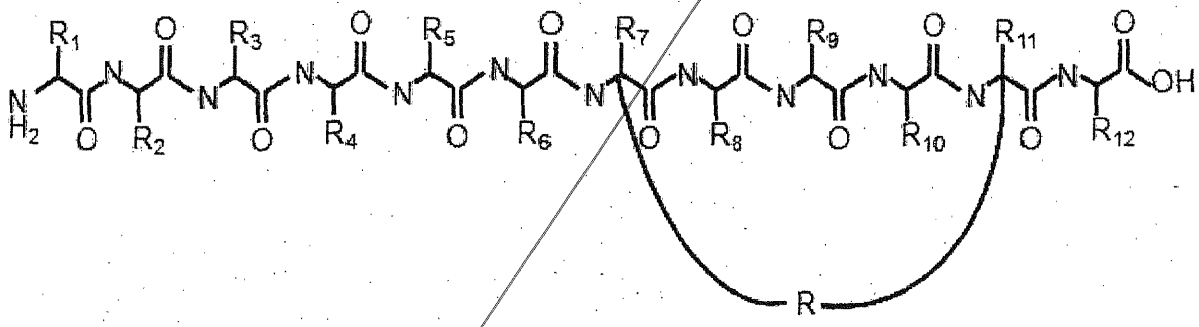
n is an integer from 1-4.

13. The peptide of claim 12, wherein R_8 and R_{12} are independently H or a C_1 to C_6 alkyl.

14. The peptide of claim 13, wherein R_8 and R_{12} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-02) cross-linking the α-carbon of the two unnatural amino-acids.

15. The peptide of claim 14, wherein R is obtained by cross-linking the pentenyl side chains having the *S* stereochemistry of (S)-2-(4′-pentenyl)alanine at position Xaa_2 (*i*; R_8 is CH_3) and at position Xaa_4 at a position four amino acids apart (*i+4*; R_{12} is CH_3), wherein the pentenyl side chains of both Xaa_2 and Xaa_4 are linked to the α-carbon of the two unnatural amino-acids and are on the same side of the α-helix (sTIP-02).

16. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula II:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 and R_{11} are independently H , a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{12} is benzyl [F], or $-CH_2CH(CH_3)_2$ [L], or aminoisobutyric acid or 2-aminobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO2R14, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

17. The peptide of claim 16, wherein R_7 and R_{11} are independently H or a C_1 to C_6 alkyl.

18. The peptide of claim 16, wherein R_7 and R_{11} are each CH_3 (methyl) and;

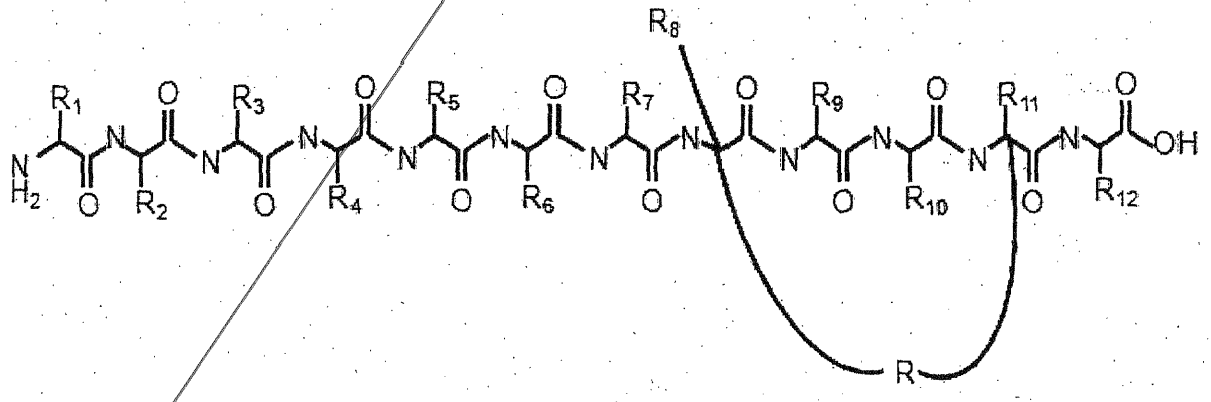
wherein R is 4'-cyclooctenyl and;

wherein R_8 is benzyl [F] and R_{12} is independently benzyl [F] (sTIP-01) or 2-aminobutyric acid (sTIP-$01^{F12\&}$), or;

wherein R_8 is $-(CH_2)_2-C(O)NH_2$ [Q] and R_{12} is $-CH_2CH(CH_3)_2$ [L] (sTIP-04) or;

wherein R_8 is methyl [A] and R_{12} is benzyl [F] (sTIP-01^{F8A}).

19. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula III:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{11} are independently H, a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{12} is benzyl [F], or $-CH_2CH(CH_3)_2$ [L], or aminoisobutyric acid or 2-aminobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

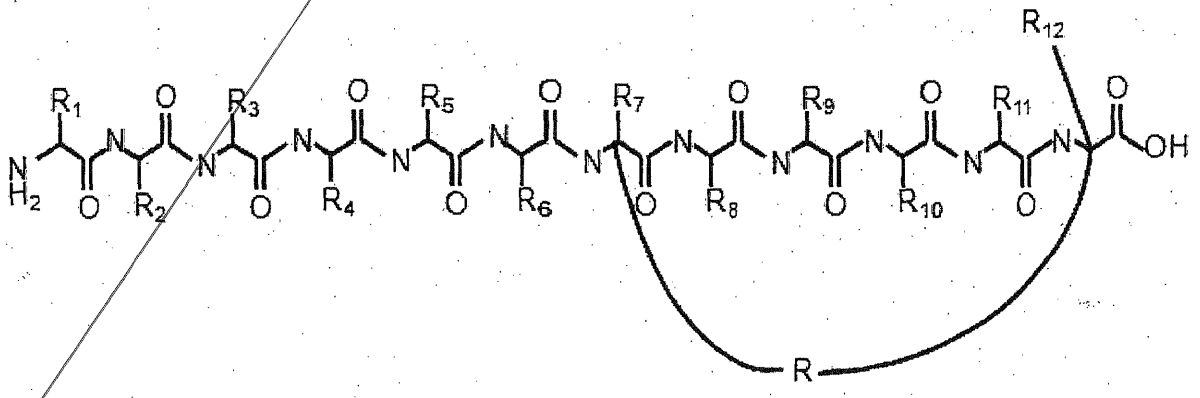
each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

20. The peptide of claim 19, wherein R_8 and R_{11} are independently H or a C_1 to C_6 alkyl.

21. The peptide of claim 20, wherein R_8 and R_{11} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-03) cross-linking the α-carbon of the two unnatural amino-acids.

22. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula IV:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 and R_{12} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

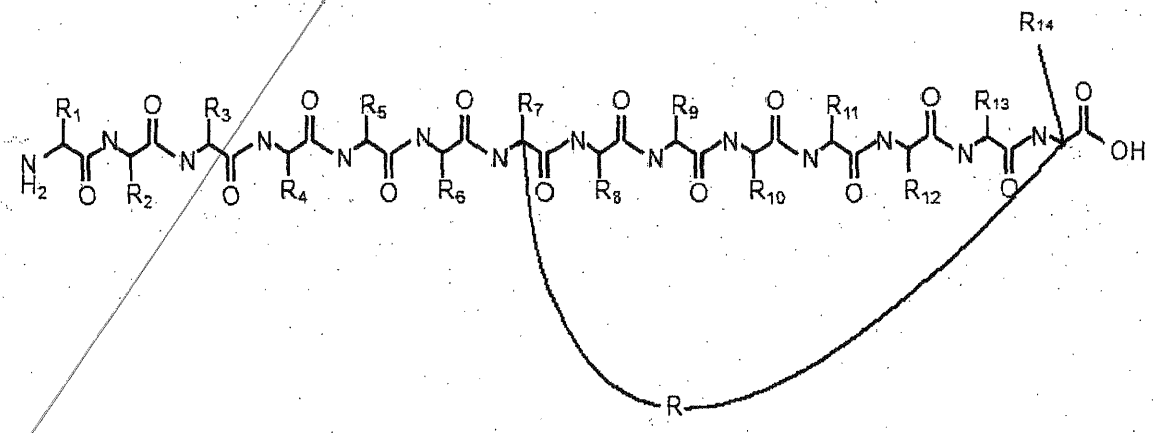
K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

23. The peptide of claim 22, wherein R_7 and R_{12} are independently H or a C_1 to C_6 alkyl.

24. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula V:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 and R_{14} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

R_{12} is benzyl [F];

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

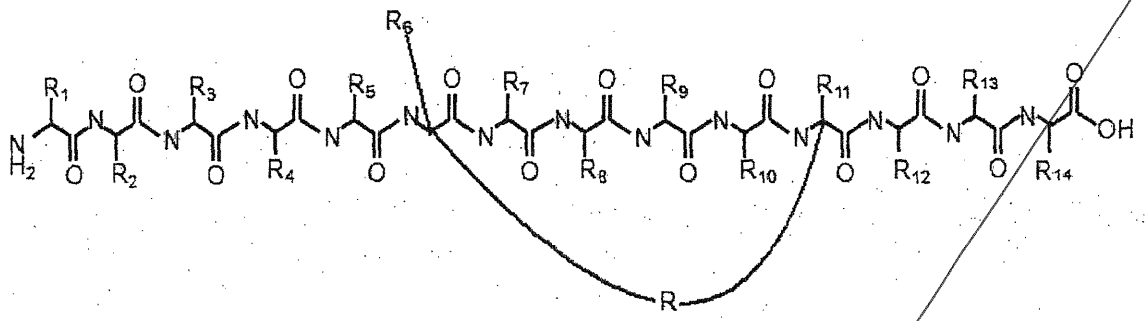
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

25. The peptide of claim 24, wherein R_7 and R_{14} are independently H or a C_1 to C_6 alkyl.

26. The peptide of claim 24, wherein R_7 and R_{14} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-05) cross-linking the α-carbon of the two unnatural amino-acids.

27. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula VI:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 and R_{11} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{12} is benzyl [F];

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

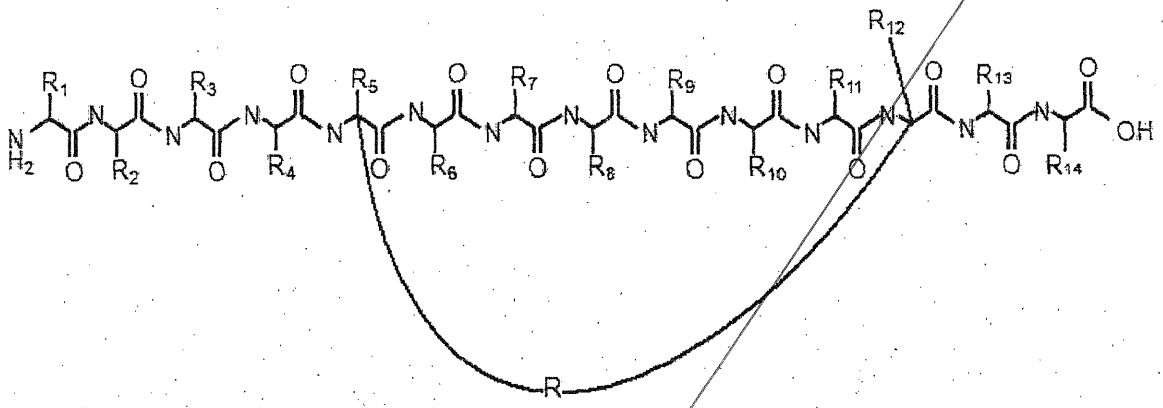
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

28. The peptide of claim 27, wherein R_6 and R_{11} are independently H or a C_1 to C_6 alkyl.

29. The peptide of claim 27, wherein R_6 and R_{11} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-06) cross-linking the α-carbon of the two unnatural amino-acids.

30. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula VII:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 and R_{12} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{11} is –H [G] or aminoisobutyric acid;

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

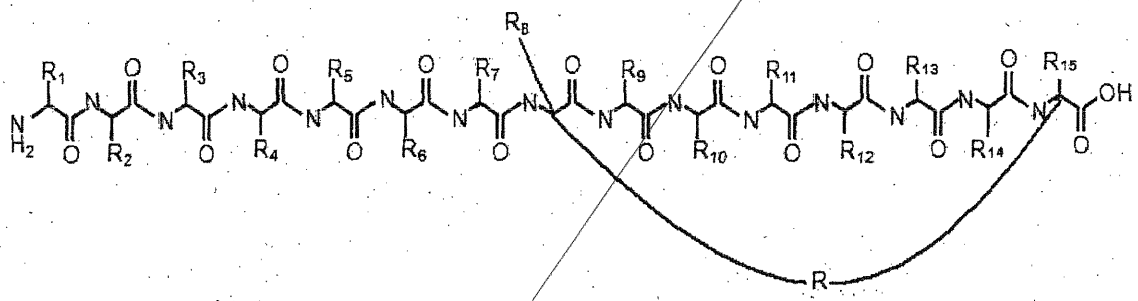
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

31. The peptide of claim 30, wherein R_5 and R_{12} are independently H or a C_1 to C_6 alkyl.

32. The peptide of claim 30, wherein R_5 and R_{12} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-07) cross-linking the α-carbon of the two unnatural amino-acids.

33. The peptide of any one of claims 1 to 11, wherein the peptide comprises formula VIII:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{15} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{11} is –H [G] or aminoisobutyric acid;

R_{12} is benzyl [F];

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

34. The peptide of claim 33, wherein R_8 and R_{15} are independently H or a C_1 to C_6 alkyl.

35. The peptide of claim 33, wherein R_8 and R_{15} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-08) cross-linking the α-carbon of the two unnatural amino-acids.

36. The peptide of any one of claims 1 to 11, selected from the group consisting of:

KKRYSRXFLLXF	SEQ ID NO: 2
KKRYSREXLLGX	SEQ ID NO: 3
KKRYSREXLLXF	SEQ ID NO: 4
KKRYSRXQLLXL	SEQ ID NO: 5
KKRYSRXFLLX	SEQ ID NO: 6
KKRYSRXFLLX&	SEQ ID NO: 7
KKRYSRXALLXF	SEQ ID NO: 8
KKRYSR*FLL*F	SEQ ID NO: 9
KKRYSRE*LLG*	SEQ ID NO: 10
KKRYSRE*LL*F	SEQ ID NO: 11
KKRYSR*QLL*L	SEQ ID NO: 12
KKRYSR*FLL*	SEQ ID NO: 13
KKRYSR*FLL*&	SEQ ID NO: 14
KKRYSR*ALL*F	SEQ ID NO: 15
KKRYSR*FLLGFQ*	SEQ ID NO: 17
KKRYS*EFLLGF*F	SEQ ID NO: 18

KKRY*REFLLG*QF	SEQ ID NO: 19
KKRYSRE*LLGFQF*	SEQ ID NO: 20

wherein X represents aminoisobutyric acid;

* represent a staple position; and

& represents 2-amino-butyric acid.

37. An isolated nucleic acid molecule encoding a peptide comprising the amino acid sequence KKRYSREFLLGF (SEQ ID NO: 1), wherein the peptide is modified to obtain any one of the peptides referred to in any one of claims 1 to 36.

38. A vector comprising a nucleic acid molecule of claim 37.

39. A host cell comprising a nucleic acid molecule of claim 37 or a vector of claim 38.

40. A pharmaceutical composition comprising a peptide of any one of claims 1 to 36, or an isolated nucleic acid molecule of claim 37, or a vector of claim 38.

41. The pharmaceutical composition of claim 40, further comprising one or more pharmaceutically acceptable excipients, or vehicles, or carriers.

42. The pharmaceutical composition according to claim 40 or 41, wherein the pharmaceutical composition further comprises a therapeutic compound.

43. The pharmaceutical composition of claim 42, wherein the therapeutic compound is an apoptosis promoting compound.

44. The pharmaceutical composition of claim 43, wherein the apoptosis promoting compound is selected from the group consisting of Cyclin-dependent Kinase (CDK) inhibitors, Receptor Tyrosine Kinase (RTK) inhibitors, BCL (B-cell lymphoma) family BH3 (Bcl-2 homology domain 3)-mimetic inhibitors and Ataxia Telangiectasia Mutated (ATM) inhibitors.

45. The pharmaceutical composition of claim 44, wherein the CDK inhibitors comprise inhibitors selected from the group consisting of:

2-(*R*)-(1-Ethyl-2-hydroxyethylamino)-6-benzylamino-9-isopropylpurine (CYC202; Roscovitine; Seliciclib);

4-[[5-Amino-1-(2,6-difluorobenzoyl)-1H-1,2,4-triazol-3-yl]amino]benzenesulfonamide (JNJ-7706621);

N-(4-piperidinyl)-4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxamide (AT-7519);

N-(5-(((5-(1,1-dimethylethyl)-2-oxazolyl)methyl)thio)-2-thiazolyl)-4-piperidinecarboxamide (SNS-032);

8,12-Epoxy-1H,8H-2,7b,12a-triazadibenzo(a,g)cyclonona(cde)triinden-1-one, 2,3,9,10,11,12-hexahydro-3-hydroxy-9-methoxy-8-methyl-10-(methylamino)- (UCN-01; 7-Hydroxystaurosporine; KRX-0601);

N,1,4,4-tetramethyl-8-((4-(4-methylpiperazin-1-yl)phenyl)amino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (PHA-848125; milciclib);

2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methylpiperidin-4-yl]chromen-4-one hydrochloride (flavopiridol; alvocidib);

6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one hydrochloride (PD 0332991);

4-(1-isopropyl-2-methyl-1H-imidazol-5-yl)-N-(4-(methylsulfonyl)phenyl)pyrimidin-2-amine (AZD5438);

(S)-3-(((3-ethyl-5-(2-(2-hydroxyethyl)piperidin-1-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)methyl)pyridine 1-oxide (Dinaciclib; SCH 727965);

N-(4-Piperidinyl)-4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxamide hydrochloride (AT-7519); and

pharmaceutically acceptable salts thereof.

46. The pharmaceutical composition of claim 44, wherein the RTK inhibitors comprise inhibitors selected from the group consisting of:

N-[3-chloro-4-[(3-fluorophenyl)methoxy] phenyl]-6- [5-[(2-methylsulfonylethylamino) methyl]-2-furyl]quinazolin-4-amine (lapatinib);

N1'-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-N1-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (foretinib);

N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (cabozantinib(XL184));

N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (cabozantinib(XL184));

3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine (crizotinib (Xalkori));

(3Z)-N-(3-Chlorophenyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-N-methyl-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide (SU11274);

(3Z)-5-[[(2,6-Dichlorophenyl)methyl]sulfonyl]-3-[[3,5-dimethyl-4-[[(2R)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-1H-pyrrol-2-yl]methylene]-1,3-dihydro-2H-indol-2-one hydrate (PHA-665752);

6-[[6-(1-Methylpyrazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl]quinoline (SGX-523);

4-[1-(6-Quinolinylmethyl)-1H-1,2,3-triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazole-1-ethanol methanesulfonate (1:1) (PF-04217903);

2-Fluoro-N-methyl-4-[7-[(quinolin-6-yl)methyl]imidazo[1,2-b]-[1,2,4]triazin-2-yl]benzamide (INCB28060);

N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide (afatinib);

3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)-pyrrolidine-2,5-dione (ARQ-197 (Tivantinib));

N-[(2R)-1,4-dioxan-2-ylmethyl]-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfuric diamide (MK-2461);

N-[4-(3-Amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea (Linifanib(ABT 869));

4-[[(3S)-3-Dimethylaminopyrrolidin-1-yl]methyl]-N-[4-methyl-3-[(4-pyrimidin-5-ylpyrimidin-2-yl)amino]phenyl]-3-(trifluoromethyl)benzamide (Bafetinib (INNO-406)); and

pharmaceutical acceptable salts thereof.

47. The pharmaceutical composition of claim 44, wherein the BCL family BH3-mimetic inhibitors comprise inhibitors selected from the group consisting of:
4-[4-[[2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (ABT 263;Navitoclax);
2-[2-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylene]-3-methoxy-2H-pyrrol-5-yl]-1H-indole methanesulfonate (Obatoclax mesylate (GX15-070));
4-[4-[(4'-chloro[1,1'-biphenyl]-2-yl)methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-Benzamide (ABT-737); and pharmaceutically acceptable salts thereof.

48. The pharmaceutical composition of claim 44, wherein the ATM inhibitors comprise inhibitors selected from the group consisting of:
2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (KU-55933);
(2R,6S)-2,6-Dimethyl-N-[5-[6-(4-morpholinyl)-4-oxo-4H-pyran-2-yl]-9H-thioxanthen-2-yl]-4-morpholineacetamide (KU-60019);
1-(6,7-Dimethoxy-4-quinazolinyl)-3-(2-pyridinyl)-1H-1,2,4-triazol-5-amine (CP466722);
α-Phenyl-N-[2,2,2-trichloro-1-[[[(4-fluoro-3-nitrophenyl)amino]thioxomethyl]amino] ethyl]benzene acetamide (CGK 733)
and pharmaceutically acceptable salts thereof.

49. Use of the peptide according to any one of claims 1 to 36 in the manufacture of a medicament for treating or preventing cancer.

50. The use of claim 49, wherein the cancer is characterized by overexpression or hyperactivity of eIF4E containing complexes.

51. The use according to claim 49, wherein cancer is selected from a group comprising or consisting of gastric cancer, colon cancer, lung cancer, breast cancer, bladder cancer, neuroblastoma, melanoma, head and neck cancer, esophagus cancer, cervix cancer, prostate cancer and leukemia.

52. Use of the peptide of any one of claims 1 to 36 or the isolated nucleic acid molecule of claim 37, or the vector according to claim 38 in the manufacture of a medicament for treating or preventing cancer.

53. The use according to claim 52 wherein the medicament is to be administered in combination with one or more further therapeutic agents to the patient, wherein administration of the medicament and the therapeutic agent is simultaneous, sequential or separate.

54. Use of a peptide according to any one of claims 1 to 36 for protein purification, or for inhibiting protein-protein interactions, or as template for protein-protein interactions.

Claims

1. An isolated peptide comprising or consisting of the amino acid sequence of:
$K^1K^2R^3Y^4Xaa_1Xaa_2Xaa_3Xaa_4L^9L^{10}Xaa_5Xaa_6Xaa_7Xaa_8Xaa_9$ (SEQ ID NO: 21)

wherein:

Xaa_1 is selected from the group consisting of S (serine), aminoisobutyric acid and an unnatural amino acid;

Xaa_2 is selected from the group consisting of R (arginine), aminoisobutyric acid and an unnatural amino acid;

Xaa_3 is selected from the group consisting of E (glutamic acid), aminoisobutyric acid and an unnatural amino acid;

Xaa_4 is selected from the group consisting of F (phenylalanine), Q (glutamine), A (alanine), aminoisobutyric acid and an unnatural amino acid;

Xaa_5 is selected from the group consisting of G (glycine), aminoisobutyric acid and an unnatural amino acid;

Xaa_6 is selected from the group consisting of F (phenylalanine), L (leucine), aminoisobutyric acid, 2-aminobutyric acid and an unnatural amino acid;

Xaa_7 is absent or selected from the group consisting of Q (glutamine), aminoisobutyric acid and an unnatural amino acid;

Xaa_8 is absent or selected from the group consisting of F (phenylalanine), aminoisobutyric acid and an unnatural amino acid;

Xaa_9 is absent or selected from the group consisting of aminoisobutyric acid and an unnatural amino acid;

wherein the peptide comprises at least one peptide-cross linker linking Xaa_1, Xaa_2, Xaa_3 or Xaa_4 with Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9.

2. The peptide of claim 1 comprising at least two peptide cross linkers.

3. The peptide of claim 2, wherein the unnatural amino acid is in the position Xaa_1, Xaa_2, Xaa_3 or Xaa_4 and cross-links to position Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9.

4. The peptide of any one of the preceding claims wherein the cross-linker is a hydrocarbon linkage.

5. The peptide of any one of the preceding claims, wherein the unnatural amino acid at position Xaa_1, Xaa_2, Xaa_3 or Xaa_4 that cross-links the unnatural amino acid to position Xaa_5, Xaa_6, Xaa_7, Xaa_8 or Xaa_9 are both olefin-bearing unnatural amino acids.

6. The peptide of claim 5, wherein the olefin-bearing unnatural amino acid is selected from the group consisting of (*S*)-2-(4′-pentenyl)alanine, (*R*)-2-(4′-pentenyl)alanine, (S)-2-(7′-octenyl)alanine, (R)-2-(7′-octenyl)alanine and any one of the aforementioned amino acids with varied length.

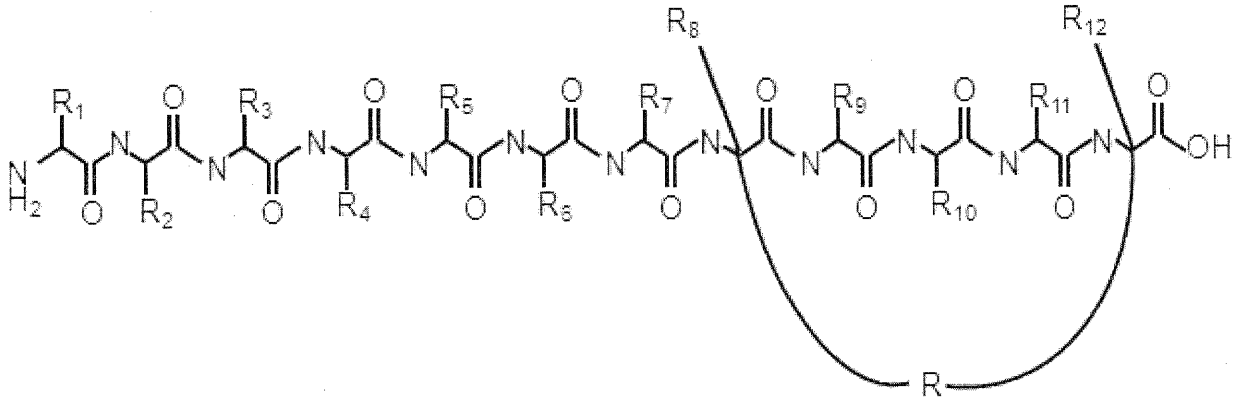
7. The peptide of any one of claims 1 to 3, wherein the cross-linker is a cysteine bridge or a Lys-Asn (Lysine-Asparagine) linker.

8. The peptide of any one of the preceding claims, wherein the C-terminus of the peptide is amidated.

9. The peptide of any one of the preceding claims, wherein the N-terminus of the peptide is acetylated.

10. The peptide of any one of the preceding claims, wherein the peptide is modified to include one or more ligands selected from the group consisting of: hydroxyl, phosphate, amine, amide, sulphate, sulphide, a biotin moiety, a carbohydrate moiety, a fatty acid-derived acid group, a fluorescent moiety, a chromophore moiety, a radioisotope, a PEG linker, an affinity label, a targeting moiety, an antibody, a cell penetrating peptide and a combination of the aforementioned ligands.

11. The peptide of any one of the preceding claims, wherein the peptide comprises formula I:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{12} are independently H , a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl,or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

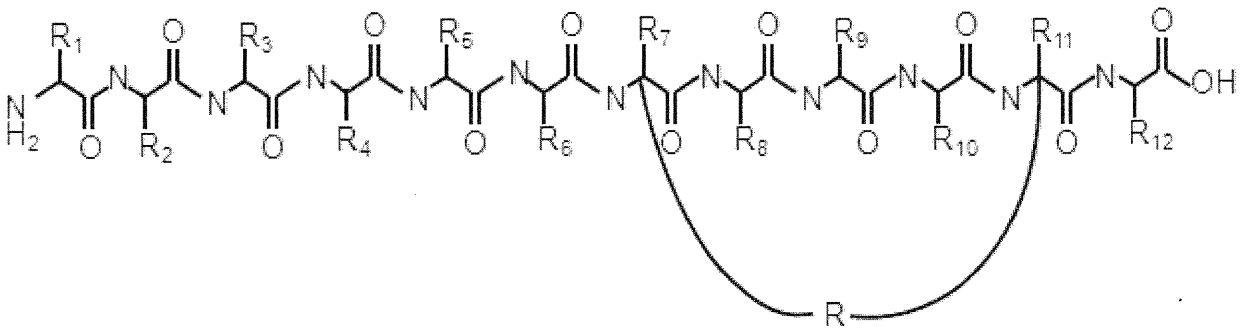
n is an integer from 1-4.

12. The peptide of claim 11, wherein R_8 and R_{12} are independently H or a C_1 to C_6 alkyl.

13. The peptide of claim 12, wherein R_8 and R_{12} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-02) cross-linking the α-carbon of the two unnatural amino-acids.

14. The peptide of claim 13, wherein R is obtained by cross-linking the pentenyl side chains having the *S* stereochemistry of (S)-2-(4′-pentenyl)alanine at position Xaa_2 (*i*; R_8 is CH_3) and at position Xaa_4 at a position four amino acids apart (*i+4*; R_{12} is CH_3), wherein the pentenyl side chains of both Xaa_2 and Xaa_4 are linked to the α-carbon of the two unnatural amino-acids and are on the same side of the α-helix (sTIP-02).

15. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula II:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 and R_{11} are independently H , a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{12} is benzyl [F], or $-CH_2CH(CH_3)_2$ [L], or aminoisobutyric acid or 2-aminobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO2R14, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

16. The peptide of claim 15, wherein R_7 and R_{11} are independently H or a C_1 to C_6 alkyl.

17. The peptide of claim 15, wherein R_7 and R_{11} are each CH_3 (methyl) and;

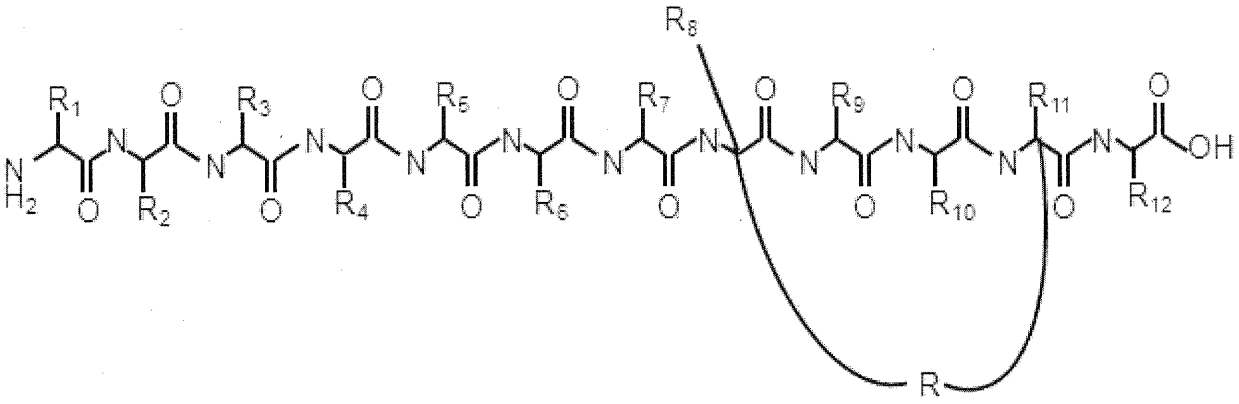
wherein R is 4'-cyclooctenyl and;

wherein R_8 is benzyl [F] and R_{12} is independently benzyl [F] (sTIP-01) or 2-aminobutyric acid (sTIP-$01^{F12\&}$), or;

wherein R_8 is $-(CH_2)_2-C(O)NH_2$ [Q] and R_{12} is $-CH_2CH(CH_3)_2$ [L] (sTIP-04) or;

wherein R_8 is methyl [A] and R_{12} is benzyl [F] (sTIP-01^{F8A}).

18. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula III:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{11} are independently H, a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L]; and

R_{12} is benzyl [F], or $-CH_2CH(CH_3)_2$ [L], or aminoisobutyric acid or 2-aminobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

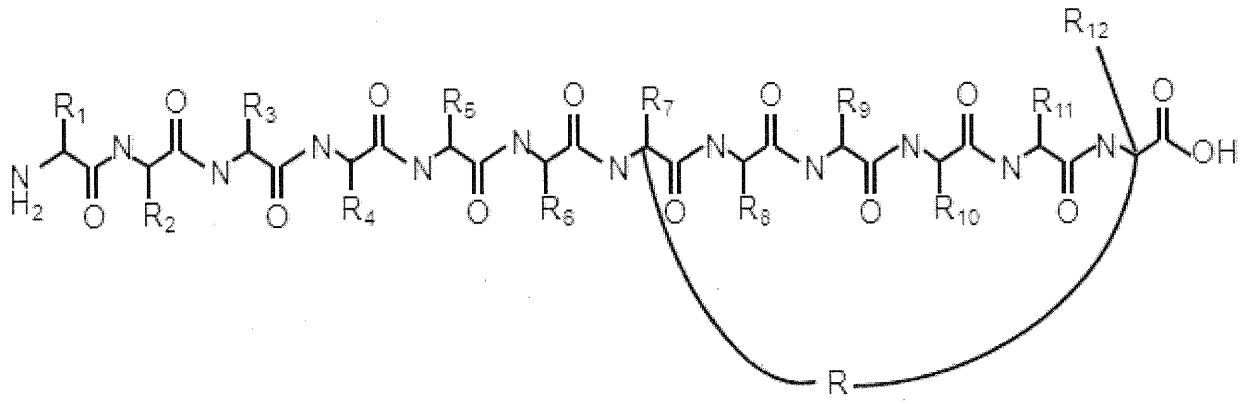
each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

19. The peptide of claim 18, wherein R_8 and R_{11} are independently H or a C_1 to C_6 alkyl.

20. The peptide of claim 19, wherein R_8 and R_{11} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-03) cross-linking the α-carbon of the two unnatural amino-acids.

21. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula IV:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is -CH_2-OH [S];

R_6 is -$(CH_2)_3$-NH-$C(NH_2)_2$ [R];

R_7 and R_{12} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or –$(CH_2)_2$-$C(O)NH_2$ [Q], or –CH_3 [A], or aminoisobutyric acid;

R_9 and R_{10} are -$CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{13};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{13} is independently halo, alkyl, OR_{14}, $N(R_{14})_2$, SR_{14}, SOR_{14}, SO_2R_{14}, CO_2R_{14}, R_{14}, a fluorescent moiety, or a radioisotope;

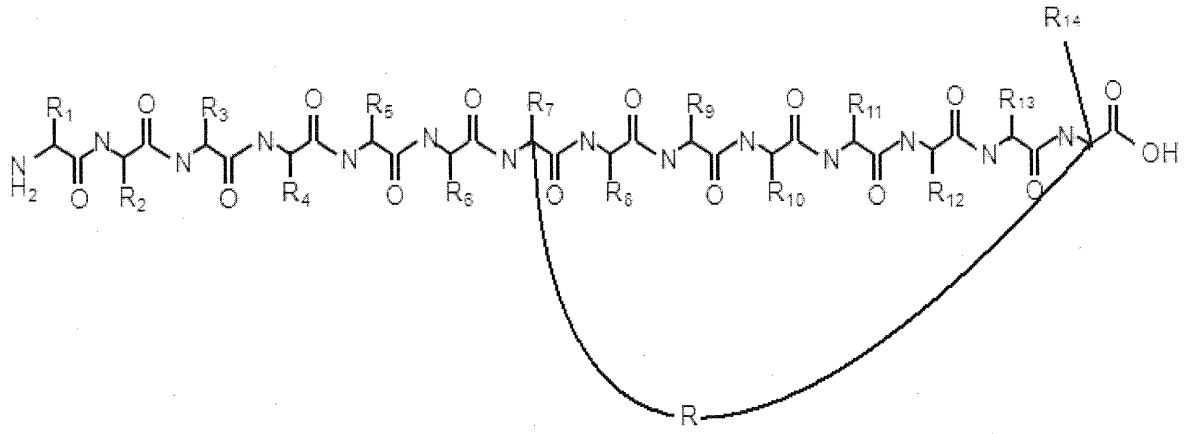
K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{14}$;

each R_{14} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

22. The peptide of claim 21, wherein R_7 and R_{12} are independently H or a C_1 to C_6 alkyl.

23. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula V:



wherein:

R_1 and R_2 are –$(CH_2)_4$-NH_2 [K];

R_3 is -$(CH_2)_3$-NH-$C(NH_2)2$ [R];

R_4 is -CH_2-Phenyl-OH [Y];

R_5 is -CH_2-OH [S];

R_6 is -$(CH_2)_3$-NH-$C(NH_2)_2$ [R];

R_7 and R_{14} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_8 is benzyl [F], or –$(CH_2)_2$-$C(O)NH_2$ [Q], or –CH_3 [A], or aminoisobutyric acid;

R_9 and R_{10} are -$CH_2CH(CH_3)_2$ [L]; and

R_{11} is –H [G] or aminoisobutyric acid;

R_{12} is benzyl [F];

R_{13} is –$(CH_2)_2$-$C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

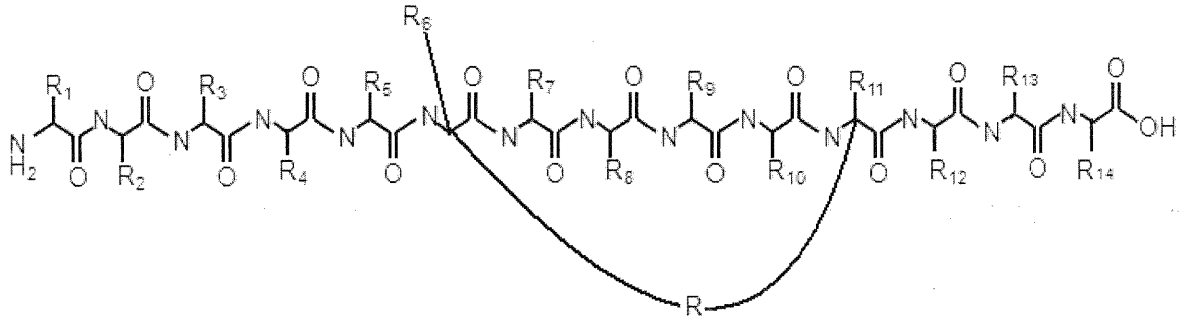
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

24. The peptide of claim 23, wherein R_7 and R_{14} are independently H or a C_1 to C_6 alkyl.

25. The peptide of claim 23, wherein R_7 and R_{14} are each -CH_3 [A] and R is a 4'-cyclooctenyl (sTIP-05) cross-linking the α-carbon of the two unnatural amino-acids.

26. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula VI:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 and R_{11} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{12} is benzyl [F];

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

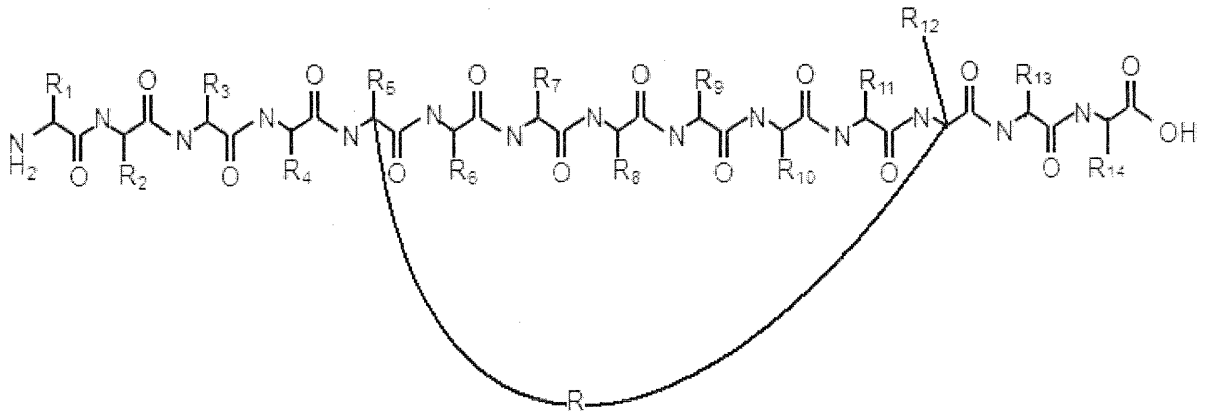
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

27. The peptide of claim 26, wherein R_6 and R_{11} are independently H or a C_1 to C_6 alkyl.

28. The peptide of claim 26, wherein R_6 and R_{11} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-06) cross-linking the α-carbon of the two unnatural amino-acids.

29. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula VII:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 and R_{12} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 is benzyl [F], or $-(CH_2)_2-C(O)NH_2$ [Q], or $-CH_3$ [A], or aminoisobutyric acid;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{11} is –H [G] or aminoisobutyric acid;

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

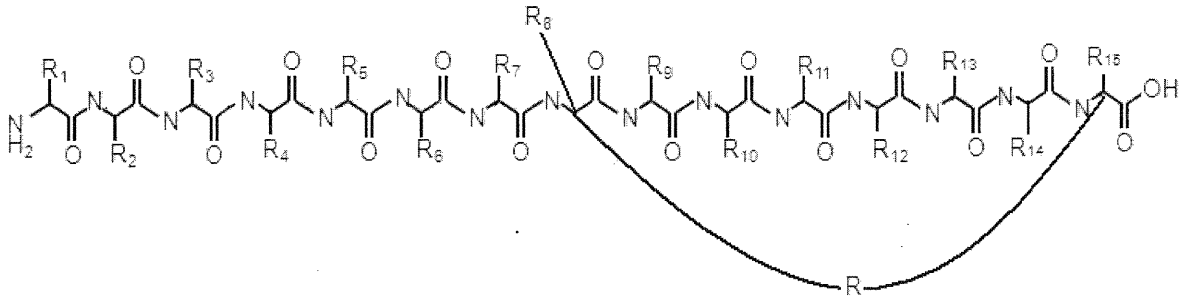
each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

30. The peptide of claim 29, wherein R_5 and R_{12} are independently H or a C_1 to C_6 alkyl.

31. The peptide of claim 29, wherein R_5 and R_{12} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-07) cross-linking the α-carbon of the two unnatural amino-acids.

32. The peptide of any one of claims 1 to 10, wherein the peptide comprises formula VIII:



wherein:

R_1 and R_2 are $-(CH_2)_4-NH_2$ [K];

R_3 is $-(CH_2)_3-NH-C(NH_2)2$ [R];

R_4 is $-CH_2$-Phenyl-OH [Y];

R_5 is $-CH_2-OH$ [S];

R_6 is $-(CH_2)_3-NH-C(NH_2)_2$ [R];

R_7 is $-(CH_2)_2C(O)OH$ [E], or aminoisobutyric acid;

R_8 and R_{15} are independently H or a C_1 to C_{10} alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, or heterocyclylalkyl;

R_9 and R_{10} are $-CH_2CH(CH_3)_2$ [L];

R_{11} is –H [G] or aminoisobutyric acid;

R_{12} is benzyl [F];

R_{13} is $-(CH_2)_2-C(O)NH_2$ [Q];

R_{14} is benzyl [F];

and wherein

R is anyone of alkyl, alkenyl, alkynyl, or [R'–K–R"]*n*; each of which is substituted with 0-6 R_{16};

R' and R" are independently alkylene, alkenylene or alkynylene;

each R_{16} is independently halo, alkyl, OR_{17}, $N(R_{17})_2$, SR_{17}, SOR_{17}, SO_2R_{17}, CO_2R_{17}, R_{17}, a fluorescent moiety, or a radioisotope;

K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_{17}$;

each R_{17} is independently H, alkyl, or a therapeutic agent;

n is an integer from 1-4.

33. The peptide of claim 32, wherein R_8 and R_{15} are independently H or a C_1 to C_6 alkyl.

34. The peptide of claim 33, wherein R_8 and R_{15} are each $-CH_3$ [A] and R is a 4'-cyclooctenyl (sTIP-08) cross-linking the α-carbon of the two unnatural amino-acids.

35. The peptide of claim 1, selected from the group consisting of:

KKRYSR*FLL*F	SEQ ID NO: 9
KKRYSRE*LLG*	SEQ ID NO: 10
KKRYSRE*LL*F	SEQ ID NO: 11
KKRYSR*QLL*L	SEQ ID NO: 12
KKRYSR*FLL*&	SEQ ID NO: 14
KKRYSR*ALL*F	SEQ ID NO: 15
KKRYSR*FLLGFQ*	SEQ ID NO: 17
KKRYS*EFLLGF*F	SEQ ID NO: 18
KKRY*REFLLG*QF	SEQ ID NO: 19
KKRYSRE*LLGFQF*	SEQ ID NO: 20

wherein X represents aminoisobutyric acid;

* represent a staple position; and

& represents 2-amino-butyric acid.

36. A pharmaceutical composition comprising a peptide of any one of claims 1 to 35.

37. The pharmaceutical composition of claim 36, further comprising one or more pharmaceutically acceptable excipients, or vehicles, or carriers.

38. The pharmaceutical composition according to claim 36 or 37, wherein the pharmaceutical composition further comprises a therapeutic compound.

39. The pharmaceutical composition of claim 38, wherein the therapeutic compound is an apoptosis promoting compound.

40. The pharmaceutical composition of claim 39, wherein the apoptosis promoting compound is selected from the group consisting of Cyclin-dependent Kinase (CDK) inhibitors, Receptor Tyrosine Kinase (RTK) inhibitors, BCL (B-cell lymphoma) family BH3 (Bcl-2 homology domain 3)-mimetic inhibitors and Ataxia Telangiectasia Mutated (ATM) inhibitors.

41. The pharmaceutical composition of claim 40, wherein the CDK inhibitors comprise inhibitors selected from the group consisting of:

2-(*R*)-(1-Ethyl-2-hydroxyethylamino)-6-benzylamino-9-isopropylpurine (CYC202; Roscovitine; Seliciclib);

4-[[5-Amino-1-(2,6-difluorobenzoyl)-1H-1,2,4-triazol-3-yl]amino]benzenesulfonamide (JNJ-7706621);

N-(4-piperidinyl)-4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxamide (AT-7519);

N-(5-(((5-(1,1-dimethylethyl)-2-oxazolyl)methyl)thio)-2-thiazolyl)-4-piperidinecarboxamide (SNS-032);

8,12-Epoxy-1H,8H-2,7b,12a-triazadibenzo(a,g)cyclonona(cde)triinden-1-one, 2,3,9,10,11,12-hexahydro-3-hydroxy-9-methoxy-8-methyl-10-(methylamino)- (UCN-01; 7-Hydroxystaurosporine; KRX-0601);

N,1,4,4-tetramethyl-8-((4-(4-methylpiperazin-1-yl)phenyl)amino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (PHA-848125; milciclib);

2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methylpiperidin-4-yl]chromen-4-one hydrochloride (flavopiridol; alvocidib);

6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one hydrochloride (PD 0332991);
4-(1-isopropyl-2-methyl-1H-imidazol-5-yl)-N-(4-(methylsulfonyl)phenyl)pyrimidin-2-amine (AZD5438);
(S)-3-(((3-ethyl-5-(2-(2-hydroxyethyl)piperidin-1-yl)pyrazolo[1,5-a]pyrimidin-7-yl)amino)methyl)pyridine 1-oxide (Dinaciclib; SCH 727965);
N-(4-Piperidinyl)-4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxamide hydrochloride (AT-7519); and
pharmaceutically acceptable salts thereof.

42. The pharmaceutical composition of claim 40, wherein the RTK inhibitors comprise inhibitors selected from the group consisting of:
N-[3-chloro-4-[(3-fluorophenyl)methoxy] phenyl]-6- [5-[(2-methylsulfonylethylamino) methyl]-2-furyl]quinazolin-4-amine (lapatinib);
N1'-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-N1-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (foretinib);
N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (cabozantinib(XL184));
N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (cabozantinib(XL184));
3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine (crizotinib (Xalkori));
(3Z)-N-(3-Chlorophenyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-N-methyl-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide (SU11274);
(3Z)-5-[[(2,6-Dichlorophenyl)methyl]sulfonyl]-3-[[3,5-dimethyl-4-[[(2R)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-1H-pyrrol-2-yl]methylene]-1,3-dihydro-2H-indol-2-one hydrate (PHA-665752);
6-[[6-(1-Methylpyrazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl]sulfanyl]quinoline (SGX-523);
4-[1-(6-Quinolinylmethyl)-1H-1,2,3-triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazole-1-ethanol methanesulfonate (1:1) (PF-04217903);

2-Fluoro-N-methyl-4-[7-[(quinolin-6-yl)methyl]imidazo[1,2-b]-[1,2,4]triazin-2-yl]benzamide (INCB28060);

N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide (afatinib);

3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)-pyrrolidine-2,5-dione (ARQ-197 (Tivantinib));

N-[(2R)-1,4-dioxan-2-ylmethyl]-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfuric diamide (MK-2461);

N-[4-(3-Amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea (Linifanib(ABT 869));

4-[[(3S)-3-Dimethylaminopyrrolidin-1-yl]methyl]-N-[4-methyl-3-[(4-pyrimidin-5-ylpyrimidin-2-yl)amino]phenyl]-3-(trifluoromethyl)benzamide (Bafetinib (INNO-406)); and pharmaceutical acceptable salts thereof.

43. The pharmaceutical composition of claim 40, wherein the BCL family BH3-mimetic inhibitors comprise inhibitors selected from the group consisting of:

4-[4-[[2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (ABT 263;Navitoclax);

2-[2-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylene]-3-methoxy-2H-pyrrol-5-yl]-1H-indole methanesulfonate (Obatoclax mesylate (GX15-070));

4-[4-[(4'-chloro[1,1'-biphenyl]-2-yl)methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-Benzamide (ABT-737); and pharmaceutically acceptable salts thereof.

44. The pharmaceutical composition of claim 40, wherein the ATM inhibitors comprise inhibitors selected from the group consisting of:

2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (KU-55933);

(2R,6S)-2,6-Dimethyl-N-[5-[6-(4-morpholinyl)-4-oxo-4H-pyran-2-yl]-9H-thioxanthen-2-yl]-4-morpholineacetamide (KU-60019);

1-(6,7-Dimethoxy-4-quinazolinyl)-3-(2-pyridinyl)-1H-1,2,4-triazol-5-amine (CP466722);

α-Phenyl-N-[2,2,2-trichloro-1-[[[(4-fluoro-3-nitrophenyl)amino]thioxomethyl]amino] ethyl]benzene acetamide (CGK 733)
and pharmaceutically acceptable salts thereof.

45. Use of the peptide according to any one of claims 11, 15, 18, 21, 23, 26, 29, 32 and 35in the manufacture of a medicament for treating or preventing cancer.

46. The use of claim 45, wherein the cancer is characterized by overexpression or hyperactivity of eIF4E containing complexes.

47. The use according to claim 45, wherein cancer is selected from a group comprising or consisting of gastric cancer, colon cancer, lung cancer, breast cancer, bladder cancer, neuroblastoma, melanoma, head and neck cancer, esophagus cancer, cervix cancer, prostate cancer and leukemia.

48. The use according to claim 45 wherein the medicament is to be administered in combination with one or more further therapeutic agents to the patient, wherein administration of the medicament and the therapeutic agent is simultaneous, sequential or separate.

49. Use of a peptide according to any one of claims 11, 15, 18, 21, 23, 26, 29, 32 and 35for protein purification, or for inhibiting protein-protein interactions, or as template for protein-protein interactions.