complement system are limited to pathogenic cells. Many complement-related disorders and diseases are associated with abnormal destruction of self cells by the complement cascade. In one example, subjects suffering from paroxysmal nocturnal hemoglobinuria (PNH) are unable to synthesize functional versions of the complement regulatory proteins CD55 and CD59 on hematopoietic stem cells. This results in complement-mediated hemolysis and a variety of downstream complications. Other complement-related disorders and diseases include, but are not limited to autoimmune diseases and disorders, neurological diseases and disorders, blood diseases and disorders and infectious diseases and disorders. Experimental evidence suggests that many complement-related disorders are alleviated through inhibition of complement activity. Therefore, there is a need for the development of compounds capable of selectively blocking complement-mediated cell destruction.

SUMMARY

[0009] In one aspect, the present invention refers to a polypeptide of the formula R1-Xaa0-Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14-Xaa15-Xaa16-Xaa17-Xaa18-R2 (SEQ ID NO: 212), wherein a. R1 is an acetyl group, absent, or selected from the group consisting of H, an acyl group containing a linear or branched, saturated or unsaturated hydrocarbon chain from 1 to 20 carbon atoms, a heptanoyl group, an amide, a carbamate, urea, PEG, hydroxyalkyl starch and a polypeptide; b. Xaa0 is absent, or an amino acid selected from the group consisting of Met and norvaline; c. Xaa1 is Lys, absent, or selected from the group consisting of (S)-2-amino-5-azidopentanoic acid, chloroacetic acid, (S)-2-aminohept-6-enoic acid, 4-aminobutyric acid, 5-aminopentanoic acid, 5-aminohexanoic acid, ornithine, homolysine, Glu, Asp, 3-thiopropionic acid and Cys; d. Xaa2 is Val, absent, or selected from the group consisting of Ala, D-Ala, tertbutyl-glycine, Lys, Ser, and Cys; e. Xaa3 is Glu, absent, or selected from the group consisting of Ala, norvaline, and Val; f. Xaa4 is Arg, absent, or selected from the group consisting of Ala, Cys, Ser, Glu, phenylglycine and norvaline; g. Xaa5 is Phe, absent, or selected from the group consisting of Tyr, Arg, Cys, N-methyl-tyrosine and Ala; h. Xaa6 is Asp, absent, or selected from the group consisting of Glu, N-methyl-glutamic acid, cyclohexylglycine, Lys, Tyr, Pro, N-methyl-serine, tertbutyl-glycine, Val, norleucine, norvaline, 7-azatryptophan, Asn, (S)-2-aminopent-4-ynoic acid, (S)-2-aminopent-4-enoic acid, Cys and Ala; i. Xaa7 is N-methyl-aspartic acid, absent, or selected from the group consisting of Asn, N-methyl-asparagine, N-methyl-glycine, N-methyl-serine, homocysteine, Thr, Tyr, phenylglycine, tert-butylglycine, alpha-methyl L-aspartic acid, (S)-2-amino-3-(1H-tetrazol-5-yl)propanoic acid, cycloleucine, 4-amino-tetrahydro-pyran-4-carboxylic acid, Arg, Glu, Asp, Cys and Ala; j. Xaa8 is tert-butylglycine, absent, or selected from the group consisting of tert-butylglycine, phenylglycine, D-phenylglycine, cyclohexylglycine, D-cyclohexylglycine, 1,2,3,4-

tetrahydroisoquinoline-1-carboxylic acid , Tyr, Asn, Cys, N-methyl-4-fluorophenylalanine, 2-O-methylphenylglycine, Phe, Val and Ala; k. Xaa9 is selected from the group consisting of Tyr, N-methyl-tyrosine, Thr, Glu, norvaline, Lys, Ala, D-Ala, His, Cys, phenylglycine, N-methyl-serine, N-methyl-glycine, amino isobutyric acid and Arg; l. Xaa10 is selected from the group consisting of 7-azatryptophan, 3-aminomethyl-L-phenyalanine, N-methyl-tryptophan, 1-methyl-tryptophan , 5-fluorotryptophan, Phe, D-Trp , 5-methyl-O-tryptophan, Ala, His, Leu, tert-butylglycine, Cys and Trp; m. Xaa11 is selected from the group consisting of Glu, D-Glu, N-methyl-glutamic acid, Asn, Asp, Gln, tert-butylglycine, Cys, N-methyl-4-fluorophenylalanine, N-methyl-serine, (S)-2-amino-3-(1H-tetrazol-5-yl)propanoic acid and Ala; n. Xaa12 is Tyr, absent, or selected from the group consisting of Trp, homophenylalanine, meta-chloro homophenylalanine, 2-naphthylalanine, 3-aminomethyl-L-phenyalanine, N-methyl-tyrosine, Cys, Phe, Ala, Glu, Gly, N-methyl-glycine, phenylglycine, 4-fluorophenylalanine, O-methyl-tyrosine, homophenylalanine, 3-chlorophenylalanine and norvaline; o. Xaa13 is Pro, absent, or selected from the group consisting of propargyl-glycine, Ala, N-methyl-glycine, Ser, N-methyl-serine, N-methyl-alanine, norvaline, Cys and Tbg; p. Xaa14 is cyclohexylglycine, absent, or selected from the group consisting of amino isobutyric acid, tert-butylglycine, Cys, Pro, Asn, phenylglycine, D-phenylglycine, N-methyl-phenylglycine, norvaline, His, Ala, and D-Ala; q. Xaa15 is absent or selected from the group consisting of norvaline, Lys, N-ε-caprylic lysine, N- ε -capryl lysine, N- ε -lauryl lysine, N- ε -palmitoyl lysine, Pro, Cys, Tyr, Gly, propargyl-glycine, homoCys, N-methyl-serine and tert-butylglycine; r. Xaa16 is absent or selected from the group consisting of norvaline, Cys, Lys and Ala; s. Xaa17 is absent or selected from the group consisting of Pro, Glu and Nvl; t. Xaa18 is absent or is norvaline; and u. R_2 is B28, absent, or selected from the group consisting of B20, K14, $-NH_2$ and $-N(CH_3)_2$. The present disclosure describes compounds, including polypeptides (e.g., peptidomimetics, cyclic polypeptides and cyclic peptidomimetics,) small molecules, antibodies, antibody fragments, and aptamers, and methods of using said compounds for the modulation of complement. According to the present invention, polypeptides may have the sequences set forth in SEQ ID NOs 1-201 or 211. They may be linear or cyclic and may comprise a cyclic loop formed by a bridging moiety between two amino acids. The bridging moieties may comprise a feature selected from the group consisting of a disulfide bond, an amide bond (lactam), a thioether bond, an aromatic ring, an unsaturated aliphatic hydrocarbon chain, a saturated aliphatic hydrocarbon chain, a triazole ring or combinations thereof. Furthermore, the cyclic loop may vary in length and may be 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9, amino acids, 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, or more.

[0010] The bridging moiety may comprise a disulfide between two cysteine resides or an aromatic ring produced by reaction with a poly(bromomethyl)benzene and such poly(bromomethyl)benzene may be selected from the group consisting of 1,2-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene.

[0011] The bridging moiety may also comprise an aromatic ring produced by reaction with a compound selected from the group consisting of 2,6-bis(bromomethyl)pyridine, (E)-1,4-dibromobut-2-ene and 1,2-bis(bromomethyl)-4-alkylbenzene.

[0012] The bridging moiety may also comprise an amide bond produced by the reaction of the side chains of the following pairs of amino acids: lysine and glutamate, lysine and aspartate, ornithine and glutamate, ornithine and aspartate, homolysine and glutamic acid, homolysine and aspartic acid, other combinations of amino acids, unnatural amino acids or non-amino acid residues comprising a primary amine and a carboxylic acid.

[0013] According to the present disclosure, the polypeptides are useful in that they may exhibit complement C5 inhibitory activity. In some cases, such activity may range from a half-maximal inhibitory concentration (IC_{50}) of about 50 nM to about 200 nM or be less than 50 nM.

[0014] In some examples, the present disclosure describes polypeptides having tryptophan or one or more tryptophan analogs selected from the group consisting of 5-fluorotryptophan, 5-methyl-O-tryptophan, 1-methyltryptophan, D-tryptophan and 7-azatryptophan present within the amino acid sequence. Such compounds include those of SEQ ID NOs: 3, 9, 11, 19, 45, 46, 50 and 59, among others.

[0015] In some examples, polypeptides of the present disclosure may bind to a region on C5, wherein said region is distal to the C5a-C5b cleavage site. In some cases, polypeptides of the present invention may inhibit the cleavage of C5 into C5a and C5b cleavage products.

[0016] In some cases, polypeptides disclosed herein may be part of an antibody.

[0017] Polypeptides of the present disclosure may be comprised in compositions. In one aspect, the present invention refers to a composition comprising the polypeptide disclosed herein and an acceptable carrier or excipient. Such compositions may comprise one or more acceptable carrier or excipient. Such polypeptides may further be conjugated to another non-polypeptide moiety such as for example a water-soluble polymer. These polymers may be hydrophilic or hydrophobic. In some examples the hydrophilic polymer is selected from the group consisting of polyalkylene oxide homopolymers, polypropylene glycols, polyoxyethylenated polyols and copolymers thereof. It may also comprise polyethylene glycol (PEG). Compositions may further comprise polypeptides conjugated to an albumin binding polypeptide selected from the group consisting of SEQ ID NOs: 202-204. In some cases compositions may comprise polypeptides conjugated to a cell penetrating polypeptide selected from the group consisting of SEQ ID NOs: 205-210. Compositions may further comprise polypeptides conjugated to a lipidic moiety. Lipidic moieties

may include, but are not limited to fatty acids, phospholipids and sterols. In some examples, lipidic moieties may be directly conjugated to polypeptides of the invention or linked to a polypeptide-PEG conjugate. Some compositions may comprise a pharmaceutically acceptable excipient.

[0018] In one aspect, the present invention refers to a method of inhibiting C5 cleavage in a cellular system, said method comprising contacting said cellular system with the composition as disclosed herein or a polypeptide as disclosed herein. In some examples, the present disclosure describes a method of inhibiting C5 cleavage in a cellular system comprising the use of a composition disclosed herein, such as those described above. Some such methods may reduce C5a levels. Further methods may reduce membrane attack complex (MAC) formation.

[0019] Some methods of the invention may lead to C5 cleavage inhibition with an IC_{50} of from about 50 nM to about 200 nM. In some cases, methods disclosed herein may comprise C5 cleavage inhibition with an IC_{50} of less than 50 nM. In another aspect, the present invention refers to use of the composition as disclosed herein or a polypeptide as disclosed herein in the manufacture of a medicament for treating a subject suffering from a complement-related disease, disorder and/or condition.

[0020] Some methods disclosed herein may be applied to a cellular systems that is selected from an *in vitro* system, an *in vivo* system and an *ex vivo* system. Some *in vivo* systems may include subjects, such as human subjects. In some cases, the polypeptides and polypeptide compositions may be used in the treatment or prevention of a complement-related disease, disorder and/or condition in a subject. Administration to a subject may be selected from the group consisting of buccal, intranasal, oral, intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal and intravitreal. In some cases, compositions may be used to treat paroxysmal nocturnal hemoglobinuria and/or atypical hemolytic uremic syndrome. In some cases, compositions of the invention may be used to treat one or more of an inflammatory indication, a wound, an injury, an autoimmune disease, a vascular indication, a neurological indication, a kidney-related indication, and an ocular disease.

[0021] In some examples, the present disclosure describes methods of inhibiting thrombin-induced complement activation in cellular systems comprising contacting such systems with polypeptides of the invention. Further disclosed are methods of treating hemolysis in subjects, comprising administering a polypeptide described herein. According to some such methods, the hemolysis treated is caused by thrombin-induced complement activation.

[0022] In some examples disclose kits for the diagnosis, prognosis, prophylaxis or treatment of a disease, disorder and/or condition in a mammal, including a human. Such kits would contain one or more polypeptides or polypeptide compositions of the present invention and optionally reagents and/or instructions for use. In such kits, the polypeptides may comprise a

detectable label or the ability to bind to a detectable label to form a detectable complex. According to one example, the label comprises a BODIPY-TMR label.

DESCRIPTION OF THE FIGURES

[0023] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[0024] Figure 1 is a graph displaying the results of an enzyme immunoassay (EIA) for the detection of C5a in supernatant from a human red blood cell (RBC) hemolysis assay with increasing concentrations of inhibitors R3002 (SEQ ID NO: 3) and R3008 (SEQ ID NO: 9). Levels of C5a correlate with complement activity and are therefore an indicator of the ability of the compounds tested to inhibit complement activity. Supernatant from the hemolysis assay was diluted 1:50 and assayed for C5a levels. C5a levels decreased in human hemolysis assay supernatant samples with increasing levels of either inhibitor assayed. R3002 (SEQ ID NO: 3) had an IC_{50} of 5.4 nM while R3008 (SEQ ID NO: 9) had an IC_{50} of 54.5 nM. As used herein, the term "IC_{50}" refers to the half maximal inhibitory concentration, a value used to indicate the amount of the inhibitor needed to reduce a given reaction or process by half.

[0025] Figure 2 is a graph displaying the results of an EIA for the detection of the membrane attack complex (MAC) in supernatant from a human RBC hemolysis assay with increasing concentrations of R3008 (SEQ ID NO: 9). Levels of the MAC correlate with complement activity and are therefore an indicator of the ability of R3008 (SEQ ID NO: 9) to inhibit complement activity. Supernatant from the hemolysis assay was diluted 1:5 and assayed for MAC levels. MAC levels decreased in hemolysis assay supernatant samples with increasing levels of the inhibitor assayed with an IC_{50} of 33 nM.

[0026] Figure 3 is a graph displaying competitive fluorescence polarization (FP) data for test articles R3003 (SEQ ID NO: 4), R3011 (SEQ ID NO: 31), R3014 (SEQ ID NO: 55), R3023 (SEQ ID NO: 104), R3043 (SEQ ID NO: 50) and R3050 (SEQ ID NO: 23). FP allows binding events to be measured in a homogenous solution. A competitive binding assay was conducted wherein a 25 nM solution of compound R3076 (SEQ ID NO: 40), which has a fluorescent tag,

CLAIMS

What is claimed is:

1. A polypeptide of the formula R1-Xaa0-Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14-Xaa15-Xaa16-Xaa17-Xaa18-R2 (SEQ ID NO: 212), wherein:

    a. R_1 is an acetyl group, absent, or selected from the group consisting of H, an acyl group containing a linear or branched, saturated or unsaturated hydrocarbon chain from 1 to 20 carbon atoms, a heptanoyl group, an amide, a carbamate, urea, PEG, hydroxyalkyl starch and a polypeptide;

    b. Xaa0 is absent, or an amino acid selected from the group consisting of Met and norvaline;

    c. Xaa1 is Lys, absent, or selected from the group consisting of (S)-2-amino-5-azidopentanoic acid, chloroacetic acid, (S)-2-aminohept-6-enoic acid, 4-aminobutyric acid, 5-aminopentanoic acid, 5-aminohexanoic acid, ornithine, homolysine, Glu, Asp, 3-thiopropionic acid and Cys;

    d. Xaa2 is Val, absent, or selected from the group consisting of Ala, D-Ala, tertbutyl-glycine, Lys, Ser, and Cys;

    e. Xaa3 is Glu, absent, or selected from the group consisting of Ala, norvaline, and Val;

    f. Xaa4 is Arg, absent, or selected from the group consisting of Ala, Cys, Ser, Glu, phenylglycine and norvaline;

    g. Xaa5 is Phe, absent, or selected from the group consisting of Tyr, Arg, Cys, -N-methyl-tyrosine and Ala;

h. Xaa6 is Asp, absent, or selected from the group consisting of Glu, N-methyl-glutamic acid, cyclohexylglycine, Lys, Tyr, Pro, N-methyl-serine, tertbutyl-glycine, Val, norleucine, norvaline, 7-azatryptophan, Asn, (S)-2-aminopent-4-ynoic acid, (S)-2-aminopent-4-enoic acid, Cys and Ala;

i. Xaa7 is N-methyl-aspartic acid, absent, or selected from the group consisting of Asn, N-methyl-asparagine, N-methyl-glycine, N-methyl-serine, homocysteine, Thr, Tyr, phenylglycine, tert-butylglycine, alpha-methyl L-aspartic acid, (*S*)-2-amino-3-(1*H*-tetrazol-5-yl)propanoic acid, cycloleucine, 4-amino-tetrahydro-pyran-4-carboxylic acid, Arg, Glu, Asp, Cys and Ala;

j. Xaa8 is tert-butylglycine, absent, or selected from the group consisting of tert-butylglycine, phenylglycine, D-phenylglycine, cyclohexylglycine, D-cyclohexylglycine, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid , Tyr, Asn, Cys, N-methyl-4-fluorophenylalanine, 2-O-methylphenylglycine, Phe, Val and Ala;

k. Xaa9 is selected from the group consisting of Tyr, N-methyl-tyrosine, Thr, Glu, norvaline, Lys, Ala, D-Ala, His, Cys, phenylglycine, N-methyl-serine, N-methyl-glycine, amino isobutyric acid and Arg;

l. Xaa10 is selected from the group consisting of 7-azatryptophan, 3-aminomethyl-L-phenyalanine, N-methyl-tryptophan, 1-methyl-tryptophan , 5-fluorotryptophan, Phe, D-Trp , 5-methyl-O-tryptophan, Ala, His, Leu, tert-butylglycine, Cys and Trp;

m. Xaa11 is selected from the group consisting of Glu, D-Glu, N-methyl-glutamic acid, Asn, Asp, Gln, tert-butylglycine, Cys, N-methyl-4-fluorophenylalanine, N-methyl-serine, (*S*)-2-amino-3-(1*H*-tetrazol-5-yl)propanoic acid and Ala;

n. Xaa12 is Tyr, absent, or selected from the group consisting of Trp, homophenylalanine, meta-chloro homophenylalanine, 2-naphthylalanine, 3-aminomethyl-L-phenyalanine, N-methyl-tyrosine, Cys, Phe, Ala, Glu, Gly, N-methyl-

glycine, phenylglycine, 4-fluorophenylalanine, O-methyl-tyrosine, homophenylalanine, 3-chlorophenylalanine and norvaline;

o. Xaa13 is Pro, absent, or selected from the group consisting of propargyl-glycine, Ala, N-methyl-glycine, Ser, N-methyl-serine, N-methyl-alanine, norvaline, Cys and Tbg;

p. Xaa14 is cyclohexylglycine, absent, or selected from the group consisting of amino isobutyric acid, tert-butylglycine, Cys, Pro, Asn, phenylglycine, D-phenylglycine, N-methyl-phenylglycine, norvaline, His, Ala, and D-Ala;

q. Xaa15 is absent or selected from the group consisting of norvaline, Lys, N-ε-caprylic lysine, N-ε-capryl lysine, N-ε-lauryl lysine, N-ε-palmitoyl lysine, Pro, Cys, Tyr, Gly, propargyl-glycine, homoCys, N-methyl-serine and tert-butylglycine;

r. Xaa16 is absent or selected from the group consisting of norvaline, Cys, Lys and Ala;

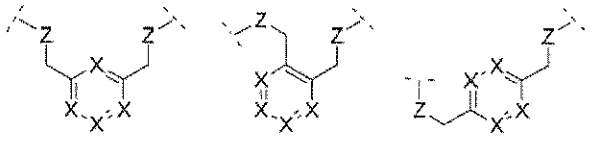
s. Xaa17 is absent or selected from the group consisting of Pro, Glu and Nvl;

t. Xaa18 is absent or is norvaline; and

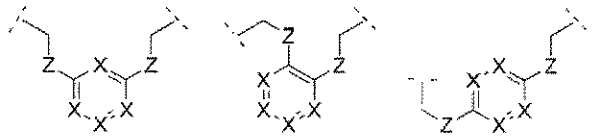
u. R_2 is B28, absent, or selected from the group consisting of B20, K14, $-NH_2$ and $-N(CH_3)_2$.

2. The polypeptide of claim 1, further comprising a bridging moiety between two amino acids.

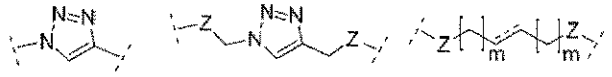
3. The polypeptide of claim 2, wherein said bridging moiety comprises a structure selected from the group consisting of structures I-XIX;



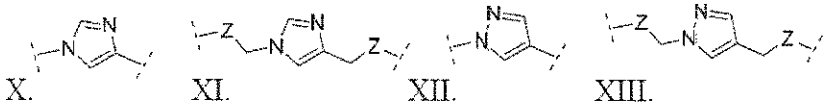
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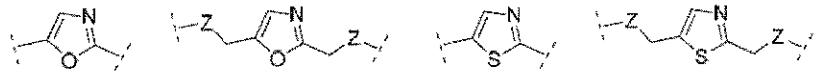
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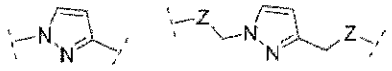
VII. VIII. IX.



X. XI. XII. XIII.



XIV. XV. XVI. XVII.



XVIII. XIX.

wherein each X is independently N or CH, such that no ring contains more than 2 N; each Z is independently a bond, NR, O, S, CH_2, C(O)NR, NRC(O), $S(O)_vNR$, $NRS(O)_v$; each m is independently selected from 0, 1, 2, and 3; each v is independently selected from 1 and 2; each R is independently selected from H and C_1-C_6; and each bridging moiety is connected to the polypeptide by independently selected C_0-C_6 spacers.

4. The polypeptide of claim 2, wherein the bridging moiety comprises a feature selected from the group consisting of a disulfide bond, an amide bond (lactam), a thioether bond, an aromatic ring, an unsaturated aliphatic hydrocarbon chain, a saturated aliphatic hydrocarbon chain and a triazole ring.

5. The polypeptide of any of claims 2-4, wherein the peptide comprises a cyclic loop, wherein the cyclic loop is of a length selected from the group consisting of 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9, amino acids, 10 amino

acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids and 16 amino acids.

6. The polypeptide of claim 4, wherein said feature comprises an aromatic ring and wherein said bridging moiety is formed by reaction with a poly(bromomethyl)benzene.

7. The polypeptide of claim 6, wherein the poly(bromomethyl)benzene is selected from the group consisting of 1,2-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene.

8. The polypeptide of claim 7 wherein the reagent is 1,3-bis(bromomethyl)benzene.

9. The polypeptide of claim 4, wherein said feature comprises an aromatic ring and wherein said bridging moiety is produced by reaction with a compound selected from the group consisting of 2,6-bis(bromomethyl)pyridine, (*E*)-1,4-dibromobut-2-ene and 1,2-bis(bromomethyl)-4-alkylbenzene.

10. The polypeptide of claim 1, wherein said polypeptide is selected from the group consisting of SEQ ID NOs 1-201 and 211.

11. A composition comprising the polypeptide of claim 1 and an acceptable carrier or excipient.

12. The composition of claim 11 comprising an excipient, wherein said excipient comprises a pharmaceutically acceptable excipient.

13. An *in vitro* or *ex vivo* method of inhibiting C5 cleavage in a cellular system, said method comprising contacting said cellular system with the composition of any of claims 11 to 12 or a polypeptide of any of claims 1 to 10.

14. The method of claim 13, wherein said polypeptide inhibits the cleavage of C5 with an IC_{50} of less than 50 nM.

15. Use of the composition of any of claims 11 to 12 or a polypeptide of any of claims 1 to 10 in the manufacture of a medicament for inhibiting C5 cleavage in the treatment of a subject suffering from a complement-related disease, disorder and/or condition, wherein said complement-related disease, disorder and/or condition is selected from the group consisting of an inflammatory indication, a wound, an injury, an autoimmune disease, a vascular indication, a neurological indication, a kidney-related indication, an ocular disease, paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

16. The use of claim 15, wherein said polypeptide inhibits the cleavage of C5 with an IC_{50} of less than 50 nM.

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1 5 10

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<210> 38
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<400> 38
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<210> 41
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<400> 45
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<210> 47
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<400> 51
Val Cys Gly Thr Trp Glu Tyr Pro His Cys Val
1 5 10

<210> 52
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1 5 10

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<400> 55
Cys Gly Thr Trp Glu Tyr Ser His Cys Val Pro Val
1 5 10

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Val Ser Ala Glu Asn Gly Tyr Trp Glu Tyr Pro Gly Val
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<400> 61
Val Cys Gly Thr Trp Glu Tyr Ser His Cys Val
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<220>
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<220>
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<220>
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1 5 10

<210> 68
<211> 11
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<220>
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<220>
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1 5 10

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<223> (N-Me)Ser

<220>
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<400> 69
Tyr Val Cys Gly Thr Trp Glu Tyr Ser His Cys Val
1 5 10

<210> 70
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<220>
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1 5 10

<210> 71
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<400> 71
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1 5 10

<210> 72
<211> 9
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<210> 73
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<210> 74
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<220>
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<220>
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<400> 74
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1 5 10

<210> 75
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<400> 75
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1 5 10

<210> 76
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Val Ser Tyr Glu Asn Gly Tyr Ala Glu Tyr Pro Gly Val
1 5 10

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1   5   10

<210> 78
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<400> 78
Val Cys Gly Thr Trp Glu Tyr Ser His Cys Val Pro Val
1   5   10

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<212> PRT
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<223> 7-azatryptophan

<220>
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<220>
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<400> 79
Cys Gly Tyr Trp Glu Tyr Ser His Cys
1   5

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<212> PRT
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1 5 10

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<223> C-term NH2

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Val Cys Gly Thr Trp Glu Tyr Ser His Cys Val
1 5 10

<210> 83
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<210> 84
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<210> 86
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Val Cys Gly Thr Trp Ala Tyr Ser His Cys Val

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Val Cys Gly Thr Trp Glu Ala Ser His Cys Val
1 5 10

<210> 88
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Met Cys Val Glu Arg Phe Cys Asp Val Tyr Trp
1 5 10

<210> 89
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<210> 91
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Val Cys Gly Thr Phe Glu Tyr Ser Ala Cys Val
1 5 10

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Val Cys Gly Thr Trp Glu Phe Ser Ala Cys Val
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<400> 94
Val Cys Gly Xaa Trp Glu Tyr Ser His Cys Val
1 5 10

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<220>
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<400> 95
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1 5 10

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<220>
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<220>
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<220>
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<400> 176

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<223> N-term Ac

<220>
<221> misc_feature
<222> (1)..(6)
<223> Bridging moiety between residues

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
<221> MOD_RES
<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Phg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Lys-C16

<400> 190
Cys Ala Glu Arg Phe Cys Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 191
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> misc_feature
<222> (1)..(6)
<223> Cyclic

<220>
<221> MOD_RES
<222> (7)..(7)
<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
<221> MOD_RES
<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> N-epsilon-(PEG2-gamma-glutamic acid-N-alpha-octadecanedioic acid) lysine

<400> 191
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 192
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> misc_feature
<222> (1)..(6)
<223> Cyclic

<220>
<221> MOD_RES
<222> (7)..(7)
<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
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<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)

<223> Chg

<400> 192
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 193
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
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<222> (1)..(6)
<223> Cyclic

<220>
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<222> (7)..(7)
<223> (N-Me)Asp

<220>
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<222> (8)..(8)
<223> Tbg

<220>
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<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<223> C-term NH2

<400> 193
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 194
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<222> (1)..(6)
<223> Cyclic

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<222> (7)..(7)
<223> (N-Me)Asp

<220>
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<222> (8)..(8)
<223> Tbg

<220>
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<222> (10)..(10)
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<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> N-epsilon-(PEG24-gamma-glutamic acid-N-alpha-hexadecanoyl)lysine

<400> 194
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 195
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
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<223> Cyclic

<220>
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<223> (N-Me)Asp

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<220>
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<222> (14)..(14)
<223> Chg

<220>
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<222> (15)..(15)
<223> Lys-C16

<220>
<223> C-term NH2

<400> 195
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 196
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (15)..(15)
<223> Lys-C16

<400> 196
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 197
<211> 15
<212> PRT
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<220>
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<220>
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<220>
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<223> Cyclic

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<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<400> 197
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 198
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<220>
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<222> (1)..(6)
<223> Cyclic

<220>
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<222> (7)..(7)
<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> N-epsilon-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl-L-lysine

<400> 198
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 199
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
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<223> Cyclic

<220>
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<222> (1)..(1)
<223> (desamino)Cys

<220>
<221> MOD_RES
<222> (7)..(7)
<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
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<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Lys-C16

<400> 199
Cys Val Glu Arg Phe Cys Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 200
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> misc_feature
<222> (1)..(6)

<223> Cyclic

<220>
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<222> (1)..(1)
<223> (desamino)Cys

<220>
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<222> (2)..(2)
<223> D-Ala

<220>
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<222> (7)..(7)
<223> (N-Me)Asp

<220>
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<222> (8)..(8)
<223> Tbg

<220>
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<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Lys-C16

<400> 200
Cys Ala Glu Arg Phe Cys Asp Gly Tyr Trp Glu Tyr Pro Gly Lys
1 5 10 15

<210> 201
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<221> misc_feature
<222> (1)..(6)
<223> Cyclic

<220>
<221> MOD_RES
<222> (7)..(7)
<223> (N-Me)Asp

<220>
<221> MOD_RES
<222> (8)..(8)

<223> Tbg

<220>
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<222> (10)..(10)
<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Aib

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Lys-C16

<400> 201
Lys Val Glu Arg Phe Asp Asp Gly Tyr Trp Glu Tyr Pro Xaa Lys
1 5 10 15

<210> 202
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<223> C-term NH2

<400> 202
Arg Leu Ile Glu Asp Ile Cys Leu Ile Pro Arg Trp Gly Cys Leu Trp
1 5 10 15

Glu Asp Asp

<210> 203
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> C-term NH2

<400> 203
Gln Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
1 5 10 15

Glu Asp Asp Phe
20

<210> 204
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term Ac

<220>
<223> C-term NH2

<400> 204
Gln Arg Leu Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
1 5 10 15

Glu Asp Asp Phe
20

<210> 205
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 205
Arg Lys Lys Arg Arg Arg Glu Ser Arg Lys Lys Arg Arg Arg Glu Ser
1 5 10 15

<210> 206
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 206
Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5

<210> 207
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 207
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> 208
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 208
Ala Ala Val Leu Leu Pro Val Leu Leu Ala Ala Pro
1 5 10

<210> 209
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 209
Val Pro Thr Leu Lys
1 5

<210> 210
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 210
Pro Leu Ile Leu Leu Arg Leu Leu Arg Gly Gln Phe
1 5 10

<210> 211
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> N-term Ac

<220>
<221> misc_feature
<222> (1)..(6)
<223> Bridging moiety between residues

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Tbg

<220>
<221> MOD_RES
<222> (10)..(10)

<223> azaTrp

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Chg

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Nvl

<400> 211
Cys Val Glu Arg Phe Cys Asp Gly Tyr Trp Glu Tyr Pro Gly Val
1 5 10 15

<210> 212
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<223> N-term may be H, an acetyl group, an acyl group containing a linear or branched, saturated or unsaturated hydrocarbon chain from 1 to 20 carbon atoms, a heptanoyl group, an amide, a carbamate, urea, PEG or hydroxyalkyl starch

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Met, Nvl or not present

<220>
<221> MOD_RES
<222> (2)..(2)
<223> (S)-2-amino-5-azidopentanoic acid, (S)-2-aminohept-6-enoic acid, 4-aminobutyric acid, 5-aminopentanoic acid, 5-aminohexanoic acid, ornithine, Lys, homolysine, Glu, Asp, 3-thiopropionic acid, Cys or not present

<220>
<221> MOD_RES
<222> (3)..(3)
<223> Ala, D-Ala, tertbutyl-Gly, Lys, Ser, Cys, Val or not present

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Ala, Nvl, Val, Glu or not present

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Ala, Cys, Arg, Ser, Glu, Phg, Nvl or not present

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Tyr, Arg, Cys, Phe, N-methyl-tyrosine, Ala or not present

<220>
<221> MOD_RES

<222> (7)..(7)
<223> Glu, N-methyl-glutamic acid, Chg, Lys, Tyr, Pro, N-methyl-serine, tertbutyl-glycine, Val, norleucine, Nvl, 7-azatryptophan, Asn, Asp, (S)-2-aminopent-4-ynoic acid, (S)-2-aminopent-4-enoic acid, Cys, Ala or not present

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Asn, N-methyl-Asn, N-methyl-Gly, N-methyl-Ser, homo-Cys, Thr, Tyr, Phg, Tbg, alpha-methyl L-Asp, (S)-2-amino-3-(1H-tetrazol-5-yl)propanoic acid, N-methyl-Asp, Cle, 4-amino-tetrahydro-pyran-4-carboxylic acid, Arg, Glu, Asp, Cys, Ala or not present

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Tbg, Phg, D-Phg, Chg, D-Chg, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, Tyr, Tbg, Asn, Cys, N-methyl-4-fluoro-phenylalanine, 2-O-methyl-Phg, Phe, Val, Ala or not present

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Tyr, N-methyl-tyrosine, Thr, Glu, Nvl, Lys, Ala, D-Ala, His, Cys, Phg, N-methyl-serine, N-methyl-glycine, amino isobutyric acid or Arg

<220>
<221> MOD_RES
<222> (11)..(11)
<223> 3-aminomethyl-L-phenyalanine, 7-azatryptophan, N-methyl-tryptophan, 1-methyl-tryptophan, 5-fluorotryptophan, Phe, D-Trp, 5-methyl-O-tryptophan, Ala, His, Leu, Tbg, Cys or Trp

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Glu, D-Glu, N-methyl-glutamic acid, Asn, Asp, Gln, Tbg, Cys, N-methyl-4-fluorophenylalanine, N-methyl-serine, (S)-2-amino-3-(1H-tetrazol-5-yl)propanoic acid or Ala

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Trp, homo-Phe, meta-chloro homo-Phe, 2-naphthylalanine, 3-aminomethyl-L-Phe, Tyr, N-methyl-Tyr, Cys, Phe, Ala, Glu, Gly, N-methyl-Gly, Phg, 4-fluoro-Phe, O-methyl-Tyr, Homo-Phe, 3-chloro-Phe, Nvl or not present

<220>
<221> MOD_RES
<222> (14)..(14)
<223> Propargyl-glycine, Pro, Ala, N-methyl-glycine, Ser, N-methyl-serine, N-methyl-alanine, Nvl, Cys, Tbg or not present

<220>
<221> MOD_RES
<222> (15)..(15)
<223> Amino isobutyric acid, Tbg, Cys, Pro, Asn, phenylglycine, D-phenylglycine, N-methyl-Phg, Nvl, His, Ala, D-Ala, Chg or not present

<220>
<221> MOD_RES
<222> (16)..(16)
<223> Norvaline, Lys, N-epsilon-caprylic lysine, N-epsilon-capryl

lysine, N-epsilon-lauryl lysine, N-epsilon-palmitoyl lysine, Pro, Cys, Tyr, Gly, propargyl-glycine, homoCys, N-methyl-serine, tert-butylglycine or not present

<220>
<221> MOD_RES
<222> (17)..(17)
<223> Nvl, Cys, Lys, Ala or not present

<220>
<221> MOD_RES
<222> (18)..(18)
<223> Pro, Glu, Nvl or not present

<220>
<221> MOD_RES
<222> (19)..(19)
<223> Nvl and may not be present

<220>
<221> MOD_RES
<222> (20)..(20)
<223> N-epsilon-(PEG2-gamma-glutamic acid-N-alpha-octadecanedioic acid) lysine, N-epsilon-(PEG24-gamma-glutamic acid-N-alpha-hexadecanoyl)lysine, N-epsilon-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl-L-lysine or not present

<220>
<223> C-term may be NH2 or N(CH3)2 modified

<220>
<223> See specification as filed for detailed description of substitutions and preferred embodiments

<400> 212
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Val Lys
20