

MODIFIED LIPIDATED RELAXIN B CHAIN PEPTIDES AND THEIR THERAPEUTIC USE

FIELD OF THE INVENTION

5 The present invention relates to peptide analogues of the B-chain of Relaxin-2 able to activate the RXFP1 receptor.

 In particular, the present invention relates to lipidated peptide analogues of the B-chain of Relaxin-2 able to activate the RXFP1 receptor.

 Moreover, the present invention provides pharmaceutical compositions
10 comprising at least said peptides, and a peptide or pharmaceutical composition thereof according to the invention for its use as a medicament, and in particular for its use in the treatment and/or prevention of various diseases or conditions implicating RXFP1 receptor, more particularly a disease or condition selected from:

 - the group consisting of fibrosis; fibrotic diseases, in particular systemic
15 sclerosis, scleroderma and fibromyalgia; idiopathic pulmonary fibrosis; kidney diseases involving fibrosis; pulmonary hypertension and preeclampsia;

 - the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular
20 complication of diabetes; and/or

 - the group consisting of renal failures, in particular renal dysfunction in cirrhosis; chronic kidney disease and acute kidney injury.

BACKGROUND OF THE INVENTION

25 Human Relaxin-2 (H2 Relaxin) is a 6-kDa peptidic hormone of 53 amino acids. Its structure consists of two separate polypeptide chains, i.e. H2 Relaxin chain A (SEQ ID NO: 100) and H2 Relaxin chain B (SEQ ID NO: 101) cross-linked by two disulfide (S-S) bonds, with a third S-S intra-chain bond located in the A chain as follows:

H2 Relaxin A chain : H-Gln-Leu-Tyr-Ser-Ala-Leu-Ala-Asn-Lys-Cys*-Cys**-
30 His-Val-Gly-Cys*-Thr-Lys-Arg-Ser-Leu-Ala-Arg-Phe-Cys***-OH (SEQ ID NO: 100)

H2 Relaxin B chain : H-Asp-Ser-Trp-Met-Glu-Glu-Val-Ile-Lys-Leu-Cys**-
Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Cys***-Gly-Met-Ser-Thr-Trp-Ser-OH
(SEQ ID NO: 101)

wherein Cys*, Cys** and Cys*** indicate the disulfide bonds between
5 Cysteines with same label.

Relaxin-2 is a naturally occurring peptide hormone produced by *corpus luteum*
with a peak in the circulation during the first trimester of pregnancy of a woman. Relaxin-2
belongs to the insulin-like peptide family which members exert numerous effects after
binding to different kinds of receptors, classified as Relaxin family peptide (RXFP)
10 receptors (RXFP1, RXFP2, RXFP3, and RXFP4).

RXFP1 is the main receptor for Relaxin. RXFP1 contains a large extracellular
domain with a single low-density lipoprotein class A (LDLa) module at the amino
terminus and 10 extracellular leucine-rich repeat domains (LRRs), followed by 7
transmembrane (7TM) helical domains. The LDLa module of RXFP1 is joined to the LRR
15 domain via a 32-residue linker.

Activation of RXFP1 is a complex multistep process. Previous studies have
demonstrated that Arg13, Arg17 and Ile20, of the arginine cassette (RxxxRxxI/V, where x
is any residue) of the H2 Relaxin B-chain bind to Asp231, Asp279, Glu233 and Glu277
located on LRR4–8 of the LRR domain of RXFP1. Ligand binding alone is not sufficient
20 to activate the receptor. Truncation or substitution of the LDLa module results in an
inactive receptor despite binding to the extracellular domain. A study (Bruell, S. *et al.*,
Front. Endocrinol. (Lausanne) 4, 171 (2013)), swapping the LDLa modules of RXFP1 and
RXFP2 highlighted the role of the linker in receptor activation. The LRRs (high affinity
site) and the first exoloops (low affinity sites) of the transmembrane domains participate in
25 Relaxin binding, whereas the LDLa module is required for receptor activation involving
exoloop 2 (Sethi A. *et al.* Nature Communications (2016)).

In some species, Relaxin can also activate RXFP2, the native leucine-rich
repeat containing GPCR for the insulin-like peptide 3 (INSL3). This suggests that a
potential cross reactivity might be associated with Relaxin various biological activities,
30 even though there is currently no evidence of a physiological role for Relaxin acting solely
through RXFP2.

Recent published data showed that there are interspecies differences in the capacity of agonists to activate RXFP1 with a specific difference in the ECL3 domain between human and rodent (Huang *et al.* Frontiers in Endocrinology 2015 Aug 17;6:128). In parallel, biased agonist activity was described for some Relaxin-derived single chain mimetics (Hossain *et al.* Chem. Sci., 2016, 7, 3805). However based on IUPHAR nomenclature, RXFP1 is a Gs coupled receptor and the main signalling pathway of RXFP1 leads to cAMP (cyclic adenosine monophosphate) accumulation.

Relaxin has been identified first as a pregnancy hormone involved not only in uterus remodelling and embryo implantation but also in the hemodynamic adaptation of pregnant women. This includes decrease vascular resistance, increase in cardiac output and increase GFR, a combination of effect aiming to improve cardiac afterload. These properties have led to the use of recombinant human Relaxin 2 in several clinical trials in the context of acute heart failure.

Beneficial cardiovascular effects of Relaxin, which are attributed to alterations in the renal and systemic vasculature, have also been demonstrated in congestive and acute heart failure patients in preclinical studies and phase II clinical trials. In conscious normotensive and hypertensive male and female rats, acute intravenous and chronic subcutaneous administration of Relaxin increases cardiac output and global arterial compliance and reduces systemic vascular resistance, without affecting mean arterial pressure.

Relaxin has also been shown to reduce mean arterial pressure in rat models of hypertension. The vascular actions of Relaxin extend to modification of passive wall compliance. Chronic subcutaneous Relaxin infusion in rats and mice increases arterial compliance in small renal, mesenteric, uterine and carotid arteries. In addition Relaxin has anti-fibrotic properties in animal model of cardiac and kidney fibrosis.

Thus Relaxin could benefit to patients with chronic heart failure by decreasing after load and relieving heart activity as well as to patients with pulmonary hypertension, with heart failure with reduced or preserved ejection fraction and to patients with fibrotic diseases including systemic sclerosis, idiopathic pulmonary fibrosis and any kidney disease involving fibrosis.

Relaxin-2 is thus clearly of high therapeutic interest.

Nevertheless, H2-Relaxin complex heterodimeric structure makes its chemical synthesis and purification difficult which leads to low yields of final product (Curr. Opin. Chem. Biol. 2014, 22, 47-55).

Accordingly, there is an interest in obtaining stable Relaxin peptides that
5 possess the ability of Relaxin to activate the RXFP1 receptors, and more particularly peptides that retain the biological activity of Relaxin, while being structurally simpler than the native Relaxin.

Peptides with simpler structures could require less complex and more efficient syntheses than H2-Relaxin. Thereby reducing the costs of treatment linked to H2-Relaxin
10 synthesis.

Furthermore, due to their simpler and smaller structure, such peptides may exhibit an improved uptake compared to native Relaxin, leading to an improved *in vivo* therapeutic activity.

Several simplified H2-Relaxin analogues have been described in the literature.
15 M.A. Hossain et al. (J. Biol. Chem. (2011), 43, 3755) identified the minimal structure of H2-Relaxin showing that its B-chain could be truncated by up to 6 or 7 amino acids at the N-terminus with minimal loss of potency. The structures described in this publication are double chain Relaxin analogues that are still difficult to synthesize and offer no advantage compared to native H2-Relaxin.

Further attempts were made to simplify Relaxin family peptides. Recently,
20 M.A. Hossain *et al.* in Chem. Sci. (2016), 7, 3805-3819 and WO2015/157829 proposed RXFP1 agonist peptides that comprise only the H2-Relaxin B chain. However, as illustrated in the present text, the peptides of WO2015/157829 present an insufficient capacity to activate the RXFP1 receptor.

25 There is thus a need for new peptides analogues of the B-chain of Relaxin-2 able to activate the RXFP1 receptor, in particular having an improved ability to activate the RXFP1 receptor.

There is also a need for new modified Relaxin peptides having a simple
30 structure, in particular a simpler structure than the already known Relaxin-peptides, and that possess an improved ability to activate the RXFP1 receptor.

SUMMARY OF THE INVENTION

The present invention aims to meet the here-above indicated needs.

The inventors indeed provide new modified Relaxin peptides, and in particular lipidated peptides, demonstrating a significantly improved capacity to activate the RXFP1
5 receptor compared to first simplified Relaxin family peptides proposed in the prior art, as demonstrated in the following examples.

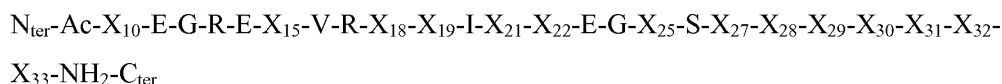
As described here-after, several deletions and modifications have been brought by the inventors to the native Relaxin B-chain amino acid sequence, leading to shorter peptides having improved properties compared to the native Relaxin and to the Relaxin
10 peptides already proposed in the prior art. In particular, the enclosed experiments demonstrate that while peptide B7-33 C11.23S (SEQ ID NO: 102) and analogous peptide from WO2015/157829, AcB7-33 C11.23S (SEQ ID NO: 103) and KKKK(AcB7-29 C11.23S) (SEQ ID NO: 104) have a 50% activation concentration (EC_{50}) of RXFP1 of 1641 nM, 929 nM and 206 nM respectively, in the cellular assay used to select the peptides
15 of this invention, the EC_{50} values obtained with the lipidated peptides according to the invention go from 36.4 nM down to 0.07 nM. Moreover, the majority of the tested peptides of the invention have an EC_{50} value lower or equal to 5 nM.

Moreover, while the prior art below suggested that the B-Chain of relaxin could not be truncated by more than 7 amino-acids (J. Biol. Chem. (2011), 43, 3755;
20 WO2015/157829) without significant reduction in potency, peptides of this invention are truncated by 9 amino-acids at the N-Terminus (Nter) and still show high activity on the RXFP1 receptor.

Compared to RXFP1 agonist peptides of WO2015/157829, peptides of the invention display improved solubility at pH 4.5 or pH 7.5, improved rat and human plasma
25 or blood stability and *in-vivo* half-lives.

These properties will allow to formulate the peptides of this invention in broad concentration ranges for use as medicament that will retain their *in-vivo* efficacy for longer period of time, permitting for example once a day administration by the intravenous or subcutaneous route.

30 Accordingly, one of the objects of the present invention relates to a peptide having the following formula (I):



wherein:

N_{ter} represents the N-terminal end of the peptide;

5 C_{ter} represents the C-terminal end of the peptide;

Ac represents acetyl group;

X_{10} represents an amino acid selected from the group consisting of leucine, 2-amino-isobutyric acid (Aib), N ϵ -acetyl-lysine (K(Ac)) and α -methyl-leucine (Mel);

E represents glutamic acid (Glu);

10 G represents glycine (Gly);

R represents arginine (Arg);

X_{15} represents an amino acid selected from the group consisting of lysine (Lys), arginine (Arg), homolysine (Hly), homoarginine (Har), ornithine (Orn), glutamine (Gln), phenylalanine (Phe) and leucine (Leu);

15 V represents valine (Val);

X_{18} represents an amino acid selected from the group consisting of alanine (Ala), 2-amino-isobutyric acid (Aib), leucine (Leu), N ϵ -acetyl-lysine (K(Ac)) and glutamine (Gln);

X_{19} represents an amino acid selected from the group consisting of lysine (Lys), N ϵ -acetyl-lysine (K(Ac)), citruline (Cit), glutamine (Gln), alanine (Ala) and 2-amino-isobutyric acid

20 (Aib);

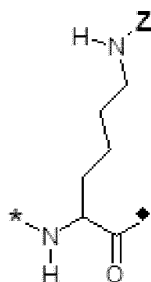
I represents isoleucine (Ile);

X_{21} represents an amino acid selected from the group consisting of 2-amino-isobutyric acid (Aib) and alanine (Ala);

X_{22} represents an amino acid selected from the group consisting of 2-amino-isobutyric acid

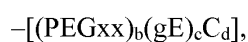
25 (Aib) and isoleucine (Ile);

X_{25} represents the following structure:



in which:

- 5 - * represents a covalent bond with the glycine preceding X₂₅ in formula (I);
 - ♦ represents a covalent bond with the serine following X₂₅ in formula (I); and
 Z represents a group of formula (II):



b and c independently represent 1, 2, 3, 4 or 5;

PEGxx independently represents a polyethylene glycol derivative selected from the group consisting of PEG₂, PEG₂DGA, and TTDS;

10 gE represents gamma-glutamic acid; and

C_d represents a linear saturated C₁₂-C₂₂ acyl group;

S represents Serine (Ser);

X₂₇ represents an amino acid selected from the group consisting of threonine (Thr), lysine (Lys), arginine (Arg) and glutamine (Gln);

15 X₂₈ represents an amino acid selected from the group consisting of tryptophan (Trp), phenylalanine (Phe), 5-fluoro-tryptophan (Trp(5F)), 5-chloro-tryptophan (Trp(5Cl)), 5-methoxy-tryptophan (Trp(5OMe)), tyrosine (Tyr), 4-fluoro-phenylalanine (Pfp), 1-naphtylalanine (1-Nal), 2-naphtylalanine (2-Nal), α -methyl-tryptophane (Mtr), α -methyl-phenylalanine (Mph) and 5-hydroxy-tryptophane (Wox);

20 X₂₉ represents an amino acid selected from the group consisting of serine (Ser), D-serine (Dser), 2-amino-isobutyric acid (Aib), threonine (Thr), α -methyl-serine (Mse), N ϵ -acetyl-lysine (K(Ac)) and valine (Val);

X₃₀ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid (Aib), α -methyl-lysine (Mly), D-lysine (Dlys), lysine, homolysine (Hly), ornithine (Orn), arginine (Arg) and α -methyl-arginine (Mar);

X₃₁ represents an amino acid selected from the group consisting of arginine (Arg), Nω-methyl-arginine (Rme), alanine (Ala), Nω,Nω'-dimethyl-arginine (Rds, symmetrical dimethyl arginine) and citruline (Cit);

X₃₂ represents an amino acid selected from the group consisting of lysine (Lys), alanine (Ala), arginine (Arg), Nε-acetyl-lysine (K(Ac)) and Nε,Nε,Nε-tri-methyl-lysine (Tml); and
5 X₃₃ represents an amino acid selected from lysine (Lys), Nε-acetyl-lysine (K(Ac)), leucine (Leu), arginine (Arg) and alanine (Ala);
or a salt or solvate thereof.

In a particular embodiment the invention provides a peptide having the formula
10 (I) or a pharmaceutically acceptable salt or a solvate thereof wherein the peptide is able to activate the RXFP1 receptor.

Another object of the present invention is a pharmaceutical composition comprising at least one peptide according to the invention, or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable
15 carrier.

A further object of the present invention relates to a peptide of the invention, a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof according to the invention, for its use as a medicament.

Accordingly, the present invention further relates to a peptide of the invention,
20 a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof according to the invention, for its use in the treatment and/or prevention of various diseases or conditions implicating the RXFP1 receptor, more particularly in the treatment and/or prevention of diseases or conditions selected from:

- the group consisting of fibrosis; fibrotic diseases, in particular systemic
25 sclerosis, scleroderma and fibromyalgia; idiopathic pulmonary fibrosis; kidney diseases involving fibrosis; pulmonary hypertension and preeclampsia;

- the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular
30 complication of diabetes; and/or

- the group consisting of renal failures in particular renal dysfunction in cirrhosis, chronic kidney disease and acute kidney injury.

In one embodiment, said disease or condition can be selected from the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular complication of diabetes.

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DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein:

- “X_y” used in the formulae of the invention with y having different values
10 represents an amino acid as defined in the definition of said formulae. y indicates the position of said amino acid in the native B-chain of Relaxin-2. For example, X₁₀ represents the amino acid in position 10 of the amino acid sequence of the native B-chain of Relaxin-2.
- “pharmaceutically acceptable carrier” is intended for a fluid, especially a
15 liquid comprising a peptide of the invention, such that the pharmaceutical composition is physiologically tolerable, i.e. can be administered to the individual body without toxicity or undue discomfort.
- a “biologically active” peptide according to the invention is a peptide able to activate the RXFP1 receptor.
- 20 - When applicable, amino acids in the peptides of the invention can each independently be L-amino acids or D-amino acids. In a particular embodiment, amino acids according to the present invention are L-amino acids. In the present text, if no information is indicated regarding the L- or D- form of a given amino acid, then this amino acid is an L-amino acid.
- 25 - N_{ter} and C_{ter} are conventional labels used to indicate, respectively, the N-terminal end of the peptide and the C-terminal end of the peptide of the invention.
- A “peptide” or “Relaxin peptide” according to the invention is a modified lipidated Relaxin B chain peptide in accordance with the present invention. In particular, such “peptide” or “Relaxine peptide” means a peptide which is biologically active, i.e. that
30 displays a biological activity typically associated with Relaxin and in particular which is as indicated here-above able to activate the RXFP1 receptor. The level of such Relaxin biological activity displayed by the modified peptides according to the invention may be

equivalent or advantageously enhanced when compared with the activity of a naturally occurring or native Relaxin, or even when compared to already disclosed Relaxin peptides different from the one of the present invention.

- The term “native” as used in the present text in connection with Relaxin
5 refers to naturally occurring or wild type molecules.

- “Preventing” is intended to mean reducing the risk of manifestation of the phenomenon under consideration. This reduction may be total or partial, i.e. results in a degree of risk that is lower than that pre-existing the use according to the invention.

- “Treating” is intended to mean reducing or even eliminating the undesirable
10 condition or disease under consideration.

- “individual” or “patient” is intended for a human or non-human mammal affected or likely to be affected with a condition considered according to the invention. Said individual is in particular a human being.

The present inventors have designed new modified peptides, in particular
15 lipidated peptides.

The inventors have unexpectedly found herein that a shorter and strongly amended peptide according to the invention, i.e. amino acids sequence according to the invention, has a superior biological activity, in particular a superior capacity to activate the RXFP1 receptor in comparison to single B-chain Relaxin known in the art.

20

Peptides of the invention

Peptides according to the invention are characterized in that they are of formula

(I):

$$N_{\text{ter}}\text{-Ac-X}_{10}\text{-E-G-R-E-X}_{15}\text{-V-R-X}_{18}\text{-X}_{19}\text{-I-X}_{21}\text{-X}_{22}\text{-E-G-X}_{25}\text{-S-X}_{27}\text{-X}_{28}\text{-X}_{29}\text{-X}_{30}\text{-X}_{31}\text{-X}_{32}\text{-X}_{33}\text{-NH}_2\text{-C}_{\text{ter}}$$

25

wherein:

N_{ter} represents the N-terminal end of the peptide;

C_{ter} represents the C-terminal end of the peptide;

Ac represents acetyl group;

30 X_{10} represents an amino acid selected from the group consisting of leucine, 2-amino-isobutyric acid, N ϵ -acetyl-lysine and α -methyl-leucine;

E represents glutamic acid;

G represents glycine;

R represents arginine;

X₁₅ represents an amino acid selected from the group consisting of lysine, arginine, homolysine, homoarginine, ornithine, glutamine, phenylalanine and leucine;

5 V represents valine;

X₁₈ represents an amino acid selected from the group consisting of alanine, 2-amino-isobutyric acid, leucine, Nε-acetyl-lysine and glutamine;

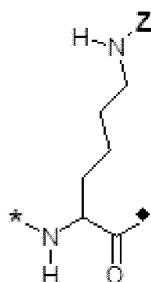
X₁₉ represents an amino acid selected from the group consisting of lysine, Nε-acetyl-lysine, citruline, glutamine, alanine and 2-amino-isobutyric acid;

10 I represents isoleucine;

X₂₁ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and alanine;

X₂₂ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and isoleucine;

15 X₂₅ represents the following structure:

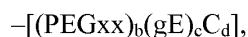


in which:

-* represents a covalent bond with the glycine preceding X₂₅ in formula (I);

-◆ represents a covalent bond with the serine following X₂₅ in formula (I); and

20 Z represents a group of formula (II):



b and c independently represent 1, 2, 3, 4 or 5;

PEG_{xx} independently represents a polyethylene glycol derivative selected from the group consisting of PEG₂, PEG₂DGA, and TTDS;

25 gE represents gamma-glutamic acid; and

C_d represents a linear saturated C₁₂-C₂₂ acyl group;

S represents serine;

X₂₇ represents an amino acid selected from the group consisting of threonine, lysine, arginine and glutamine;

X₂₈ represents an amino acid selected from the group consisting of tryptophan, phenylalanine, 5-fluoro-tryptophan, 5-chloro-tryptophan, 5-methoxy-tryptophan, tyrosine, 4-fluoro-phenylalanine, 1-naphtylalanine, 2-naphtylalanine, α -methyl-tryptophane, α -methyl-phenylalanine and 5-hydroxy-tryptophane;

X₂₉ represents an amino acid selected from the group consisting of serine, D-serine, 2-amino-isobutyric acid, threonine, α -methyl-serine, N ϵ -acetyl-lysine and valine;

X₃₀ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid, α -methyl-lysine, D-lysine, lysine, homolysine, ornithine, arginine and α -methyl-arginine;

X₃₁ represents an amino acid selected from the group consisting of arginine, N ω -methyl-arginine, alanine, N ω ,N ω' -dimethyl-arginine and citruline;

X₃₂ represents an amino acid selected from the group consisting of lysine, alanine, arginine, N ϵ -acetyl-lysine and N ϵ ,N ϵ ,N ϵ -tri-methyl-lysine;

X₃₃ represents an amino acid selected from lysine, N ϵ -acetyl-lysine, leucine, arginine and alanine;

or a salt or solvate thereof.

The present invention also includes salts of the peptides of the formulae (I) or (Ia) defined herein, in one embodiment pharmaceutically acceptable salts, for example salts as acid adduct with inorganic acids such as hydrochloric acid, sulphuric acid, nitric acid, hydrobromic acid, phosphoric acid, perchloric acid, thiocyanic acid and boric acid; or with organic acid such as formic acid, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, citric acid, tartaric acid, succinic acid, gluconic acid, lactic acid, malonic acid, fumaric acid, anthranilic acid, benzoic acid, cinnamic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and sulfanilic acid; and salts with metals such as alkali metal, e.g. sodium, potassium, lithium, zinc, and aluminium.

In one embodiment the salts of the peptides are pharmaceutically acceptable salts, for example acid adducts with hydrochloric acid, sulphuric acid, phosphoric acid, formic acid, acetic acid, propionic acid, glycolic acid, citric acid, tartaric acid, succinic acid, gluconic acid, lactic acid, malonic acid, fumaric acid, anthranilic acid, benzoic acid, cinnamic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and

sulfanilic acid; and salts with metals such as alkali metal, e.g. sodium, potassium, lithium and zinc.

The present invention also includes solvates, in one embodiment pharmaceutically acceptable solvates, of the peptides of the above formulae (I) or (Ia).

5 Solvates mean complexes of the compounds of the invention or salts thereof with solvent molecules, e.g. organic solvent molecules and/or water.

According to an embodiment of the invention, the invention also includes pharmaceutically acceptable salt or solvate of the peptides of the invention.

10 As illustrated, a peptide according to the invention is an amino acid sequence.

In keeping with standard polypeptide nomenclature (J. Biol. Chem., 243:3552-59 (1969)) abbreviations for α -amino acid residues used in the present invention are as follows:

One letter code	Three letter code	Amino acid
A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic acid or aspartate
E	Glu	Glutamic acid or glutamate
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine

15

For non natural or modified aminoacids the following abbreviations are used :

Aib	2-amino-isobutyric acid
Cit	Citruline
Dser	D-serine
Dlys	D-lysine
Har	Homoarginine
Hly	Homolysine
Hph	Homophenylalanine
gE	γ -Glutamic acid (glutamic acid connected by its γ -carboxylic acid function)
Nle	Norleucine, 2-amino hexanoic acid
K(Ac)	N ϵ -Acetyl-lysine, 2-amino-4-acetamido-hexanoic acid
Mar	α -Methyl-arginine
Mel	α -Methyl-leucine
Mly	α -Methyl-lysine
Mph	α -Methyl-phenylalanine
Mse	α -Methyl-serine
Mtr	α -Methyl-tryptophane
1-Nal	1-Naphtylalanine
2-Nal	2-Naphtylalanine
Orn	Ornithine
Pfp	4-Fluoro-phenylalanine
Rds	N ω , N ω' -dimethyl-arginine (symmetrical)
Rme	N ω -methyl-arginine
Tml	N ϵ ,N ϵ ,N ϵ -trimethyl-lysine
Trp(5-Cl) or Trp(5Cl)	5-Chlorotryptophan
Trp(5-F) or Trp(5F)	5-Fluorotryptophan
Trp(5-OMe) or Trp(5OMe)	5-Methoxytryptophan
Wox	5-Hydroxy-tryptophane

In all the formulae according to the invention, where the amino acid sequence is represented by using the above mentioned abbreviations and X_y representations such as X₁₈ for example, the left and right orientation is in the conventional direction of amino-terminus to carboxy-terminus.

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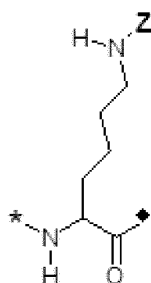
Accordingly, for example, with X₂₈ representing an amino acid selected from the group of tryptophan, 5-fluoro-tryptophan, 5-chloro-tryptophan, 5-methoxy-tryptophan, tyrosine, phenylalanine, 4-fluoro-phenylalanine, 1-naphtylalanine, 2-naphtylalanine,

α -methyl-tryptophane, α -methyl-phenylalanine and 5-hydroxy-tryptophane, the N-terminus or amine group of said amino acid is linked to the amino acid represented by X_{27} and the C-terminus or carboxyl group of said amino acid is linked to the amino acid represented by X_{29} .

5 On its N-terminal (N_{ter}) extremity, a peptide of the invention is substituted with an acetyl group (Ac) : $\text{CH}_3\text{C}(\text{O})-$.

On its C-terminal (C_{ter}) extremity, a peptide of the invention is substituted with an $-\text{NH}_2$ group.

10 On its position X_{25} , a peptide of the invention comprises the following structure:



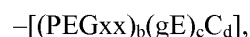
This structure corresponds to a lysine amino acid wherein:

- the alpha (α) nitrogen atom (*) is bound to the previous part of the peptide, i.e. with the group in N_{ter} of X_{25} on the basis of the $N_{\text{ter}}-C_{\text{ter}}$ orientation represented in the formulae according to the invention, through a covalent bond, in particular through a peptide bond, i.e. with the glycine in position 24 (X_{24});

- the carbon atom of the carboxyl group (◆) is bound to the part of the peptide following position X_{25} , i.e. with the group in C_{ter} of X_{25} on the basis of the $N_{\text{ter}}-C_{\text{ter}}$ orientation represented in the formulae according to the invention, through a covalent bond, in particular through a peptide bond, i.e. with the serine in position 26 (X_{26}); and

- the nitrogen atom of its lateral chain is bound to a Z group.

This Z group is defined as being of formula (II):



25 In formula (II), the – represents a covalent bound with the nitrogen atom of the lateral chain of the lysine structure in X_{25} .

b and c independently represent 1, 2, 3, 4 or 5, in particular 2, 3, 4 or 5.

In a particular embodiment, b represents 2, 3, 4 or 5.

In a particular embodiment, c represents 2, 3 or 4.

In a preferred embodiment, b represents 2, 3, 4 or 5 and c independently
5 represents 2, 3 or 4.

PEG_{xx} in the formulae of the invention independently represents a polyethylene glycol derivative selected from the group consisting of PEG₂, PEG₂DGA and TTDS.

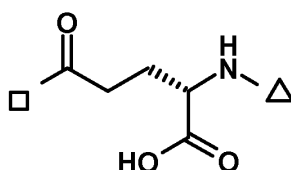
10 Said groups are defined as follows:

Abbreviation	Structure	IUPAC name
PEG ₂		2-[2-(2-aminoethoxy)ethoxy]acetyl
PEG ₂ DGA		2-[2-[3-[2-[2-(3-aminopropoxy)ethoxy]ethoxy]propylamino]-2-oxo-ethoxy]acetyl
TTDS		4-[3-[2-[2-(3-aminopropoxy)ethoxy]ethoxy]propylamino]-4-oxo-butanoyl

in which, in (PEG_{xx})_b of formula (II), Δ represents a covalent bond with the (gE)_c group and □ represents a covalent bond linking the group of formula (II) with the nitrogen atom of lateral chain of the lysine structure in X₂₅.

15 In a particular embodiment, (PEG_{xx})_b represents a polyethylene glycol derivative selected from the group consisting of (TTDS)₂, (TTDS)₃, (PEG₂DGA)₃, (PEG₂)₃, (PEG₂)₄ and (PEG₂)₅.

As indicated previously, gE, which can also be represented as γE, gGlu or γGlu, represents a gamma-glutamic acid. This amino acid has the following structure:



in which, when represented in formula (II) as (gE)_c, Δ represents a covalent bond with C_d and □ represents a covalent bond with the (PEG_{xx})_b group.

C_d represents a linear saturated C₁₂-C₂₂ acyl group, in particular a linear saturated acyl group selected from the group consisting of C₁₂ (Lau), C₁₄ (Myr), C₁₅ (Penta), C₁₆ (Palm), C₁₇ (Hepta), C₁₈ (Stea), C₂₀ (Eico) and C₂₂ (Doco) acyl group. In one embodiment C_k represents a linear saturated acyl group selected from the group consisting of C₁₂ (Lau), C₁₄ (Myr), C₁₅ (Penta), C₁₆ (Palm), C₁₇ (Hepta) or C₁₈ (Stea) acyl group, in particular a linear saturated C₁₄, C₁₆ or C₁₈ acyl group, and even more particularly a linear C₁₆ or C₁₈ acyl group.

In a particular embodiment, C_d represents a linear saturated C₁₂ acyl group. A linear saturated C₁₂ acyl group of the invention is a lauroyl group (also represented as “Lau” in the present text).

In a particular embodiment, C_d represents a linear saturated C₁₄ acyl group. A linear saturated C₁₄ acyl group of the invention is a Myristoyl group (also represented as “Myr” in the present text).

In a particular embodiment, C_d represents a linear saturated C₁₅ acyl group. A linear saturated C₁₅ acyl group of the invention is a pentadecanoyl group (also represented as “Penta” in the present text).

In a particular embodiment, C_d represents a linear saturated C₁₆ acyl group. A linear saturated C₁₆ acyl group of the invention is a palmitoyl group (also represented as “Palm” in the present text).

In a particular embodiment, C_d represents a linear saturated C₁₇ acyl group. A linear saturated C₁₇ acyl group of the invention is a heptadecanoyl group (also represented as “Hepta” in the present text).

In another particular embodiment, C_d represents a linear saturated C₁₈ acyl group. A linear saturated C₁₈ acyl group of the invention is a stearoyl group (also represented as “Stea” in the present text).

In another particular embodiment, C_d represents a linear saturated C_{20} acyl group. A linear saturated C_{20} acyl group of the invention is a Eicosanoyl group (also represented as “Eico” in the present text).

In another particular embodiment, C_d represents a linear saturated C_{22} acyl group. A linear saturated C_{22} acyl group of the invention is a Docosanoyl group (also represented as “Doco” in the present text).

In a particular embodiment, Z is selected from the group consisting of

10 $-(TTDS)_2$ -(gamma glutamic acid)₃-Palmitoyl $-(TTDS)_2$ -(gE)₃-Palm), $-(TTDS)_3$ -(gamma glutamic acid)₃-Palmitoyl $-(TTDS)_3$ -(gE)₃-Palm), $-(PEG_2DGA)_3$ -(gamma glutamic acid)₃-Palmitoyl $-(PEG_2DGA)_3$ -(gE)₃-Palm), $-(PEG_2)_4$ -(gamma glutamic acid)₃-Palmitoyl $-(PEG_2)_4$ -(gE)₃-Palm), $-(TTDS)_2$ -(gamma glutamic acid)₂-Palmitoyl $-(TTDS)_2$ -(gE)₂-Palm), $-(TTDS)_2$ -(gamma glutamic acid)₃-Stearoyl $-(TTDS)_2$ -(gE)₃-Stea), $-(TTDS)_3$ -(gamma glutamic acid)₃-Stearoyl $-(TTDS)_3$ -(gE)₃-Stea), $-(PEG_2DGA)_3$ -(gamma glutamic acid)₃-Stearoyl $-(PEG_2DGA)_3$ -(gE)₃-Stea), $-(PEG_2DGA)_3$ -(gamma glutamic acid)₄-Stearoyl $-(PEG_2DGA)_3$ -(gE)₄-Stea), $-(PEG_2)_3$ -(gamma glutamic acid)₃-Palmitoyl $-(PEG_2)_3$ -(gE)₃-Palm), $-(PEG_2)_4$ -(gamma glutamic acid)₃-Stearoyl $-(PEG_2)_4$ -(gE)₃-Stea), $-(PEG_2)_5$ -(gamma glutamic acid)₃-Palmitoyl $-(PEG_2)_5$ -(gE)₃-Palm), $-(PEG_2)_5$ -(gamma glutamic acid)₄-Palmitoyl $-(PEG_2)_5$ -(gE)₄-Palm), $-(TTDS)_3$ -(gamma glutamic acid)₄-Stearoyl $-(TTDS)_3$ -(gE)₄-Stea), $-(TTDS)_2$ -(gamma glutamic acid)₄-Palmitoyl $-(TTDS)_2$ -(gE)₄-Palm), $-(TTDS)_3$ -(gamma glutamic acid)₂-Stearoyl $-(TTDS)_3$ -(gE)₂-Stea) and $-(TTDS)_2$ -(gamma glutamic acid)₄-Stearoyl $-(TTDS)_2$ -(gE)₄-Stea), in a more particular embodiment Z is selected from the group consisting of $-(TTDS)_2$ -(gE)₃-Palm, $-(TTDS)_3$ -(gE)₃-Palm, $-(PEG_2DGA)_3$ -(gE)₃-Palm, $-(PEG_2)_4$ -(gE)₃-Palm, $-(TTDS)_2$ -(gE)₂-Palm, $-(TTDS)_2$ -(gE)₃-Stea, $-(TTDS)_3$ -(gE)₃-Stea, $-(PEG_2)_3$ -(gE)₃-Palm, $-(PEG_2)_4$ -(gE)₃-Stea and $-(TTDS)_2$ -(gE)₄-Palm, in a special embodiment Z is selected from the group consisting of $-(TTDS)_3$ -(gE)₃-Palm, $-(TTDS)_2$ -(gE)₃-Stea and $-(TTDS)_3$ -(gE)₃-Stea, for example $-(TTDS)_3$ -(gE)₃-Palm and $-(TTDS)_3$ -(gE)₃-Stea.

30 In all these Z groups, the first – symbol represents the covalent bond between the Z group and nitrogen atom of the lateral chain of the lysine X_{25} structure.

Accordingly, when the Z group is for example represented as being $-(TTDS)_2-(\text{gamma glutamic acid})_3\text{-Palmitoyl}$ (also represented as $-(TTDS)_2-(gE)_3\text{-Palm}$), the first TTDS group is bound to the nitrogen atom of the lateral chain of the X_{25} structure. A covalent bond also binds the second TTDS group while another covalent bond binds this

5 second TTDS group to the first gamma-glutamic acid (gE). This first gamma-glutamic acid (gE) is itself bonded through a covalent bond to the second gamma-glutamic acid (gE), this second gamma-glutamic acid (gE) is bonded through another covalent bond to the third gamma-glutamic acid (gE) and this third gamma-glutamic acid (gE) group is further linked by a covalent bond to a palmitoyl (Palm) group.

10 Furthermore, it must be understood from the present application that a Z group according to the invention represented for example as $-(TTDS)_2-(\text{gamma glutamic acid})_3\text{-Palmitoyl}$ (also represented as $-(TTDS)_2-(gE)_3\text{-Palm}$) could also have been represented $-\text{TTDS-TTDS-gE-gE-gE-Palm}$.

The same applies *mutatis mutandis* for the other represented Z groups

15 according to the invention.

According to a particular embodiment, a peptide according to the invention is of formula (Ia):

20 $N_{\text{ter}}\text{-Ac-L-E-G-R-E-X}_{15}\text{-V-R-X}_{18}\text{-X}_{19}\text{-I-Aib-Aib-E-G-X}_{25}\text{-S-T-X}_{28}\text{-X}_{29}\text{-X}_{30}\text{-R-X}_{32}\text{-X}_{33}\text{-NH}_2\text{-C}_{\text{ter}}$

wherein:

N_{ter} represents the N-terminal end of the peptide;

C_{ter} represents the C-terminal end of the peptide;

Ac represents acetyl group;

25 L represents leucine;

E represents glutamic acid;

G represents glycine;

R represents arginine;

30 X_{15} represents an amino acid selected from the group consisting of lysine, arginine, homolysine, glutamine, phenylalanine and leucine;

V represents valine;

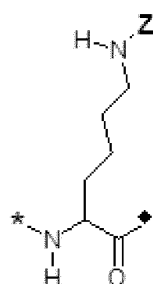
X₁₈ represents an amino acid selected from the group consisting of alanine and 2-amino-isobutyric acid;

X₁₉ represents an amino acid selected from the group consisting of lysine, Nε-acetyl-lysine, glutamine and citruline;

5 I represents isoleucine;

Aib represents 2-amino-isobutyric acid;

X₂₅ represents the following structure:



in which:

10 - * represents a covalent bond with the glycine preceding X₂₅ in formula (Ia);

- ♦ represents a covalent bond with the serine following X₂₅ in formula (Ia); and

Z is selected from the group consisting

of a -(TTDS)₂-(gE)₃-Palm, -(TTDS)₃-(gE)₃-Palm, -(PEG₂DGA)₃-(gE)₃-Palm, -(PEG₂)₄-

(gE)₃-Palm, -(TTDS)₂-(gE)₂-Palm, -(TTDS)₂-(gE)₃-Stea, -(TTDS)₃-(gE)₃-Stea,

15 -(PEG₂DGA)₃-(gE)₃-Stea, -(PEG₂DGA)₃-(gE)₄-Stea, -(PEG₂)₃-(gE)₃-Palm, -(PEG₂)₄-

(gE)₃-Stea, -(PEG₂)₅-(gE)₃-Palm, -(PEG₂)₅-(gE)₄-Palm, -(TTDS)₃-(gE)₄-Stea,

-(TTDS)₂-(gE)₄-Palm, -(TTDS)₃-(gE)₂-Stea and -(TTDS)₂-(gE)₄-Stea, wherein

gE represents gamma-glutamic acid

Palm represents Palmitoyl and

20 Stea represents Stearoyl;

S represents serine;

T represents threonine;

X₂₈ represents an amino acid selected from the group consisting of tryptophan and phenylalanine;

25 X₂₉ represents an amino acid selected from the group consisting of serine, D-serine and 2-amino-isobutyric acid;

X₃₀ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid, α-methyl-lysine, D-lysine and lysine;

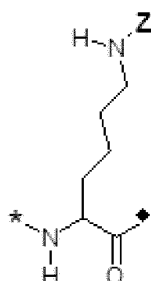
X₃₂ represents an amino acid selected from the group consisting of lysine, alanine and arginine; and

- 5 X₃₃ represents an amino acid selected from lysine and Nε-acetyl-lysine ;
or a salt or solvate thereof.

- According to a particular embodiment, a peptide according to the invention has an amino acid sequence selected from the group consisting of the amino acid sequences of
10 reference SEQ ID NO: 1-97. In particular, a peptide according to the invention has an amino acid sequence selected from the group consisting of the amino acid sequences of reference SEQ ID NO: 1-32, 34-37, 39, 42, 44, 45, 47-49, 51 and 54-97.

In a particular embodiment for a peptide having the following formula (Ia) as described above :

- 15 X₁₉ represents an amino acid selected from the group consisting of Nε-acetyl-lysine and citruline;
X₂₅ represents the following structure:



in which:

- 20 - * represents a covalent bond with the glycine preceding X₂₅ in formula (Ia);
- ♦ represents a covalent bond with the serine following X₂₅ in formula (Ia); and
Z is selected from the group consisting
of a -(TTDS)₂-(gE)₃-Palm, -(TTDS)₃-(gE)₃-Palm, -(PEG₂DGA)₃-(gE)₃-Palm, -(PEG₂)₄-(gE)₃-Palm,
-(TTDS)₂-(gE)₂-Palm, -(TTDS)₂-(gE)₃-Stea, -(TTDS)₃-(gE)₃-Stea,
25 -(PEG₂)₃-(gE)₃-Palm, -(PEG₂)₄-(gE)₃-Stea and -(TTDS)₂-(gE)₄-Palm, wherein
gE represents gamma-glutamic acid

Palm represents Palmitoyl and

Stea represents Stearoyl;

X₃₂ represents an amino acid selected from the group consisting of lysine and alanine; and

X₃₃ represents Nε-acetyl-lysine

5 or a salt or solvate thereof.

According to another embodiment, a peptide according to the invention has an amino acid sequence selected from the group consisting of the amino acid sequences of reference SEQ ID NO: 1-30.

10

In a particular embodiment, a peptide according to the invention of formula (Ia) is such that:

N_{ter} represents the N-terminal end of the peptide;

C_{ter} represents the C-terminal end of the peptide;

15 Ac represents acetyl group;

L represents leucine;

E represents glutamic acid;

G represents glycine;

R represents arginine;

20 X₁₅ represents an amino acid selected from the group consisting of lysine and homolysine;

V represents valine;

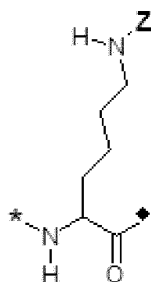
X₁₈ represents alanine;

X₁₉ represents an amino acid selected from the group consisting of Nε-acetyl-lysine and citruline;

25 I represents isoleucine;

Aib represents 2-amino-isobutyric acid;

X₂₅ represents the following structure:



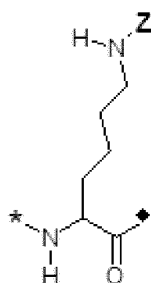
in which:

- * represents a covalent bond with the glycine preceding X_{25} in formula (Ia);
- ◆ represents a covalent bond with the serine following X_{25} in formula (Ia); and
- 5 Z is selected from the group consisting of $-(TTDS)_2-(gE)_2$ -Palm, $-(TTDS)_2-(gE)_3$ -Palm, $-(TTDS)_2-(gE)_4$ -Palm, $-(TTDS)_3-(gE)_3$ -Palm, $-(PEG_2DGA)_3-(gE)_3$ -Palm, $-(TTDS)_2-(gE)_3$ -Stea, $-(TTDS)_3-(gE)_3$ -Stea and $-(PEG_2)_4-(gE)_3$ -Stea, wherein
 - gE represents gamma-glutamic acid
 - Palm represents Palmitoyl and
 - 10 Stea represents Stearoyl;
- S represents serine;
- T represents threonine;
- X_{28} represents an amino acid selected from the group consisting of tryptophan and phenylalanine;
- 15 X_{29} represents serine;
- X_{30} represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and α -methyl-lysine;
- X_{32} represents an amino acid selected from the group consisting of lysine, alanine and arginine; and
- 20 X_{33} represents an amino acid selected from lysine and N ϵ -acetyl-lysine; or a salt or solvate thereof.

In a special embodiment, a peptide according to the invention of formula (Ia) is such that:

- 25 N_{ter} represents the N-terminal end of the peptide;
- C_{ter} represents the C-terminal end of the peptide;
- Ac represents acetyl group;

- L represents leucine;
 E represents glutamic acid;
 G represents glycine;
 R represents arginine;
 5 X₁₅ represents lysine;
 V represents valine;
 X₁₈ represents alanine;
 X₁₉ represents Nε-acetyl-lysine;
 I represents isoleucine;
 10 Aib represents 2-amino-isobutyric acid;
 X₂₅ represents the following structure:



in which:

- * represents a covalent bond with the glycine preceding X₂₅ in formula (Ia);
 - 15 -♦ represents a covalent bond with the serine following X₂₅ in formula (Ia); and
- Z is selected from the group consisting of -(TTDS)₃-(gE)₃-Palm, -(TTDS)₂-(gE)₃-Stea, -(TTDS)₃-(gE)₃-Stea and -(PEG₂)₄-(gE)₃-Stea, wherein
- gE represents gamma-glutamic acid
 - Palm represents Palmitoyl and
 - 20 Stea represents Stearoyl;
 - S represents serine;
 - T represents threonine;
 - X₂₈ represents an amino acid selected from the group consisting of tryptophan and phenylalanine;
 - 25 X₂₉ represents serine;
 - X₃₀ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and α-methyl-lysine;

X₃₂ represents an amino acid selected from the group consisting of lysine, alanine and arginine; and

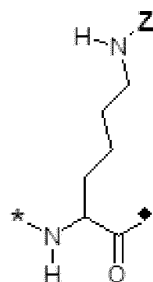
X₃₃ represents an amino acid selected from lysine and Nε-acetyl-lysine; or a salt or solvate thereof.

- 5 According to a particular embodiment, a peptide according to the invention is of formula (Ib):

N_{ter}-Ac-X₁₀-E-G-R-E-X₁₅-V-R-X₁₈-X₁₉-I-X₂₁-X₂₂-E-G-X₂₅-S-X₂₇-X₂₈-X₂₉-X₃₀-R-X₃₂-X₃₃-NH₂-C_{ter}

wherein:

- 10 N_{ter} represents the N-terminal end of the peptide;
 C_{ter} represents the C-terminal end of the peptide;
 Ac represents acetyl group;
 X₁₀ represents an amino acid selected from the group consisting of leucine, Nε-acetyl-lysine and 2-amino-isobutyric acid;
- 15 E represents glutamic acid;
 G represents glycine;
 R represents arginine;
 X₁₅ represents an amino acid selected from the group consisting of lysine, arginine, homolysine, glutamine, phenylalanine and leucine;
- 20 V represents valine;
 X₁₈ represents an amino acid selected from the group consisting of alanine, 2-amino-isobutyric acid and Nε-acetyl-lysine;
 X₁₉ represents an amino acid selected from the group consisting of lysine, Nε-acetyl-lysine, glutamine and citruline;
- 25 I represents isoleucine;
 X₂₁ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and alanine;
 X₂₂ represents an amino acid selected from the group consisting of 2-amino-isobutyric acid and isoleucine;
- 30 X₂₅ represents the following structure:



in which:

- * represents a covalent bond with the glycine preceding X_{25} in formula (Ia);
 - ♦ represents a covalent bond with the serine following X_{25} in formula (Ia); and
- 5 Z is selected from the group consisting of a $-(TTDS)_2-(gE)_3$ -Palm, $-(TTDS)_3-(gE)_3$ -Palm, $-(PEG_2DGA)_3-(gE)_3$ -Palm, $-(PEG_2)_4-(gE)_3$ -Palm, $-(TTDS)_2-(gE)_2$ -Palm, $-(TTDS)_2-(gE)_3$ -Stea, $-(TTDS)_3-(gE)_3$ -Stea, $-(PEG_2DGA)_3-(gE)_3$ -Stea, $-(PEG_2DGA)_3-(gE)_4$ -Stea, $-(PEG_2)_3-(gE)_3$ -Palm, $-(PEG_2)_4-(gE)_3$ -Stea, $-(PEG_2)_5-(gE)_3$ -Palm, $-(PEG_2)_5-(gE)_4$ -Palm, $-(TTDS)_3-(gE)_4$ -Stea, $-(TTDS)_2-(gE)_4$ -Palm, $-(TTDS)_3-(gE)_2$ -Stea,
- 10 $-(TTDS)_2-(gE)_4$ -Stea, $-(TTDS)_4-(gE)_3$ -Stea, $-(TTDS)_3-(gE)_4$ -Palm, $-(TTDS)_4-(gE)_3$ -Palm, $-(TTDS)_3-(gE)_3$ -Myr and $-(TTDS)_3-(gE)_4$ -Myr wherein
- gE represents gamma-glutamic acid
- Palm represents Palmitoyl and
- Stea represents Stearoyl;
- 15 S represents serine;
- X_{27} represents an amino acid selected from the group consisting of threonine, glutamine, arginine and lysine;
- X_{28} represents an amino acid selected from the group consisting of tryptophan, phenylalanine, 5-Chlorotryptophan, α -Methyl-phenylalanine, 4-Fluoro-phenylalanine and
- 20 5-Fluorotryptophan;
- X_{29} represents an amino acid selected from the group consisting of serine, D-serine, 2-amino-isobutyric acid, N ϵ -acetyl-lysine, threonine and valine ;
- X_{30} represents an amino acid selected from the group consisting of 2-amino-isobutyric acid, α -methyl-lysine, D-lysine, lysine, homolysine and arginine;
- 25 X_{32} represents an amino acid selected from the group consisting of lysine, alanine, arginine and N ϵ -acetyl-lysine; and
- X_{33} represents an amino acid selected from lysine, N ϵ -acetyl-lysine and arginine ;

or a salt or solvate thereof.

In particular, Z can be selected from the group consisting of a
-(TTDS)₂-(gE)₃-Palm, -(TTDS)₃-(gE)₃-Palm, -(PEG₂DGA)₃-(gE)₃-Palm, -(PEG₂)₄-(gE)₃-
Palm, -(TTDS)₂-(gE)₂-Palm, -(TTDS)₂-(gE)₃-Stea, -(TTDS)₃-(gE)₃-Stea, -(PEG₂DGA)₃-
5 (gE)₃-Stea, -(PEG₂)₃-(gE)₃-Palm, -(PEG₂)₄-(gE)₃-Stea, -(PEG₂)₅-(gE)₃-Palm, -(TTDS)₃-
(gE)₄-Stea, -(TTDS)₂-(gE)₄-Palm, -(TTDS)₂-(gE)₄-Stea, -(TTDS)₄-(gE)₃-Stea, -(TTDS)₃-
(gE)₄-Palm, -(TTDS)₄-(gE)₃-Palm, -(TTDS)₃-(gE)₃-Myr and -(TTDS)₃-(gE)₄-Myr.

In a particular embodiment of the invention, a peptide of the invention has an
10 amino acid sequence selected from the group consisting of SEQ ID NO: 3, 6, 7, 9, 10, 11,
12, 13, 20, 21, 22, 26, 28 and 30.

In a particular embodiment of the invention, a peptide of the invention has an
amino acid sequence selected from the group consisting of SEQ ID NO: 3, 6, 7, 9-12, 20-
22, 26, 28, 30-34, 45, 47-49, 51, 54-62, 64, 67-69, 71-93, 96 and 97. As indicated here-
15 above and illustrated in the enclosed examples, these peptides are particularly
advantageous in that they all have an EC₅₀ lower or equal to 1 nM.

In particular, a peptide of the invention has an amino acid sequence selected
from the group consisting of SEQ ID NO: 3, 6, 7, 13, 20, 26 and 30.

20 In particular, a peptide of the invention has an amino acid sequence selected
from the group consisting of SEQ ID NO: 3, 6, 7, 20, 26, 30-34, 45, 48, 49, 51, 54-61, 67,
71, 73, 75-79, 81, 83-92 and 97. As illustrated in the enclosed examples, the peptides
according to this embodiment are particularly advantageous in that they all have an EC₅₀
lower or equal to 0.5 nM.

25 In a particular embodiment, a peptide of the invention has an amino acid
sequence selected from the group consisting of the amino acid sequences of reference SEQ
ID NO: 3, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 20, and particularly has the
amino acid sequence of reference SEQ ID NO: 3.

30 A peptide of the invention may be produced by any technique known *per se* in
the art, such as, without limitation, any chemical, biological, genetic or enzymatic
technique, either alone or in combination. Knowing the amino acid sequence of the desired

sequence, one skilled in the art can readily produce said polypeptides, by standard techniques for production of polypeptides, even if non-natural amino acids are used or according to the methods described herein.

For instance, the peptides of the invention can be synthesized using well-known solid phase method, in particular using a commercially available peptide synthesis apparatus (such as that made by Applied Biosystems, Foster City, California, Gyros Protein technologies, Tucson, Arizona or CEM corporation, Matthews, North Carolina) and following the manufacturer's instructions.

Examples of appropriate methods are illustrated in the enclosed examples.

A peptide of the invention can be labelled with at least one detectable molecule or substance, in particular selected from the group consisting of enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials and radioactive materials.

However, it is important that said label does not alter or prevent said peptide from having its biological activity of interest as defined previously, i.e. does not prevent or alter the peptide ability to bind and activate the RXFP1 receptor.

Preferred detectable molecules or substances for the nanomaterial support are those which can be detected externally in a non-invasive manner following *in vivo* administration.

Detectable molecules or substances are well known to the man skilled in the art.

Such labelled peptide of the invention can be used in a diagnosis and/or imaging method.

The inventors have moreover observed that the half-life, and in particular the *in-vivo* half-life of the peptides of the invention is significantly superior to the one of Relaxin.

Indeed, Relaxin is rapidly cleared by the kidney and cannot be used in chronic setting. The recombinant hormone has a very short half-life *in vivo* (as illustrated in the monkey and human in B.L. Ferraiolo *et al.* Pharm.Res. (1991), 8, 1032 and in S.A. Chen *et al.* Pharm. Res. (1993), 10, 834) and requires intravenous delivery. The half-life of Relaxin

is indeed so short that continuous infusion might be required for several hours in an hospital setting for its administration to an individual in need thereof, in particular an individual suffering from an acute disease or disorder, such as for example an acute heart failure. Replacement of Relaxin in this treatment by Relaxin-peptides having an improved
5 *in vivo* half-life advantageously allows the replacement of this constraining treatment by a simpler one, such as a single daily administration by, for example, the intravenous or subcutaneous route.

Accordingly, the Relaxin peptides of the invention, that possess the ability of Relaxin to activate RXFP1, and more particularly peptides that are long lasting agonists of
10 RXFP1, have the potential for wider therapeutic applications including acute or chronic heart failure.

Compositions and medicaments

The present application also relates to a medicament or a pharmaceutical
15 composition comprising at least one peptide of the invention as described above, or one of its pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable carrier.

At least one peptide of the invention is present in a medicament or pharmaceutical composition of the invention as active principle.

20 A composition or a medicament of the invention is in a form suitable for mammalian administration.

A composition or a medicament of the invention can be administered, for example, orally, parenterally, intravenously, rectally, transdermally, topically or by inhalation. In particular, a composition according to the invention is administered by the
25 intravenous or subcutaneous route.

According to a particular embodiment, the pharmaceutically acceptable carrier of a composition of the invention is suitably selected from the group consisting of an injectable carrier liquid such as sterile water for injection; and an aqueous solution such as saline.

30 A composition or a medicament of the invention can comprise a content of peptides of the invention comprised between 0.01 mg/mL and 30 mg/mL, in particular between 0.3 mg/mL and 3 mg/mL.

A medicament or a pharmaceutical composition of the invention can comprise at least one peptide of the invention as sole active principle or can also comprise at least one other active principles, as long as said other active principle does not prevent the biological activity of the peptide according to the invention.

5 A pharmaceutical composition or a medicament according to the invention can further comprise at least one antioxidant, dispersant, emulsifier, antifoam, flavouring, preservative, solubilizer and/or colour, as long as this/these additional substances do not prevent the biological properties of the peptides according to the invention.

10 Sterile compositions of the invention for parenteral administration may in particular be aqueous or non-aqueous solutions, suspensions or emulsions. Solvents or vehicles that can be used include water, propylene glycol, a polyethylene glycol, plant oils, in particular olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents. These compositions may also comprise adjuvants, in particular wetting
15 agents, tonicity agents, emulsifiers, dispersants and stabilisers. The sterilisation may be performed in several ways, for example by aseptic filtration, by incorporating sterilising agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions that may be dissolved at the time of use in sterile water or any other injectable sterile medium.

20 The compositions for topical administration may be, for example, nasal drops or aerosols.

For subcutaneous, intramuscular or intravenous administration, the peptides of the invention used are converted, if desired with the substances customary for this purpose, such as solubilizers, emulsifiers or other excipients, into a solution, suspension or
25 emulsion. Examples of suitable solvents are: water, physiological saline or alcohols, e.g. ethanol, propanol, glycerol, as well as sugar solutions such as glucose or mannitol solutions, or else a mixture of the various solvents mentioned.

In a particular embodiment, a composition of the invention, a medicament of
30 the invention, or a peptide of the invention, or one of its pharmaceutically acceptable salt or solvate thereof, is administered to an individual by the parenteral route, and is in

particular transdermally, intravenously, subcutaneously or intramuscularly, in particular intravenously or subcutaneously administered.

Methods for preparing parenterally administrable compositions are apparent to those skilled in the art, and are for example described in more detail in Remington's
5 Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa..

The administration of a composition of the invention or of a peptide of the invention to an individual can be a systemic administration or an administration localized to a tissue, organ and/or site of the individual organism where the presence of, for example a fibrosis, is known, expected or needs to be determined.

10

Use of the peptides and compositions

The present invention relates to a peptide according to the invention, its pharmaceutically acceptable salt or solvate thereof, according to the invention, for its use as a medicament.

15 Moreover, the invention also relates to a pharmaceutical composition according to the invention for its use as a medicament.

Furthermore, the present invention relates to a peptide of the invention, its pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition of the invention for its use in the treatment and/or prevention of various diseases or conditions
20 implicating the RXFP1 receptor, more particularly in the treatment and/or prevention of diseases or conditions selected from:

- the group consisting of fibrosis; fibrotic diseases, in particular systemic sclerosis, scleroderma and fibromyalgia; idiopathic pulmonary fibrosis; kidney diseases involving fibrosis; pulmonary hypertension and preeclampsia;
- 25 - the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular complication of diabetes; and/or
- the group consisting of renal failures, in particular renal dysfunction in
30 cirrhosis; chronic kidney disease and acute kidney injury.

In one aspect, such peptide, pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition according to the invention, is administered once a day, in particular by the intravenous or subcutaneous route.

The dosage of the peptide, or of its pharmaceutically acceptable salt or solvate thereof, to be administered, and the frequency of administration, depend on the desired effect, the potency and duration of action of the compounds used; additionally also on the nature and severity of the disease or condition to be treated and on the sex, age, weight and individual responsiveness of the mammal to be treated. In general, the physician will determine the appropriate dosage as a function of the age and weight and all the other factors specific to the individual to be treated.

It is also described a method for the prevention and/or treatment in an individual of a disease or condition implicating the Relaxin receptor RXFP1 comprising administering to said individual at least one peptide of the invention, a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the invention comprising at least one peptide according to the invention or a therapeutically effective amount of least one peptide of the invention, a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the invention comprising at least one peptide according to the invention.

As previously indicated, said disease or condition is in particular selected from:

- the group consisting of fibrosis; fibrotic diseases, in particular systemic sclerosis, scleroderma and fibromyalgia; idiopathic pulmonary fibrosis; kidney diseases involving fibrosis; pulmonary hypertension and preeclampsia; - the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular complication of diabetes; and/or
- the group consisting of renal failures, in particular renal dysfunction in cirrhosis; chronic kidney disease and acute kidney injury.

It is further described the use of at least one peptide of the invention, a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the invention comprising at least one peptide according to the invention or a therapeutically effective amount of least one peptide of the invention, a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of the invention comprising at least one

peptide according to the invention for the manufacture of a medicament for the prevention and/or treatment in an individual of a disease or condition implicating the relaxin receptor RXFP1.

It is further described the use of at least one peptide according to the invention,
5 its pharmaceutically acceptable salt or solvate thereof, or of a pharmaceutical composition according to the invention for treating and/or preventing a disease or condition selected from:

- the group consisting of fibrosis; fibrotic diseases, in particular systemic sclerosis, scleroderma and fibromyalgia; idiopathic pulmonary fibrosis; kidney diseases
10 involving fibrosis; pulmonary hypertension and preeclampsia;
- the group consisting of heart and vascular diseases, in particular from the group consisting of acute or chronic heart failure, systolic or diastolic heart failure, coronary artery disease, atherosclerosis, microvascular angina and cardiovascular complication of diabetes; and/or
- 15 - the group consisting of renal failures, in particular renal dysfunction in cirrhosis; chronic kidney disease and acute kidney injury.

The present invention is illustrated by the following examples, given purely for illustrative purposes.

20

EXAMPLES

Example 1: synthesis of the peptides of the invention

Material used

Various rink amide resins were used for the synthesis of C-terminal amides
25 peptides of the invention:

- 4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)phenoxy resin, sold by Chem-Impex; or
- 4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)phenoxy acetamido methyl
resin, sold by Millipore Merck;

30 They were loaded in the range of 0.2 to 0.4 mmol.g.

Fmoc (fluorenylmethyloxycarbonyl) protected natural amino acids were purchased from different sources, i.e. Protein Technologies Inc., Merck Biosciences, Novabiochem, Iris Biotech, Bachem, Chem-Impex International or MATRIX Innovation.

The following standard amino acids were used throughout the syntheses:

- 5 Fmoc-L-Ala-OH, Fmoc-L-Arg(Pbf)-OH, Fmoc-L-Gln(Trt)-OH, Fmoc-L-Glu(OtBu)-OH, Fmoc-L-Glu-OtBu, Fmoc-Gly-OH, Fmoc-L-Ile-OH, Fmoc-L-Leu-OH, Fmoc-L-Lys(Boc)-OH, Fmoc-L-Met-OH, Fmoc-L-Phe-OH, Fmoc-L-Ser(tBu)-OH, Fmoc-L-Thr(tBu)-OH, Fmoc-L-Trp(Boc)-OH, Fmoc-L-Tyr(tBu)-OH and Fmoc-L-Val-OH.

- In addition, the following special amino acids were purchased from the same
 10 suppliers as above: Fmoc-L-hArg(Pbf)-OH, Fmoc-L-Cit-OH, Fmoc-L-Arg(Me,Pbf)-OH, Fmoc-L-hLys(Boc)-OH, Fmoc-L-Orn(Boc)-OH, Fmoc-L-Lys(Dde)-OH, Fmoc-L-Lys(ivDde)-OH, Fmoc-L-Lys(Mtt)-OH, Fmoc-L-Lys(aloc)-OH, Fmoc-L-Lys(Ac)-OH, Fmoc-Aib-OH, Fmoc-L- α -Me-Ser(tBu)-OH, Fmoc-L- α -Me-Lys(Boc)-OH, Fmoc-L- α -Me-Arg(Pbf)-OH, Fmoc-L- α -Me-Leu-OH, Fmoc-L-Nle-OH and Fmoc-L-1-Nal-OH, Fmoc-L-2-Nal-OH
 15 Fmoc-5-Wox-OH, Fmoc-Pfp-OH, Fmoc-L- α -Me-Trp-OH, Fmoc-L- α -Me-Phe-OH.

Ac	Acetyl
Aloc	Allyloxycarbonyl
Boc	Tert-Butyloxycarbonyl
tBu	Tert-Butyl
cAMP	Cyclic adenosine monophosphate
Dde	1-(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl
ivDde	1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl
DCM	Dichloromethane
DIC	N,N'-Diisopropylcarbodiimide
DIEA, DIPEA	N,N-Diisopropyl ethylamine
DMF	N,N-Dimethylformamide
DODT	2,2'-(Ethylenedioxy)diethanethiol
EDT	1,2-ethanedithiol
Fmoc	Fluorenylmethyloxycarbonyl
TFA	Trifluoroacetic acid
TIS, TIPS	Tri-isopropyl Silane
HATU	(2-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate)

HCTU	O-(1H-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	High Performance Liquid Chromatography
HTRF	HTRF Homogenous Time Resolved Fluorescence
LC/MS	Liquid Chromatography/Mass Spectrometry
Laur	Lauroyl
Mmt	Monomethoxy-trityl
Mtt	4-Methyl-trityl
Myr	Myristoyl
NMP	1-methylpyrrolidin-2-one
Oxyma	Ethyl 2-cyano-2-(hydroximino)acetate (oxyma pure™)
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
RP-HPLC	Reversed-phase high performance liquid chromatography
RT	Retention Time
TFA	Trifluoroacetic acid
Trt	Trityl, Triphenylmethyl
UV	Ultraviolet
UPLC	Ultra high Performance Chromatography

For synthesizing the C-terminally lipidated peptides of the invention, orthogonally protected lysine was used as indicated here-after.

5 1. A. General method used for synthesizing the peptides of the invention

Peptides according to the invention of sequence SEQ ID NO: 1-97 have been synthesized on the basis of the method represented in Figures 1 and 2.

0.2 mmol of Rink amide AM resin were placed in a CEM Liberty blue microwave peptide synthesizer to assemble the full peptide sequence. (see Figure 1).

10 The entire synthesis was run in DMF as solvent. The peptide was synthesized using the standard heating protocol for 0.1 to 0.2 mmol scale:

Standard heating protocol : irradiation at 170 watts, 75°C, 15 sec. then irradiation at 30 watts, 90°C, 120 sec.

Deprotection was performed with 20% v/v piperidine in DMF , followed by 3
15 DMF washing steps.

Heating protocol for deprotection : irradiation at 170 watts, 75°C, 15 sec. then irradiation at 30 watts, 90°C, 50 sec.

Amino acid couplings were performed using 5 eq. of Fmoc-AA as 0.2 M solutions in DMF using 5 eq. N,N'-Diisopropylcarbodiimide (DIC) 0.5M and 5 eq. Oxyma (ethyl 2-cyano-2-(hydroximino)acetate (oxyma pureTM)) 1M as coupling reagents.

For better final yield, each amino-acid required double couplings at 90°C for 120 seconds. For 2-aminoisobutyric acid at positions X₂₁ and X₂₂ and serine at position X₂₉ of the formula (I) according to the invention, a triple coupling at 90°C for 2 minutes was used.

10 In the case of expensive amino acid derivatives, e.g. Fmoc- α -Methyl Lysine(Boc)-OH, it may be advantageous to perform a manual coupling using 3 eq. of amino acid and 3 eq. of coupling agent such as HATU or HCTU at room temperature for 1 to 18 h or using DIC and Oxyma PureTM with microwave heating for 120 sec.

At position X₂₅, a derivative of Fmoc-Lysine-OH bearing on the side chain nitrogen an orthogonal protecting group was used. Selective deprotection allowed
15 modification of this amino acid side chain.

At the end of the synthesis, Fmoc deprotection was performed manually with 20% v/v piperidine in DMF two times 30 minutes at room temperature.

Acetylation was performed at N-terminus by treatment with 5-10 eq. of acetic anhydride and 5-10 eq. DIEA in DMF for 15 min. Then the resin containing the fully
20 protected peptide was washed with DCM/DMF/DCM, 3 times each and dried under vacuum.

Then N ϵ -protecting group of lysine at position X₂₅ (Dde, ivDde, Alloc, or Mtt) was removed using diluted hydrazine in DMF (Dde, ivDde), phenylsilane or dimethyl
25 amino borane in the presence of palladium(0) catalyst in DCM (alloc) or 1% TFA in DCM (Mtt).

Then the Z groups was attached to the side chain nitrogen of the X₂₅ lysine on solid support according to the following steps:

When the lysine in position X₂₅ was protected on its side chain by Dde or
30 iv-Dde, resin-peptide was transferred into a 50 ml polypropylene syringe. 80 ml of a solution of hydrazine 5% in DMF was percolated through the resin followed by DMF wash (3 times). The reaction was monitored by Kaiser Test.

When the lysine in position X₂₅ was protected on its side chain by the allyl-oxy-carbonyl group (aloc), resin-peptide was transferred into a 50 ml polypropylene syringe and swelled in dichloromethane and treated with 20 eq. phenylsilane (PhSiH₃) (or borane dimethylamine complex ((CH₃)₂NH.BH₃) and piperidine) and 10 % (mol/mol) tetrakis-(triphenylphosphine)palladium (Pd(PPh₃)₄) for 2 h under argon. This treatment was repeated until no starting aloc protected peptide could be detected by UPLC/MS analysis after cleavage of an aliquot part of the resin.

When the reaction was complete, the resin was washed with dichloromethane, 1% DIEA in DMF, 5% diethyl-dithio-carbamate in DMF, DMF, 10% DIEA in DMF, DMF and dichloromethane (3 times each).

When the lysine in position X₂₅ was protected on its side chain by the methyl-trityl group (Mtt), resin-peptide was transferred into a 50 ml polypropylene syringe and swelled in dichloromethane and treated with 10 mL DCM/TIS/TFA (88/5/2) mixture. After 1 h shaking, the solvent was drained, resin washed with DCM, shaken with 10 ml DCM/DIEA (90/10) mixture and washed several times with DCM.

The PEG_{xx} group(s) of the Z group was introduced, if applicable for a given peptide of the invention, by single acylation with 3 eq. of Fmoc-PEG_{xx}-OH for 18 h with 3 eq. of DIC and 3 eq of HOAt monitoring the reactions by ninhydrin (Kaiser) Test. Then the resin was treated with 20% v/v piperidine in DMF to remove Fmoc protecting group (2 x 30 min) and washed 3 times with DMF. The Fmoc-PEG_{xx}-OH coupling, Fmoc removal and washing steps were repeated x times (x = 0 – 5).

Then Fmoc-Glu-OtBu ((4S)-5-tert-butoxy-4-(9H-fluoren-9-yl methoxy carbonyl amino)-5-oxo-pentanoic acid), if gE present in the Z group of the peptide of the invention, was introduced by performing single coupling with 3 eq. of amino acid for 18 h with 3 eq. of DIC and 3 eq. of HOAt monitoring the reactions by Kaiser Test.

Then resin was treated with 20% v/v piperidine in DMF as to remove Fmoc protecting group (2 x 30 min) and washed 3 times with DMF. The Fmoc removal and Fmoc-Glu-OtBu coupling steps were repeated y times (y = 1 – 5).

Then, the side chain was lipidated using 3 eq. of Ck lauric acid (C₁₂), myristic acid (C₁₄), pentadecanoic acid (C₁₅), palmitic acid (C₁₆), heptadecanoic acid (C₁₇), stearic acid (C₁₈), eicosanoic acid (C₂₀) or docosanoic acid (C₂₂) using 3 eq. DIC and 3 eq. HOAt

in NMP, using the corresponding acyl chlorides and DIEA as a base in dichloromethane or using the corresponding N-succinimidyl esters and DIEA as base in DMF.

The reaction was monitored by Kaiser Test and left overnight.

Then the resin containing the fully protected peptide was washed with
5 DCM/DMF/DCM 3 times each and dried under vacuum.

1.B. Peptide-resin cleavage

Upon completion of solid phase synthesis, the peptide was cleaved from the solid support by treatment with cleavage reagent B: TFA/phenol/H₂O/TIPS
10 (87.5%/5%/5%/2.5%/ 25 ml) for 3 h. (TIPS stands for tri-isopropylsilane)

In certain instances, addition of a dithiol such as 1,2-ethane dithiol or DODT (2,2'-(ethylenedioxy)diethanethiol) may be advantageous (e.g. cleavage reagent K). The TFA solution containing the peptide was filtered and concentrated under reduced pressure at T < 30°C.

15 The desired product was precipitated with ice-cold MTBE (methyl tert-butyl ether) or diethyl ether and centrifuged at 3000 rpm for 30 min. The centrifuged pellet was then washed with ice-cold diethyl ether and centrifuged. This process was repeated three times.

In some instances it may be necessary to process the crude peptide to remove
20 undesired by-products such as TFA esters, CO₂ adduct on indole nitrogen of tryptophan (carbamic acid) and 2-t-butyl-sulfanylethyl adduct on Methionine residues.

To remove CO₂ adduct on indole nitrogen of tryptophan, the crude peptide was taken up in water containing 10-20% CH₃CN, 5mg/ml and lyophilized.

To remove 2-t-butyl-sulfanylethyl adduct on Met, the crude peptide was
25 dissolved (2mg/ml) in a solution of H₂O/CH₃CN (50:50 v/v) containing 0.1% formic acid.

The mixture was gently shaken at 37°C overnight.

To remove TFA esters, the crude peptide was dissolved (2mg/ml) in a solution of H₂O/CH₃CN (50:50 v/v) containing 0.1% formic acid. The mixture was gently shaken at 37°C for 1-4h.

30 In both cases, the crude peptide solution thus obtained was partially concentrated under reduced pressure and at T<30°C and lyophilized.

1.C. Purification step

Following any of the above method indicated for synthesizing a peptide of the invention, said peptide was purified before being used.

80 mg of peptide were dissolved in 1.5 mL DMSO and purified by Reverse
5 Phase High Pressure Liquid Chromatography (RP-HPLC). The RP-HPLC was described here-under.

A GX271 Liquid Handler, 333/334 pumps, and UV/VIS 151 Gilson system was used.

Two different systems were used in order to purify said peptides:

10

System A

- Column Waters Delta-Pack C4 15 μ m 300Å. 250x20 mm;
- Solution A: 0.1% trifluoroacetic acid (TFA) in H₂O;
- Solution B: 0.1% TFA in Acetonitrile;
- 15 - Gradient: 15% B for 5 min; 15% B to 50% B in 20 min;
- Flow rate: 80ml/min.

System B

- 20 - Column Waters CSH C18 5 μ m 250x50 mm, or Waters Sunfire C18 10 μ M 250x50 mm;
- Solution A = 0.1 % TFA in water;
- Solution B = 0.1% TFA in acetonitrile;
- Gradient: from 1% B to 18% B in 5min; from 18% B to 28% B in 10 min; 28% B for 15 min; from 28% B to 48% B in 10 min; then column wash from 48% B to 90% B in 10 min;
- 25 - Flow rate: 150 ml/min.

The peptide of interest was eluted in the 35-40 min time window.

The gradient was slightly adjusted according to the polarity of each peptide as characterized by its retention time on an analytical UHPLC System.

30 The fractions containing the pure peptide were then partially concentrated under reduced pressure at T<35°C and lyophilized until constant weight.

For certain uses (eg *in-vivo* testing), it was advantageous to exchange the TFA salt to the acetate salt. Three corresponding methods were used and are described in the following part 1.D.

5 1.D. Acetate Exchange

(i) Acetate Exchange with TOYOPEARL® DEAE 650 C (Tosoh Corporation)

 The ion exchange was performed using a TOYOPEARL® DEAE 650 C grade resin (a weak anion exchange resin).

10 120 ml of resin was washed sequentially with 15 volumes of NaOH 1M, 5 volumes of H₂O, 5 volumes of acetic acid 1.6 M, 5 volumes of acetic acid 0.16 M and finally 5 volumes of H₂O.

 41.8 mg of peptide was then dissolved in 4 ml of distilled water, downloaded to the resin and gently mixed for 2 h.

15 Finally the peptide was collected by elution and washed with water and lyophilized.

 Peptide Recovery: 35 mg (as acetate salt by F19 NMR (400 MHz) ns 1028).

20 **(ii) Acetate Exchange with Sepharose HiTrap Q HP column (Strong anionic exchange comun)**

 In this second method, the ion exchange was performed using a HiTrap Q HP.

 The column (5ml bed volume) was connected to a peristaltic pump set at 48 (4.5 ml/min) and before loading the peptide it was washed with 50ml (10 column volumes) of H₂O, 100 ml (20 column volumes) of a 1 M solution of sodium acetate, 150 ml (30 column volumes) of H₂O and with 50 ml (10 column volumes) of 0.16 M solution of acetic acid.

 The pure peptide was dissolved in a 0.16 M acetic acid solution at 2mg/ml, slowly loaded on the column and eluted at 4.5ml/min.

 The collected solution was freeze-dried.

30 The effectiveness of the ion exchange was attested by F19 NMR (400 MHz) ns 1028.

(iii) Acetate Exchange with BIO RAD AG1X4® anion exchange resin

In a 125 ml reactor equipped with sintered glass at the bottom was charged with 6.2 g BIO RAD AG1X4® anion exchange resin, 100–200 dry mesh size (OH- form).

The resin was shaken with 3 x 100 ml 1.6 M aqueous acetic acid (10% v/v) and
5 with 3 x 50 ml 0.16 M aqueous acetic acid (1% v/v) on a stirring plate for 20 min each.

The purified peptide as TFA salt (100 mg) was dissolved in 50 ml distilled water and poured on the exchange resin and shaken on a stirring plate for 120 min.

The aqueous solution was drained in a 100 ml round bottom flask and the resin
10 was washed with 2x15 ml 0.16 M aqueous acetic acid (1% v/v).

The combined solutions containing the peptide as acetate salt were lyophilized until constant weight. Yield = 80 mg of peptide as acetate salt.

The effectiveness of the ion exchange was attested by F19 NMR (400 MHz, ns 1028) and/or ionic chromatography.

15

Example 2: Illustrative synthesis of specific peptides of the invention

2.A Loading of Fmoc-Lys(Ac)-OH on Rink amide resin

In a 100 ml reactor equipped with a sintered glass at the bottom, 6 g of Novabiochem or ChemImpex Rink amide AM resin (Low Loading 0.47 mmol/g) was
20 swelled in 40 ml of DMF. The solvent was drained and 30 ml of 20% piperidine in DMF solution were added. After 15 min shaking, the solvent was drained. This was repeated twice to ensure complete Fmoc protecting group removal. The resin was washed with 5 x 30 ml DMF.

In a separate flask a solution containing Fmoc-Lys(Ac)-OH (3.5 g, 8 mmol, 3
25 eq.) HOBT.H₂O (1.3 g 8.5 mmol) in 30 ml DMF was prepared. Diisopropylcarbodiimide (DIC) (1 g, 8.5 mmol) was added to this solution and after 5 min the resulting mixture was added to the resin. The suspension was shaken on a stirring plate for 4 h or until completion of the reaction as judged by Kaiser Test (Ninhydrin test) on an aliquot part of the resin.

30 The solvent was then drained and the resin washed 3 times with 30 ml DMF. Fmoc-Lys(Ac)-NH₂ loaded resin was used immediately for subsequent steps or stored wet at 4°C until needed.

2.B. Synthesis of peptide having the SEQ ID NO: 3

The following synthesis was performed using 5 times an amount of resin obtained at step 2.A. corresponding to 0.2 mmol of Fmoc-Lys(Ac)-NH₂ each. The syntheses were performed separately on each individual batches using a CEM Liberty Blue microwave peptide synthesizer to assemble the second and third residue of the peptide sequence (starting from the C-terminus).

Peptide synthesis was performed by using DIC 0.5M /Oxyma 1M in DMF.

All amino acids were introduced with double couplings using standard heating protocol.

10 The resin was removed from the synthesizer and Fmoc- α -methyl-lysine(Boc)-OH (3 eq.) was coupled manually using 3 eq. OxymaTM and 3 eq. DIC with microwave heating (75°C 15 sec. and 90°C 110 sec). The completion of the reaction was controlled by Kaiser test. If positive, DIC 3 eq. was added followed by microwave heating as above.

15 When coupling of Fmoc- α -methyl-lysine(Boc)-OH was complete the rest of the peptide sequence was assembled using a CEM Liberty Blue microwave peptide synthesizer.

20 All amino acids were introduced with double couplings at 90°C as above, with the exception of amino-isobutyric acid at position 21 and serine at position 29 for which a triple coupling at 90° for 2 minutes was performed. Fmoc-Lys(Dde)-OH was used at position 25.

At the end of the 5 syntheses, the 5 batches of resin were combined and transferred into a 50 mL polypropylene syringe and the peptide was acetylated at N-terminus with acetic anhydride (944 μ L, 10 mmol) in DMF (30 mL) for 20 minutes, repeating the cycle twice.

25 Then, Dde protecting group on Lysine 25 side chain was removed by percolating 50 mL of a solution of hydrazine 5% w/v in DMF, followed by DMF washes (5x20 ml). The reaction was monitored by Kaiser Test and cleavage of an aliquot part of resin and UPLC/MS analysis.

30 Three TTDS spacer units were introduced by single coupling by performing three times the following procedure : To the resin a solution of Fmoc-TTDS-OH (1.62 g, 3 mmol) in 30 mL of DMF were added followed by HOAt (5 ml of a 0.6 ml solution in DMF, 3 mmol) and DIC (1 ml, 6 mmol). The syringe was agitated on an orbital table for

18 h. The reaction was monitored by Kaiser Test. The resin was washed with DMF (2x30 mL). Then to the resin, 30 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (2x30 mL) and dichloromethane (3x30 mL).

The three gamma-glutamic acids spacers were introduced by performing a double coupling of each Fmoc-Glu-OtBu. Thus the following procedure was applied three times:

To the resin a solution (4S)-5-tert-butoxy-4-(9H-fluoren-9-yl methoxy carbonylamino)-5-oxo-pentanoic acid (Fmoc-Glu-OtBu) (1.275 g, 3 mmol) in 30 mL of DMF were added followed by HOAt (5 ml of a 0.6 M solution in DMF 3 mmol) and DIC (1 ml, 6 mmol). The syringe was agitated on an orbital table for 4 h. The resin was washed with DMF (2x20 mL) and the coupling was repeated a second time. The reaction was monitored by Kaiser Test. The resin was washed with DMF (2x30 mL). Then to the resin, 30 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (3x30 mL) and dichloromethane (3x30 mL).

Finally, the peptide was acylated with palmitic acid (768 mg, 3 mmol), HOAt (5 ml of a 0.6 M solution in DMF, 3 mmol) and DIC (1 ml, 6 mmol) activation in DMF (30 mL) for 2.5 h. The resin was washed with DMF (2x30 mL) and dichloromethane (3x30 mL) and dried under vacuum.

The cleavage of the peptide from the resin was performed using a solution phenol (6.25 g), water (6.25 mL) and TIPS (3 mL) in TFA (QSP 125 mL) for 2.5 hours at room temperature. The resin was filtered off, and washed with 2x 30 mL TFA. The combined filtrates were transferred to a 250 mL round bottom flask and partially concentrated under vacuum at $T < 30^{\circ}\text{C}$ and the peptide was precipitated by the addition of 100 mL ice-cold MTBE and centrifuged at 3600 rpm for 30 minutes.

The centrifuged pellet was then washed with ice-cold diethyl ether and centrifuged. This process was repeated three times. 4.3 g of crude peptide were obtained. The crude peptide was dissolved (10 mg/mL) in a solution of $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (50:50 v/v) containing 0.1% formic acid and the mixture was gently shaken at 37° for 1 h, partially concentrated and lyophilized.

Purification was performed using purification system A in 10 injection of 350 mg each and the fractions containing pure desired peptide were lyophilized. The peptide as trifluoroacetate salt was obtained as a white solid.

m = 428 mg (17.5%)

5 UPLC/MS :

RT : 4.98 min. (Analytical condition A), purity 99% (UV)

Observed mass m/z (ion type) : 1454.5 (M+3H) ; 1091.1 (M+4H) ; 873.1 (M+5H).

10 2.C. Synthesis of peptide having the SEQ ID NO: 7

2 batches of resin obtained in 2.A. corresponding to 0.2 mmol of Fmoc-Lys(Ac)-NH₂ each (0.4 mmol in total) were processed in parallel following the same procedure as for example 2.B. After coupling the third (4S)-5-tert-butoxy-4-(9H-fluoren-9-yl methoxy carbonylamino)-5-oxo-pentanoic acid (Fmoc-Glu-OtBu) the combined resin
15 batches weighing 2.6 g were transferred to a 50 mL polypropylene syringe.

Then to the resin, 30 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (3x30 mL) and dichloromethane (3x30 mL).

20 The peptide was acylated by adding a solution of stearoyl chloride (362 mg, 1.2 mmol) and DIPEA (0.255 ml, 1.5 mmol) in 20 ml of DCM for 2.5 h. The resin was washed with DMF (2x30 mL) and dichloromethane (3x30mL) and dried under vacuum.

The cleavage of the peptide from the resin was performed using a solution phenol (1.5 g), water (1.5 mL) and TIPS (0.6 mL) in TFA (QSP 30 mL) for 2.5 hours at
25 room temperature. The resin was filtered off, and washed with 2 x 10 mL TFA. The combined filtrates were transferred to a 250 mL round bottom flask and partially concentrated under vacuum at T<30°C, the peptide was precipitated by the addition of 100 mL ice-cold MTBE and centrifuged at 3600 rpm for 30 minutes.

The centrifuged pellet was then washed with ice-cold diethyl ether and
30 centrifuged. This process was repeated three times. 720 mg of crude peptide were obtained. Purification was performed using purification system B in 3 injection of 240 mg each. The

fractions containing pure desired peptide were lyophilized. The peptide as trifluoroacetate salt was obtained as a white solid.

$m = 72 \text{ mg (3.6 \%)}$

UPLC/MS :

5 RT : 5.86 min. (Analytical condition A), purity 98% (UV)
Observed mass m/z (ion type) : 1463.9 (M+3H) ; 1098.2 (M+4H) ; 878.7 (M+5H).

2.D. Synthesis of peptide having the SEQ ID NO: 6

10 A batch of resin obtained in 2.A. corresponding to 0.1 mmol of Fmoc-Lys(Ac)-NH₂ was placed in the reactor of a CEM Liberty Blue microwave peptide synthesizer. Peptide synthesis was performed by using DIC 0.5M /Oxyma 1M in DMF.

All amino acids were introduced with double couplings at 90°C as above, with the exception of amino-isobutyric acid at position 21 and serine at position 29 for which a
15 triple coupling at 90° for 2 minutes was performed. Fmoc-Lys(ivDde)-OH was used at position 25.

At the end of peptide assembly, the resin was transferred to a 20 ml polypropylene syringe and peptide was acetylated at N-terminus with of acetic anhydride (95 μL , 1 mmol) and DIPEA (174 μL , 1 mmol) in DMF (10 mL) for 20 minutes, repeating
20 the cycle twice.

Then, ivDde protecting group on lysine 25 side chain was removed by stirring with 10 mL of a solution of hydrazine 5% w/v in DMF for 20 min as many times as necessary until no starting material could be detected after cleavage of an aliquot part of resin and UPLC/MS analysis. When deprotection was judged complete, resin was washed
25 with DMF (5x10 ml).

Two TTDS spacer units were introduced by single coupling by performing twice the following procedure : To the resin a solution of Fmoc-TTDS-OH (163 mg, 0.3 mmol) HOAt (42 mg, 0.3 mmol) and DIC (77 μL , 0.5 mmol) 7 mL of DMF was added. The syringe was agitated on an orbital table for 18 h. The reaction was monitored by
30 Kaiser Test. When needed, a double coupling was performed. The resin was washed with DMF (2x10 mL). Then to the resin, 10 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was

repeated a second time and the resin was washed with DMF (2x10 mL) and dichloromethane (3x10 mL).

The three gamma-glutamic acids spacers were introduced by performing a double coupling of each Fmoc-Glu-OtBu. Thus the following procedure was applied three
5 times:

To the resin a solution (4S)-5-tert-butoxy-4-(9H-fluoren-9-yl methoxy carbonylamino)-5-oxo-pentanoic acid (Fmoc-Glu-OtBu) (127 mg, 0.3 mmol), HOAt (42 mg, 0.3 mmol) and DIC (77 μ L, 0.5 mmol) in 7 mL of DMF. The syringe was agitated on an orbital table for 18 h. The reaction was monitored by Kaiser Test. The resin was washed
10 with DMF (2x10 mL). Then to the resin, 10 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (3x10 mL) and dichloromethane (3x30 mL).

Finally, the peptide was acylated with Stearoyl chloride (62 mg, 0.2 mmol) and
15 DIPEA (54 μ L, 0.3 mmol) in 5 mL DCM for 2.5 h. The resin was washed with DMF (2x30 mL) and dichloromethane (3x30 mL) and dried under vacuum.

The cleavage of the peptide from the resin was performed using a solution phenol (0.5 g), water (0.5 mL) and TIPS (0.2 mL) in TFA (QSP 10 mL) for 2.5 hours at
20 room temperature. The resin was filtered off, and washed with 2 x 4 mL TFA. The combined filtrates were transferred to a 100 mL round bottom flask and partially concentrated under vacuum at $T < 30^{\circ}\text{C}$ and the peptide was precipitated by the addition of 50 mL ice-cold MTBE and centrifuged at 3600 rpm for 30 minutes.

The centrifuged pellet was then washed with ice-cold diethyl ether and
25 centrifuged. This process was repeated three times. 240 g of crude peptide were obtained. Purification was performed using purification system B and fractions containing pure desired peptide were lyophilized. The peptide as trifluoroacetate salt was obtained as a white solid.

m = 38 mg (8 %)

30 UPLC/MS :

RT : 5.40 min. (Analytical condition A), purity 97% (UV)

Observed mass m/z (ion type) : 1376.1 (M+3H) ; 1032.0 (M+4H) ; 826.0 (M+5H).

2.E. Synthesis of peptide having the SEQ ID NO: 20

5 This compound was obtained following the same procedure as the one used in example 2.D except that three TTDS were introduced on lysine 25 side chain.

Thus from 250 mg of resin obtained in 2.A. corresponding to 0.1 mmol of Fmoc-Lys(Ac)-NH₂ a white solid was obtained.

$m = 20$ mg (4.5%)

10 UPLC/MS :

RT : 5.44 min. (Analytical condition A), purity 99% (UV)

Observed mass m/z (ion type) : 2215.0 (M+2H) ; 1476.8 (M+3H) ; 1107.9 (M+4H) ; 886.7 (M+5H).

15 2.F. Synthesis of peptide having the SEQ ID NO: 22

This compound was obtained following the same procedure as the one used in example 2.B. except that Fmoc-Lys(Aloc)-OH was used in position 25 (X₂₅) instead of Fmoc-Lys(Dde)-OH.

20 Thus 250 mg of resin obtained in 2.A. corresponding to 0.1 mmol of Fmoc-Lys(Ac)-NH₂ was processed as in 2.B. until the N-Terminal acetylation step.

The Aloc group on Lys25 side chain was removed by adding to the resin, under argon atmosphere, a solution of 1 ml (8.33 mmol) of phenyl silane in 2 ml of degazed DCM and a solution of 10mg (25.96 μ moles) of tetrakis-(triphenylphosphine) palladium in 4 ml DCM. The resin was shaken on an orbital table for 60 min and the reaction media was
25 replaced with fresh reagents twice and shaken 60 min each time.

When the reaction was complete, the resin was washed with dichloromethane, 1% DIEA in DMF, 5% diethyl-dithio-carbamate in DMF, DMF, 10% DIEA in DMF, DMF and dichloromethane (3 times each).

30 Three PEG₂DGA spacer units were introduced by single coupling by performing three times the following procedure : To the resin a solution of Fmoc-PEG₂DGA-OH (170mg, 0.3 mmol) in 8 mL of DCM were added followed by HOAt (0.5 ml of a 0.6 ml solution in DMF, 0.3 mmol) and DIC (100 μ l, 0.642mmol). The syringe was

agitated on an orbital table for 18 h. The reaction was monitored by Kaiser Test. The resin was washed with DMF (2x10 mL). Then to the resin, 10 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (2x30 mL) and dichloromethane (3x30 mL).

The three gamma-glutamic acids spacers were introduced by performing a double coupling of each Fmoc-Glu-OtBu. Thus the following procedure was applied three times:

To the resin a solution (4S)-5-tert-butoxy-4-(9H-fluoren-9-yl methoxy carbonylamino)-5-oxo-pentanoic acid (Fmoc-Glu-OtBu) (0.13 g, 0.3 mmol) in of 8 mL of DMF were added followed by HOAt (0.5 ml of a 0.6 ml solution in DMF 0.3 mmol) and DIC (0.1 ml, 0.6 mmol). The syringe was agitated on an orbital table for 4 h. The resin was washed with DMF (2x20 mL) and the coupling was repeated a second time. The reaction was monitored by Kaiser Test. The resin was washed with DMF (2x10 mL). Then to the resin, 10 mL of 20% v/v of piperidine in DMF was added. The syringe was agitated on an orbital table for 20 min. This deprotection procedure was repeated a second time and the resin was washed with DMF (3x30 mL) and dichloromethane (3x30 mL).

Finally, the peptide was acylated with palmitic acid (80 mg, 0.3 mmol), HOAt (0.5 ml of a 0.6 M solution in DMF, 3 mmol) and DIC (0.1 ml, 6 mmol) activation in DMF (10 mL) for 2.5 h. The resin was washed with DMF (2x30 mL) and dichloromethane (3x30mL) and dried under vacuum.

The cleavage of the peptide from the resin was performed using a solution phenol (0.5 g), water (0.5 mL) and TIPS (0.25 mL) in TFA (QSP 10 mL) for 2.5 hours at room temperature. The resin was filtered off, and washed with 2x 5 mL TFA. The combined filtrates were transferred to a 250 mL round bottom flask and partially concentrated under vacuum at $T < 30^{\circ}\text{C}$ and the peptide was precipitated by the addition of 100 mL ice-cold MTBE and centrifuged at 3600 rpm for 30 minutes.

The centrifuged pellet was then washed with ice-cold diethyl ether and centrifuged. This process was repeated three times. 220 mg of crude peptide were obtained.

Purification was performed using purification system B. Fractions containing pure desired peptide were lyophilized. The peptide as trifluoroacetate salt was obtained as a white solid.

m = 37 mg (8 %)

UPLC/MS :

RT : 4.99 min. (Analytical condition A), purity 99% (UV)

Observed mass m/z (ion type) : 2205.2 (M+2H) ; 1470.5 (M+3H) ; 1103.1 (M+4H) ; 882.7 (M+5H).

5

2.G. Results

The results obtained with peptides of the invention of SEQ ID NO: 1-32, 34-37, 39, 44, 45, 47-49, 51 and 54-97 were indicated in the following Table 1.

10

SEQ ID NO	UPLC Ret. Time Min. (Conditions)	Observed mass				Mono isotopic mass
		Ion type				
		M+5H	M+4H	M+3H	M+2H	
1	3.81 (C)	881.3	1101.3	1467.7		4397.54
2	3.85 (C)	861.9	1077.2	1436.3		4301.47
3	4.98 (A)	873.1	1091.1	1454.5	2181.5	4358.53
4	5.02(A)	820.5	1025.3	1366.7	2049.4	4095.36
5	4.82 (A)	815.7	1019.3	1358.8	2037.3	4071.28
6	5.40 (A)	826.0	1032.0	1376.1	2063.8	4123.39
7	5.86 (A)	878.7	1098.2	1463.9		4386.56
8	4.83 (A)	807.8	1009.5	1345.7	2018.3	4032.27
9	4.97 (A)	786.9	983.3	1310.7	1965.7	3927.30
10	4.90 (A)	838.5	1047.8	1396.8	2094.8	4185.39
11	5.03 (A)	880.9	1100.9	1467.5	2200.9	4397.54
12	4.98 (A)	870.5	1087.9	1450.2	2174.9	4345.5
13	4.99 (A)	870.3	1087.6	1449.8	2174.7	4344.5
14	4.96 (A)	870.3	1087.6	1449.8		4344.5
15	5.00 (A)	869.9	1087.1	1449.2	2173.3	4342.5
16	4.92 (A)	809.9	1012.1	1349.1	2023.2	4042.33
17	5.00 (A)	817.6	1021.8	1362.1	2042.6	4081.34
18	4.73 (A)	829.3	1036.1	1381.2		4138.40
19	4.88 (A)	786.6	983.0	1310.0	1965.3	3926.21
20	5.44 (A)	886.7	1107.9	1476.8	2215.0	4425.57
21	5.27 (A)	821.4	1026.3	1369.1	2051.6	4099.31
22	4.99 (A)	882.7	1103.1	1470.5	2205.2	4406.5
23	5.24 (A)	870.1	1087.4	1449.5	2173.8	4343.52
24	5.25 (A)	876.9	1095.1	1460.8	2190.8	4377.50
25	5.17 (A)	873.1	1091.4	1454.5	2181.3	4358.49
26	5.24 (A)	813.4	1016.5	1355.0	2032.1	4060.3

27	4.97 (A)	878.7	1098.1	1463.8	2194.9	4386.54
28	4.97 (A)	875.9	1094.6	1459.1	2188.2	4372.55
29	5.00 (A)	875.9	1094.6	1459.2	2188.3	4372.54
30	5.44 (A)	886.5	1107.9	1476.9		4425.57
31	5.07 (A)	886.5	1107.9	1476.8		4425.5
32	5.42 (A)	888.3	1110.3	1479.8	2219.5	4434.5
34	5.45 (A)	818.2	1022.5	1363.4		4084.4
35	5.03 (A)	877.8	1096.8	1462.4	2192.9	4381.5
36	4.96 (A)	870.1	1087.6	1450.1	2174.3	4344.5
37	5.1 (A)	883.3	1103.6	1471.5	2207.4	4410.5
39	5.20 (A)	890.1	112.8	1483.1	2224.6	4444.52
44	4.80 (A)	877.8	1097.1	1462.8		4383.5
45	4.81 (A)	836.6	1045.7	1393.7	2090.6	4177.3
47	4.85 (A)	864.6	1080.3	1440.4	2160.5	4316.5
48	9.23 (D)	864.6	1080.6	1440.8	2160.2	4316.5
49	9.00 (D)	864.6	1080.6	1440.4	2160.3	4316.5
51	5.38 (A)	912.3	1140.1	1519.8	2279.2	4554.6
54	5.41 (A)	851.8	1064.5	1419.1	2128.2	4252.4
55	5.03 (A)	892.1	1114.8	1486.1		4453.6
56	5.42 (A)	876.1	1094.8	1459.5		4373.5
57	4.90 (A)	880.9	1100.9	1467.1	2201.2	4316.5
58	5.48 (A)	946.8	1183.3	1577.5		4727.7
59	5.44 (A)	972.7	1215.6	1620.5		4856.8
60	5.34 (A)	818.2	1022.5	1363.0	2044.0	4084.4
61	5.41 (A)	878.4	1098.1	1463.7	2195.1	4386.6
62	5.34 (A)	906.6	1133.1	1510.5		4526.6
63	4.98 (A)	886.3	1107.6	1476.5		4424.6
64	4.8 (A)	891.9	1114.6	1485.9		4452.6
65	4.97 (A)	892.2	1115.1	1486.4	2228.7	4454.6
66	4.97 (A)	897.5	1121.7	1495.2		4480.6
67	4.98 (A)	886.3	1107.8	1476.8		4425.5
68	5.05 (A)	880.9	1100.9	1467.5		4397.5
69	5.06 (A)	886.5	1107.8	1476.8		4425.5
70	9.29 (D)	886.5	1107.8	1476.8		4425.6
71	4.84 (A)	860.9	1076.3	1434.4		4298.5
72	7.86 (D)	875.4	1094.1	1458.5	2187.4	4370.5
73	4.87 (A)	866.5	1082.8	1443.4		4325.5
74	5.12 (A)	946.9	1183.4	1577.5		4727.8
75	5.28 (A)	952.4	1190.6	1590.9		4755.7
76	5.28 (A)	884.2	1105.1	1473.1		4414.5
77	5.20 (A)	944.5	1180.7	1573.8		4716.7
78	4.09 (A)	933.5	1166.7	1554.9		4660.7
79	4.66 (A)	878.5	1098.1	1463.5		4385.6

80	4.90 (A)	898.8	1123.5	1497.7		4487.5
81	4.84 (A)	884.5	1105.3	1473.4	2210.1	4415.6
82	4.90 (A)	883.7	1104.4	1472.1		4411.6
83	4.71 (A)	886.5	1107.6	1476.7	2214.4	4424.6
84	5.12 (A)	878.7	1097.9	1463.8	2195.1	4386.6
85	4.98 (A)	894.7	1118.6	1490.8		4467.6
86	5.14 (A)	873.1	1091.1	1454.4	2181.6	4358.5
87	4.81 (A)	875.7	1094.6	1459.1	2187.7	4372.5
88	4.82 (A)	873.1	1090.9	1454.2	2181.3	4358.5
89	4.28 (A)	732.4	878.7	1098.2	1436.9	4386.5
90	4.82(A)	870.1	1087.3	1449.5	2174.2	4344.5
91	4.89 (A)	887.7	1109.6	1479.2	2218.9	4432.5
92	4.20 (A)	895.7	1119.4	1492.2		4471.5
93	4.83 (A)	878.5	1097.7	1463.9	2194.9	4386.5
94	4.84 (A)	878.2	1097.5	1463.3	2194.5	4384.6
95	4.40 (A)	867.8	1084.2	1445.3	2167.9	4330.5
96	4.24 (A)	859.0	1073.5	1431.3	2146.5	4288.5
97	3.77 (A)	884.9	1105.9	1474.2		4417.5

Table 1

Condition A is the following:

- Column: Acquity Peptide CSH, C18, 130Å, 2.1x100mm, 1.7µm;
- 5 - Column Temperature: 50°C; Flow = 0.6ml/min;
- Solvent A: 0.1% TFA in H₂O;
- Solvent B: 0.1% TFA in CH₃CN;
- Gradient: from 0 to 1min B=2%, from 1 to 7min B=2% to 70%, from 7 to 8min B =70% to 100% ;
- 10 - UV detector: wavelength: 220 nm; MS acquisition: ESI+ 200 to 3000 uma.

Conditons B is the following:

- Column : Acquity BEH C18, 130Å, 2.1x50mm, 1.7µm
- Column temperature 60°C ; Flow 0.6 ml/mn
- 15 - Solvent A : 0.05% TFA in H₂O
- Solvent B : 0.05 % TFA in CH₃CN
- Gradient : from 0 to 1min B=2%, from 1 to 16min B=2% to 100%, from 16 to 17min B= 100%
- UV detector : wavelength : 220 nm ; MS acquisition : ESI+ 200 to 3000 uma

Condition C is the following:

- Column: ACQUITY BEH C4, 130Å, 2.1x50mm, 1.7 µm;
 - Column temperature 45°C; Flow rate: 0.4ml/min;
 - Solvent A: 0.1% TFA in H₂O;
 - 5 - Solvent B : 0.05 % TFA in CH₃CN
- Gradient : from 0 to 1min B=30%, from 1 to 5min B=30% to 50%, from 5 to 6min B = 80%
- UV detector : wavelength : 220 nm ; MS acquisition : ESI+ 200 to 3000 uma

10 Condition D is the following:

- Column: Acquity Peptide CSH, C18, 130Å, 2.1x150mm, 1.7um;
- Column Temperature: 60°C; Flow = 0.4ml/min;
- Solvent A: 0.1% TFA in H₂O;
- Solvent B: 0.1% TFA in CH₃CN;
- 15 - Gradient: from 0 to 1min B=2%, from 1 to 14min B=2% to 70%, from 14 to 16min B =70% to 100% ;
- UV detector: wavelength: 220 nm; MS acquisition: ESI+ 200 to 3000 uma.

The following peptides according to invention can be prepared respectively as described
20 above: SEQ ID NO 33, 38, 40, 41, 43, 46, 50, 52 and 53.

Example 3: *In vitro* analysis of peptides of the invention on RXFP1 receptors (OVCAR5 cAMP assay)

A. Method

25 OVCAR5 cells expressing endogenous RXFP1 were used to test RXP1 agonist properties of peptides of the invention, and in particular of the peptides of sequence SEQ ID NO: 1-97.

Since RXFP1 is a Gs coupled GPCR, cAMP was used as readout of RXFP1 activation.

30 Isobutyl Methyl Xanthine (IBMX) was used to inhibit phosphodiesterase activity facilitating cAMP measurements. HTRF (Homogenous Time Resolved Fluorescence) technology was used to detect cAMP due to its great sensitivity.

In summary, OVCAR5 were grown in regular medium (RPMI) containing 10% fetal calf serum (FCS) and 1% antibiotics (penicillin/streptomycin).

Before the experiments, cells were detached with accutase and incubated for 40 minutes at 37°C with 1 mM (3-isobutyl-1-methylxanthine) IBMX.

5 Cells were then distributed in 384 black well plates containing increasing concentrations of the different peptides in a fix volume of medium (without FCS).

After an incubation of 30 min at 37°C in an humid incubator in 5% CO₂, the reaction was stopped by adding a fixed volume of a solution containing a lysis buffer and cAMP-D2 (cAMP labeled with the dye d2) and the anti cAMP antibody linked to
10 Europium and used for cAMP detection.

Readout of the experiment were performed on a fluorimeter allowing HTRF measurement. Activation curves were generated by plotting the intracellular value of cAMP versus log10 of the compound concentration.

The 50% activation concentration (EC₅₀) was calculated by nonlinear
15 regression using the sigmoidal dose-response (variable slope) equation with Prism 5 software.

Emax % was determined as the maximal intracellular value of cAMP for test compound (upper limit of cAMP vs concentration curve) divided by the maximal intracellular value of cAMP for H2-relaxin determined in the same test occasion multiplied
20 by 100.

$$\text{Emax\%} = 100 \times [\text{cAMP}_{\text{test cpd}}] / [\text{cAMP}_{\text{H2-RLX}}]$$

B. Results

The results obtained with peptides of the invention are represented in the following Table 2.

25

SEQ ID NO	OVCAR 5 cells (cAMP)	
	EC50 (nM)	EMax
1	1.50	99%
2	2.40	99%
3	0.34	97%
4	1.50	89%
5	9.10	85%
6	0.27	95%

7	0.07	95%
8	1.86	92%
9	0.70	93%
10	0.79	95%
11	0.83	93%
12	0.93	90%
13	2.12	91%
14	3.20	90%
15	2.10	85%
16	6.80	88%
17	4.60	91%
18	1.54	92%
19	11.5	94%
20	0.15	96%
21	0.65	93%
22	1.00	92%
23	11.1	92%
24	36.4	100%
25	28.7	100%
26	0.43	96%
27	1.80	98%
28	0.62	88%
29	1.60	88%
30	0.21	89%
31	0.19	94%
32	0.10	97%
34	0.14	90%
35	2.33	91%
36	3.60	93%
37	5.60	98%
39	8.70	93%
42	1.50	84%
44	2.2	97%
45	0.45	96%
47	0.64	95%
48	0.45	96%
49	0.19	97%
51	0.10	98%
54	0.16	96%

55	0.18	93%
56	0.15	91%
57	0.44	98%
58	0.08	98%
59	0.09	99%
60	0.15	95%
61	0.10	97%
62	0.60	98%
63	1.45	97%
64	0.52	95%
65	1.19	95%
66	6.31	93%
67	0.48	95%
68	0.88	98%
69	0.78	97%
70	1.34	94%
71	0.36	95%
72	0.56	91%
73	0.20	95%
74	0.54	94%
75	0.19	97%
76	0.18	96%
77	0.11	98%
78	0.18	99%
79	0.45	95%
80	0.63	93%
81	0.16	98%
82	0.54	95%
83	0.25	94%
84	0.10	95%
85	0.30	92%
86	0.30	95%
87	0.10	96%
88	0.17	96%
89	0.10	97%
90	0.14	97%
91	0.09	97%
92	0.10	99%
93	0.77	86%

94	1.74	88%
95	1.80	91%
96	0.88	92%
97	0.29	98%

Table 2

It appears that peptides according to the invention possess very interesting RXP1 agonist properties, and are very effective to bind and activate RXP1.

5 They are moreover all significantly and unexpectedly superior to the peptides from the prior art when it comes to activate the RXP1 receptor.

The same experiment has been performed with peptides from the prior art (WO2015/157829) known under the names B7-33 C11.23S, AcB7-33 C11.23S and
10 KKKK(AcB7-29 C11.23S).

The following EC₅₀ results have been obtained for these three peptides.

Name	cAMP assay in OVCAR 5 cells	
	EC50 (nM)	E _{max}
B7-33 C11.23S	1641	90%
AcB7-33 C11.23S	929	70%
KKKK(AcB7-29 C11.23S)	206	84%

Table 3

As demonstrated above, the peptides according to the invention possess very
15 interesting RXP1 agonist properties, and are very effective to activate RXP1. They are moreover all significantly and unexpectedly superior to the peptides from the prior art.

Example 4: Solubility testing of peptides of the invention in buffer

A. Method

Prior to the testing of solubility of a peptide batch, its purity (HPLC-UV) was
20 determined.

Study media:

Phosphate buffer 50 mM pH 6.5: 15.9 ml Na₂HPO₄ 0.1 M (Carlo Erba 480087) +
34.1 ml NaH₂PO₄ 0.1 M (Carlo Erba 480141) + H₂O MilliQ QSP 100 ml

Phosphate buffer 50 mM pH 7.4: 40.5 ml Na_2HPO_4 0.1 M (Carlo Erba 480087) + 9.5 ml NaH_2PO_4 0.1 M (Carlo Erba 480141) + H_2O MilliQ QSP 100 ml

- Acetate Buffer 50 mM pH4,5 : 0.75g $\text{C}_2\text{H}_3\text{CO}_2\text{Na}\cdot 3\text{H}_2\text{O}$ (Sigma S7545) + 0.35ml $\text{CH}_3\text{CO}_2\text{H}$ 100% solution dissolved in Millipore water, adjusted to pH with diluted (1:1) $\text{CH}_3\text{CO}_2\text{H}$ and diluted to 250ml with Millipore water.

- In a 4 ml Ependorph vial, an accurately weighed sample of compound was diluted in study media to obtain target concentration of 2, 6 or 10 mg/ml of pure compound. The sample vials were shaken (rock 'roll shaker) for ~19h. 300 μL aliquots were filtered through a Millipore "Solvinert" plate (0,45 μm - PTFE hydrophilic). The solubility was then determined by comparison of a 0.2 pL-injection of the filtrate with the UV peak areas obtained with a stock solution of the peptide at a concentration of 1.2 mg/ml in DMSO (based on % purity), injecting various volumes ranging from 0.2 —2pL.

Analysis :

pH was measured with a micro electrode

- 15 HPLC conditions :

Waters Acquity UPLC System with DAD detector

Column : Waters Peptide Column CSH C18 (130 Å ; 1.7 μm ; 50*2.1 mm)

Column temperature : 60°C

Flow : 0.3 ml/min

- 20 Full loop (about 5 μL) – overfill factor 5

Weak et Strong wash : $\text{H}_2\text{O}/\text{ACN}$ (75/25; V/V) ; Seal wash : $\text{H}_2\text{O}/\text{IsOH}$ (95/5; V/V).

Mobile phase :

Solvent A : 0.05% TFA in H_2O ; Solvent B : 0.035% TFA in CH_3CN

Gradient : from 0 to 12 min B=2% to 60%, from 12 to 14 min B= 60% to 100%. Column

- 25 washing 100% B 1 min, column equilibration 2% B 2.5 min.

UV detector : wavelenght : 220 nm.

B. Results

- 30 The solubility results obtained are represented in the following Table 4.

SEQ ID NO	Solubility Acetate buffer pH 4.5*	Solubility phosphate buffer pH 7.4*
3	11.1 mg/ml	11.5 mg/ml
4	9.63 mg/ml	7.71 mg/ml
5	6.24 mg/ml	6.41 mg/ml
7	11.45 mg/ml	11.83 mg/ml
13	ND	7.68 mg/ml
16	6.33 mg/ml	6.72 mg/ml
17	9.22 mg/ml	6.81 mg/ml
18	6.75 mg/ml	6.58 mg/ml
20	9.34 mg/ml	9.95 mg/ml
21	6.28 mg/ml	6.59 mg/ml
23	0.55 mg/ml	6.77 mg/ml
24	0.28 mg/ml	6.93 mg/ml
25	6.58 mg/ml	6.75 mg/ml
26	6.68 mg/ml	6.76 mg/ml
44	11.07 mg/ml	10.72 mg/ml
55	9.26 mg/ml	8.84 mg/ml
70	8.24 mg/ml	9.68 mg/ml
71	8.28 mg/ml	8.77 mg/ml
72	8.25 mg/ml	8.72 mg/ml
74	7.39 mg/ml	8.47 mg/ml
75	8.58 mg/ml	9.56 mg/ml

Table 4 : * Target solubility : 10.0 mg/ml

The same experiment has been performed with peptides from the prior art (WO2015/157829) known under the names B7-33 C11.23S, AcB7-33 C11.23S and KKK(AcB7-29 C11.23S).

- 5 The following solubility results have been obtained for these three peptides.

Name	Solubility Acetate buffer pH 4.5**	Solubility phosphate buffer pH 7.4**
B7-33 C11.23S	1.9 mg/ml	0.014 mg /ml
AcB7-33 C11.23S	1.54 mg/ml	<0.001 mg/ml
KKKK(AcB7-29 C11.23S)	2.3 mg/ml	0.177 mg/ml

Table 5

**** Target solubility: 2.0 mg/ml**

- 10 The peptides of the invention display improved solubility compared to compounds of the prior art. This property would allow a larger range of concentration when preparing injectable solutions thus expanding *in-vivo* dosage ranges.

Example 5: Stability testing of peptides in rat or human plasma or blood

- 15 A. Method

Prior to the testing of stability in plasma (or blood) of a peptide batch, its purity (HPLC-UV) was determined.

Study media:

Rat and Human plasma: anti-coagulant sodium or lithium heparin.

- 20 Rat and Human blood: anti-coagulant sodium or lithium heparin.

Stock solution:

100 μ M solution of study compound in 50 mM phosphate buffer pH 7.4.

950 μ L plasma (or blood) was pre-incubated for 5 min at 37°C. 50 μ L of compound stock solution was added. Final compound concentration = 5 μ M. Vortex and transfer 150 μ L plasma (or blood) into an Eppendorf for each time point. The time points 0 - 1 and - 4 h were carried out in duplicate for each species.

5 After incubation, 150 μ L plasma (or blood) was extracted with 600 μ L Acetonitrile containing 1% TFA. Said mixture was then vortexed and centrifuged 10 min at 14600 rpm. 200 μ L supernatant was dried under N₂. Sample was then reconstituted in 200 μ L of H₂O/CH₃CN 98/2 + 0.1% FA + 50ng/ml Labetalol and analyzed using the analytical system used in solubility and stability studies.

10 For determination of the amount of the remaining peptide, the peak areas of the target compound at t0 and each time point days were compared, resulting in "% remaining peptide", following the equation:

$$\% \text{ remaining peptide} = [(\text{peak area peptide time}) \times 100] / \text{peak area peptide t0}.$$

The stability was expressed as "% remaining peptide".

15 Acceptance criteria: The tests compounds were considered stable if precision was ~ 15 % and the recovery was within 85 - 115 % range.

B. Results

20 The Plasma and blood stability results obtained are represented in the following Table 6.

SEQ ID NO	Human Plasma stability			Rat plasma stability		
	% remaining			% remaining		
	T=0	1h	4h	T=0	1h	4h
3	99	95	100	98	100	87
3*	100*	95*	95*	100*	95*	84*
4	100	100	100	100	100	59
4*	100*	100*	99*	100*	102*	86*
6	97	92	91	97	94	ND
7	92	94	87	77	100	66
13	100	91	89	89	100	ND
20	87	100	83	100	100	ND

Table 6 : * Blood stability

The same experiment has been performed with peptides from the prior art (WO2015/157829) known under the names B7-33 C11.23S, AcB7-33, and KKKK(AcB7-29 C11.23S).

The following plasma stability results have been obtained for these three peptides.

Name	Human Plasma stability			Rat plasma stability		
	% remaining			% remaining		
	T=0	1h	4h	T=0	1h	4h
B7-33 C11.23S	100	18	3	100	15	2
Ac B7-33	100	67	18	100	16	2
KKKK(AcB7-29 C11.23S)	100	41	31	100	23	14

Table 7

The peptides of the invention appear to be more stable in plasma and/or blood than compounds of the prior art.

10

Example 6 : Pharmacokinetic (PK) determination of peptides after *in-vivo* administration to rats.

A. Method:

Prior to the testing of a peptide batch, its purity (HPLC-UV) was determined.
15 Dose was corrected for presence of salts, solvent and purity.

Bioanalytical screening method for quantification of peptides in rat:

Sprague Dawley rats were dosed with study peptide at a dose of 1 mg/kg intravenously (i.v.) or 3 mg/kg subcutaneously (s.c.) as a solution in PBS (0.2 mg/ml and 0.6 mg/ml respectively).

20 Blood samples were collected after: 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48 and 72 h (i.v. route) and 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, 48 and 72 h (s.c route) post application.

Plasma samples were analyzed after protein precipitation via liquid chromatography mass spectrometry (LC/MS).

PK parameters and half-life were calculated using Phoenix 64 (WinNonlin 6.4) - Pharsight (Certara™) (non-compartment model). Values below the limit of quantification (BLQ) were replaced by zero for subsequent calculations and PK analysis.

5 **B. Results:**

The PK parameters obtained are represented in the following Table 8.

The following abbreviations are used :

$T_{1/2}$: in-vivo half-life, time required for test compound plasma concentration to be divided by two during the PK experiment.

10 C_0 : Extrapolated test compound plasma concentration at t=0 time point (i.v. route).

C_{max} : maximal test compound plasma concentration at the indicated time point (s.c. route).

T_{max} : Time point where C_{max} was attained.

15 $F\%$: s.c. vs i.v. bioavailability, dose-corrected area under curve (AUC) s.c. route divided by AUC i.v.

SEQ ID NO	Rat PK, 1 mg/kg i.v.		Rat PK, 3 mg/kg s.c.		
	$T_{1/2}$ (h)	C_0 (μM)	C_{max} (μM)	T_{max} (h)	$F\%$
3	7.8	3.2	2.3	8	83
4	8.71	2.75	1.99	8	69
6	5.59	5.17	2.71	8	72
7	6.34	4.16	1.53	10	61
20	5.13	3.09	1.99	10	80
55	4.89	4.91	2.07	6	65

Table 8

20 The same experiment has been performed with H2-Relaxin.

Compound	Rat PK, 1 mg/kg i.v.	
	T _{1/2} (h)	C ₀ (μM)
H2-Relaxin	0.46	0.87

Table 9

- Compared to H2-relaxin, selected peptides of the invention display improved pharmacokinetic parameters. In particular their *in-vivo* half-life in rat, range from 4h to 9h.
- 5 Such peptides could then retain their efficacy for longer period of time allowing once a day administration by the intravenous or subcutaneous route.

Sequence listingSEQ ID NO: 1

5 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-
S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 2

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-
S-T-F-S-Aib-R-A-K(Ac)-NH₂

SEQ ID NO: 3

15 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-
S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 4

20 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Palm)-S-T-
W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 5

25 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-
Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 6

30 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Stea)-S-T-W-
S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 7

35 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-
S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 8

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-
Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 9

45 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-Palm)-S-T-F-S-
Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 10

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-gE-Palm)-S-
T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 11

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-
S-T-W-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 12

Ac-L-E-G-R-E-K-V-R-A-Cit-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

5 SEQ ID NO: 13

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-K-R-A-K(Ac)-NH₂

SEQ ID NO: 14

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-Dscr-K-R-A-K(Ac)-NH₂

SEQ ID NO: 15

15 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-Aib-K-R-A-K(Ac)-NH₂

SEQ ID NO: 16

20 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Dlys-R-A-K(Ac)-NH₂

SEQ ID NO: 17

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Dlys-R-A-K(Ac)-NH₂

25 SEQ ID NO: 18

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Dlys-R-K-K(Ac)-NH₂

SEQ ID NO: 19

30 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 20

35 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 21

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 22

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂DGA-PEG₂DGA-PEG₂DGA-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

45 SEQ ID NO: 23

Ac-L-E-G-R-E-L-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 24

Ac-L-E-G-R-E-F-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

5 SEQ ID NO: 25

Ac-L-E-G-R-E-Q-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 26

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-Stea)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 27

15 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 28

20 Ac-L-E-G-R-E-Hly-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 29

Ac-L-E-G-R-E-K-V-R-Aib-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

25 SEQ ID NO: 30

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-W-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 31

30 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 32

35 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂DGA-PEG₂DGA-PEG₂DGA-gE-gE-gE-Stea)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 33

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 34

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Stea)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

45 SEQ ID NO: 35

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-Aib-K-R-A-K(Ac)-NH₂

SEQ ID NO: 36

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Dlys-R-A-K(Ac)-NH₂

5 SEQ ID NO: 37

Ac-L-E-G-R-E-L-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 38

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 39

15 Ac-L-E-G-R-E-F-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 40

20 Ac-L-E-G-R-E-Q-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 41

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂DGA-PEG₂DGA-PEG₂DGA-gE-gE-gE-Palm)-S-T-W-S-Mly-R-A-K(Ac)-NH₂

25 SEQ ID NO: 42

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-Palm)-S-T-W-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 43

30 Ac-L-E-G-R-E-Hly-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-W-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 44

35 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-Dser-K-R-A-K(Ac)-NH₂

SEQ ID NO: 45

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 46

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂-PEG₂-PEG₂-PEG₂-PEG₂-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

45 SEQ ID NO: 47

Ac-L-E-G-R-E-K-V-R-A-K-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 48

Ac-L-E-G-R-E-K-V-R-A-Q-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

5 SEQ ID NO: 49

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K-NH₂

SEQ ID NO: 50

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂DGA-PEG₂DGA-PEG₂DGA-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 51

15 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 52

20 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 53

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(PEG₂DGA-PEG₂DGA-PEG₂DGA-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

25 SEQ ID NO: 54

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 55

30 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 56

35 Ac-L-E-G-R-E-K-V-R-A-Cit-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 57

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Hly-R-A-K(Ac)-NH₂

SEQ ID NO: 58

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-gE-Stea)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

45 SEQ ID NO: 59

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-gE-Stea)-S-T-F-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 60

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-gE-gE-gE-Stea)-S-T-F-S-Aib-R-K-K(Ac)-NH₂

5 SEQ ID NO: 61

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Stea)-S-T-F-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 62

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 63

15 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-Q-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 64

20 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-R-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 65

Ac-L-E-G-R-E-K-V-R-K(Ac)-Q-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

25 SEQ ID NO: 66

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-K(Ac)-Aib-R-A-K(Ac)-NH₂

SEQ ID NO: 67

30 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 68

35 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K(Ac)-K-NH₂

SEQ ID NO: 69

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K(Ac)-R-NH₂

SEQ ID NO: 70

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-I-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

45 SEQ ID NO: 71

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-A-K-NH₂

SEQ ID NO: 72

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-Aib-R-R-A-K(Ac)-NH₂

5 SEQ ID NO: 73

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-K-W-S-Aib-R-A-K-NH₂

SEQ ID NO: 74

10 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-I-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 75

15 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 76

20 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 77

Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Aib-R-R-K(Ac)-NH₂

25 SEQ ID NO: 78

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 79

30 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-K-F-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 80

35 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-Trp(5-Cl)-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 81

40 Ac-K(Ac)-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 82

Ac-L-E-G-R-E-K-V-R-Aib-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-W-S-Aib-R-A-K(Ac)-NH₂

45 SEQ ID NO: 83

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-K-W-S-Aib-R-K-K(Ac)-NH₂

SEQ ID NO: 84

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-I-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

5 SEQ ID NO: 85

Ac-L-E-G-R-E-R-V-R-Aib-K(Ac) I Aib Aib E G K(TTDS-TTDS-TTDS-gE-gE-gE-Palm) S T W S Aib R R K(Ac)-NH₂

SEQ ID NO: 86

10 Ac-Aib-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-I-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 87

15 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-R-R-A-K(Ac)-NH₂

SEQ ID NO: 88

20 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Hly-R-A-K(Ac)-NH₂

SEQ ID NO: 89

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-Mph-S-R-R-A-K(Ac)-NH₂

25 SEQ ID NO: 90

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-A-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 91

30 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-Pfp-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 92

35 Ac-L-E-G-R-E-R-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-Trp(5-F)-S-Aib-R-R-K(Ac)-NH₂

SEQ ID NO: 93

40 Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-T-R-R-A-K(Ac)-NH₂

SEQ ID NO: 94

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Palm)-S-T-F-V-R-R-A-K(Ac)-NH₂

45 SEQ ID NO: 95

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Myr)-S-T-F-S-Mly-R-A-K(Ac)-NH₂

SEQ ID NO: 96

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-Myr)-S-T-F-S-Mly-R-A-K-NH₂

5 SEQ ID NO: 97

Ac-L-E-G-R-E-K-V-R-A-K(Ac)-I-Aib-Aib-E-G-K(TTDS-TTDS-TTDS-gE-gE-gE-gE-Myr)-S-T-F-S-Mly-R-A-K-NH₂

SEQ ID NO: 100 = H2-relaxin chain A

10 H-Gln-Leu-Tyr-Ser-Ala-Leu-Ala-Asn-Lys-Cys-Cys-His-Val-Gly-Cys-Thr-Lys-Arg-Ser-Leu-Ala-Arg-Phe-Cys-OH

SEQ ID NO: 101 = H2-relaxin chain B

15 H-Asp-Ser-Trp-Met-Glu-Glu-Val-Ile-Lys-Leu-Cys-Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Cys-Gly-Met-Ser-Thr-Trp-Ser-OH

SEQ ID NO: 102 = SEQ ID B7-33 C11.23S*

H-Val-Ile-Lys-Leu-Ser-Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Ser-Gly-Met-Ser-Thr-Trp-Ser-Lys-Arg-Ser-Leu-NH₂

20

SEQ ID NO: 103 = SEQ ID AcB7-33 C11.23S*

Ac-Val-Ile-Lys-Leu-Ser-Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Ser-Gly-Met-Ser-Thr-Trp-Ser-Lys-Arg-Ser-Leu-NH₂

25 SEQ ID NO: 104 = SEQ ID KKKK(AcB7-29 C11.23S)*

Ac-Val-Ile-Lys-Leu-Ser-Gly-Arg-Glu-Leu-Val-Arg-Ala-Gln-Ile-Ala-Ile-Ser-Gly-Met-Ser-Thr-Trp-Ser-Lys-Lys-Lys-Lys-NH₂

*comparison examples

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