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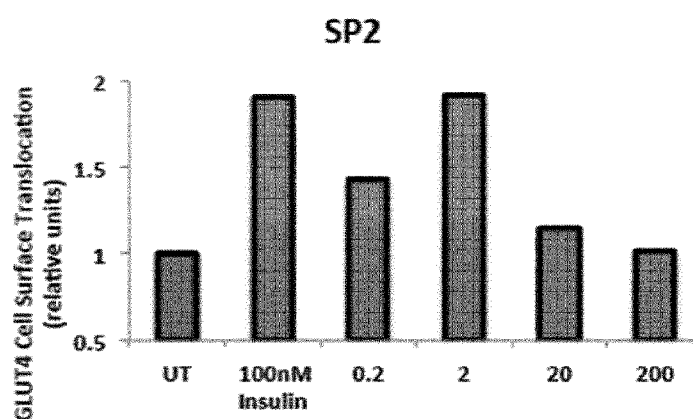


Figure 1

(57) Abstract: A topical, cosmetic or pharmaceutical, composition comprising a cosmetically or pharmaceutically effective amount of a peptide comprising an amino acid sequence of SEQUENCE ID NO.1 or a variant thereof.



**Title**

Topical compositions

**Field of the Invention**

The present invention relates to a topical cosmetic or pharmaceutical compositions.

**5 Background to the Invention**

Many topical cosmetic and pharmaceutical compositions have been described. Improvement is always desirable.

Currently, there are different approaches for improving muscle health or muscle-glucose-absorption. However, finding an alternative that helps muscle recover and maintenance is  
10 desirable. Furthermore, finding an alternative that also allows glucose to enter the muscle without targeting the insulin receptor is becoming essential for the billions of people suffering from muscle loss and diabetes.

Maintaining a normal level of inflammation is very important for our health and wellbeing, both inside and out. Unfortunately, inflammation is on the rise. One of the major factors of this  
15 increase comes from our exposure to an increasing variety of external agents that our bodies are not accustomed to. Most anti-inflammatory treatments used today are drugs. These drugs however have drastic side-effects. Therefore, there is a clear need for the identification of agents having anti-inflammatory activity that are not immunosuppressive and/or cause other undesirable side effects.

20

The growing will of maintaining a youthful appearance is leading to more and more research of new dermatological procedures for treatment of skin aging, especially when people keeps living longer and healthier. Recently, there has been an increasing enthusiasm on minimally  
25 invasive treatments and techniques designed to deal with problems like wrinkles, volume loss and other skin damages. The most common topical anti-ageing solutions are creams and serums.

US2004/0132667 discloses compositions comprising tetrapeptides, optionally in combination with one or more additional ingredients. The compositions disclosed provide relief from one or more skin conditions, including those caused by various sources of stress, pollution and  
30 general aging.

US2014/0120141 discloses cosmetic and pharmaceutical compositions containing peptides for use in the treatment and/or care of conditions, disorders and/or diseases of the skin and/or mucous membranes.

- 5 It is an object of the invention to overcome at least one of the above-referenced problems and provide a topical composition.

### Summary

- 10 A first aspect of the invention provides a topical, cosmetic or pharmaceutical, composition (hereinafter “topical composition of the invention”) comprising a cosmetically or pharmaceutically effective amount of a peptide comprising an amino acid sequence of SEQUENCE ID NO. 1 or a variant thereof (hereafter “peptide of the invention”).

Preferably, said peptide is a bioactive peptide.

Typically, said variant is a bioactive variant.

- 15 Suitably, the topical composition comprises a plurality of peptides.

Typically, the topical composition further comprises at least one cosmetically or pharmaceutically acceptable excipient or additive.

Typically, the topical composition further comprises at least one cosmetically or pharmaceutically acceptable active.

- 20 Suitably, the peptide comprises an amino acid sequence consisting of SEQUENCE ID NO. 1.

Typically, said variant or bioactive variant has from about 70% to about 99% sequence identity with SEQUENCE ID NO. 1.

- 25 Typically, said variant or bioactive variant has at least about 70%, 75%, 80%, 85%, 90% or 95% sequence identity with SEQUENCE ID NO. 1.

Preferably, said variant or bioactive variant has an amino acid sequence comprising any one of SEQUENCE ID NO. 3 to 80.

Preferably, said variant or bioactive variant has an amino acid sequence comprising any one of SEQUENCE ID NO. 3 to 80 and 84 to 114.

Typically, said variant or bioactive variant has an amino acid sequence consisting of any one  
5 of SEQUENCE ID NO. 3 to 80.

Typically, said variant or bioactive variant has an amino acid sequence consisting of any one of SEQUENCE ID NO. 3 to 80 and 84 to 114

10 Typically, said peptide comprises from about 3 to about 50 amino acids in length. Preferably from about 5 to about 20 amino acids in length, preferably about 14 amino acids in length.

Typically, said variant comprises from about 3 to about 50 amino acids in length. Preferably from about 5 to about 20 amino acids in length, preferably about 14 amino acids in length.  
15

Typically, said variant is a fragment of SEQ ID NO. 1 comprising at least three amino acids in length. Typically, said fragment is bioactive. Typically, said fragment has one or more of anti-inflammatory activity, cellular growth promoting activity, anti-aging activity and glucose transport-promoting activity.

20 Alternatively, said variant is a fragment of SEQ ID NO. 1 having at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 amino acids in length.

Suitably, the peptide or variant has anti-inflammatory activity.

25 Suitably, the peptide or variant has cellular growth promoting activity.

Suitably, the peptide or variant has anti-aging activity.

30 Suitably, the peptide or variant has glucose transport-promoting activity.

The peptide or variant may have one or more of anti-inflammatory activity, glucose transport-promoting activity, cellular growth promoting activity and anti-aging activity. The peptide or variant may have anti-inflammatory activity, glucose transport-promoting activity, cellular growth promoting activity and anti-aging activity.

5

Still preferred, the peptide comprises (or consists of) an amino acid sequence of SEQUENCE ID NO'S 1, or the variant comprises (or consists of) an amino acid sequence of SEQUENCE ID NO. 3 to 80 and 84 to 114, wherein the peptide or variant typically has glucose transport-promoting activity.

10

Still preferred, the peptide comprises (or consists of) an amino acid sequence of SEQUENCE ID NO'S 1, or the variant comprises (or consists of) an amino acid sequence of SEQUENCE ID NO. 3 to 80 and 84 to 114, wherein the peptide or variant typically has anti-inflammatory activity.

15

Still preferred, the peptide comprises (or consists of) an amino acid sequence of SEQUENCE ID NO'S 1, or the variant comprises (or consists of) an amino acid sequence of SEQUENCE ID NO. 3 to 80 and 84 to 114, wherein the peptide or variant typically cellular growth promoting activity.

20

Still preferred, the peptide comprises (or consists of) an amino acid sequence of SEQUENCE ID NO'S 1, or the variant comprises (or consists of) an amino acid sequence of SEQUENCE ID NO. 3 to 80 and 84 to 114, wherein the peptide or variant typically has anti-aging activity.

25

A further aspect of the current invention provides a topical composition of the invention as a medicament.

A further aspect of the current invention provides a topical composition of the invention for use in improving muscle status in a mammal.

30

A further aspect of the current invention provides a topical composition of the invention for use in promoting recovery of muscle, typically following exercise.

A further aspect of the current invention provides topical a composition of the invention for use in maintaining or restoring muscle health (for example lean tissue mass) in a mammal.

5 A further aspect of the current invention provides a topical composition of the invention for use in enhancing physical performance.

10 A further aspect of the current invention provides a topical composition of the invention for use in treatment or prevention of a disease or condition characterised by lethargy or low energy levels.

A further aspect of the invention provides a topical composition of the invention for use in promoting growth of tissue.

15 The invention also provides a topical composition of the invention for use in promoting growth of epithelial tissue.

The invention also provides a topical composition of the invention for use in promoting growth of skin.

20 The invention also provides a topical composition of the invention for use in promoting growth of an organ.

The invention also provides a topical composition of the invention for use in promoting growth of an organism.

25 Preferably, the cell, tissue or organism has a normal pathology (for example ageing skin). Typically, the cell, tissue or skin has abnormal pathology (for example tissue damaged due to trauma, drug use, or epithelial tissue in the GI tract damaged due to an inflammatory disorder).

30 The growth promoting uses may be *in-vivo* or *in-vitro* uses. The growth promoting uses may involve administration to mammal externally (i.e. to the skin) or internally (i.e. to the GI tract).

The invention also provides a composition of the invention for use in slowing or inhibiting, or preventing ageing of human skin. Typically, administration may be by means of a plaster or patch or a formulation suitable for topical application.

- 5 Another aspect of the invention provides the topical composition of the invention for use in treatment of a wound in a mammal.

- Another aspect of the invention provides the topical composition for use in the treatment or prevention of a disease or condition characterised by damaged epithelial cells or tissue, and/or  
10 damaged dermal or epithelial cells or tissue. Preferably, the disease or condition is characterised by damaged dermal or epithelial cells or tissue is selected from cancer, trauma

The invention also provides a topical composition of the invention for use in maintaining or restoring gut health in a mammal.

15

The invention also relates to a topical composition of peptides of the invention for use in maintaining or restoring muscle health (for example lean tissue mass) in a mammal.

- A further aspect of the invention provides a topical composition of the invention for use in  
20 treatment or prevention of an inflammatory disorder and/or inflammation in a mammal.

Preferably, the inflammation is symptomatic inflammation.

- A still further aspect of the invention provides a topical composition of the invention for use in  
25 treatment or prevention of pain in a mammal.

Another aspect relates to a topical composition of the invention for use in treatment or prevention of a metabolic disorder in a mammal.

- 30 A further aspect of the invention relates to a method of treating, preventing or caring for any one of the aforementioned and described herein diseases, conditions and/or disorders comprising a step of administering the topical composition of the invention.

The uses of the invention may be therapeutic or non-therapeutic.

A further aspect of the invention relates to a topical composition comprising one or more of the peptides selected from SEQUENCE ID NO. 1, 3 to 80, 84 to 114 and 120 to 1251.

In one embodiment, the composition of the invention comprises substantially all of the peptides of SEQUENCE ID NOS 1, 3 to 80, 84 to 114 and 120 to 1251.

5

A further aspect of the current invention relates to a man-made treatment composition comprising the topical composition of the invention. Preferably, the treatment composition is a wound treatment composition. Preferably the treatment composition is a muscle treatment composition. Preferably, the treatment composition is an anti-aging composition. Preferably the treatment composition is an anti-inflammatory composition. In one embodiment, the composition comprises a cream, gel, lotion, rub, powder.

10

The invention also relates to a plaster, bandage or dressing suitable for application to the keratinous tissue or a wound and comprising the topical composition of the invention.

15

Preferably the topical composition or product is man-made.

### Definitions

20 All publications, patents, patent applications and other references mentioned herein are hereby incorporated by reference in their entireties for all purposes as if each individual publication, patent or patent application were specifically and individually indicated to be incorporated by reference and the content thereof recited in full.

25 Where used herein and unless specifically indicated otherwise, the following terms are intended to have the following meanings in addition to any broader (or narrower) meanings the terms might enjoy in the art:

30 Unless otherwise required by context, the use herein of the singular is to be read to include the plural and vice versa. The term "a" or "an" used in relation to an entity is to be read to refer to one or more of that entity. As such, the terms "a" (or "an"), "one or more," and "at least one" are used interchangeably herein.

As used herein, the term "comprise," or variations thereof such as "comprises" or "comprising," are to be read to indicate the inclusion of any recited integer (e.g. a feature, element, characteristic, property, method/process step or limitation) or group of integers (e.g. features, element, characteristics, properties, method/process steps or limitations) but not the exclusion  
5 of any other integer or group of integers. Thus, as used herein the term "comprising" is inclusive or open-ended and does not exclude additional, unrecited integers or method/process steps.

As used herein, the term "disease" is used to define any abnormal condition that impairs  
10 physiological function and is associated with specific symptoms. The term is used broadly to encompass any disorder, illness, abnormality, pathology, sickness, condition or syndrome in which physiological function is impaired irrespective of the nature of the aetiology (or indeed whether the aetiological basis for the disease is established). It therefore encompasses conditions arising from infection, trauma, injury, surgery, radiological ablation, poisoning or  
15 nutritional deficiencies.

As used herein, the term "treatment" or "treating" refers to an intervention (e.g. the administration of an agent to a subject) which cures, ameliorates or lessens the symptoms of a disease or removes (or lessens the impact of) its cause(s) (for example, the reduction in  
20 accumulation of pathological levels of lysosomal enzymes). In this case, the term is used synonymously with the term "therapy".

Additionally, the terms "treatment" or "treating" refers to an intervention (e.g. the administration of an agent to a subject) which prevents or delays the onset or progression of a  
25 disease or reduces (or eradicates) its incidence within a treated population. In this case, the term treatment is used synonymously with the term "prophylaxis".

As used herein, an effective amount or a therapeutically effective amount of an agent defines an amount that can be administered to a subject without excessive toxicity, irritation, allergic  
30 response, or other problem or complication, commensurate with a reasonable benefit/risk ratio, but one that is sufficient to provide the desired effect, e.g. the treatment or prophylaxis manifested by a permanent or temporary improvement in the subject's condition. The amount will vary from subject to subject, depending on the age and general condition of the individual, mode of administration and other factors. Thus, while it is not possible to specify an exact

effective amount, those skilled in the art will be able to determine an appropriate "effective" amount in any individual case using routine experimentation and background general knowledge. A therapeutic result in this context includes eradication or lessening of symptoms, reduced pain or discomfort, prolonged survival, improved mobility and other markers of clinical improvement. A therapeutic result need not be a complete cure.

The term "bioactive" when used herein refers to a peptide or a peptide variant that has biological activity. For example, the biological activity may be one or more of "Glucose transport promoting" or "glucose transport promoting activity", anti-inflammatory" or "anti-inflammatory activity", and "growth promoting" or "growth promoting activity", or "anti-aging activity".

“Glucose transport promoting” or “glucose transport promoting activity” as applied to a peptide or variant or fragment means a peptide, variant or fragment that is capable of increasing GLUT4 translocation into skeletal muscle compared with an untreated control when employed at a concentration of 2 $\mu$ M in the following *in-vitro* assay. L6-GLUT4myc cells were grown in 10% FBS and 2  $\mu$ g/ml blasticidin. Cells were grown for 48-72 hours before being seeded in 24-well plates at 15,000 cells per well in 2% FBS and allowed to differentiate for 6 to 8 days prior to experimentation. L6-GLUT4myc cells were serum-starved for three hours prior to incubation with 100 nM of insulin for 30mins, or 200, 20, 2.0 and 0.2  $\mu$ M of SP, and 2, 1, 0.5 and .25mg/ml of composition for 3 hours respectively. A 3 hour incubation period was selected based on previous findings identifying that incubation with branch chain amino acid containing di-peptides for 3 hours increases glucose uptake in L6 myotubes 1. Treatments were staggered in order to determine GLUT4myc translocation at the same time point. The quantity of myc-tagged GLUT4 at the cell surface was measured by antibody-coupled colorimetric assay. Briefly, after incubation with either insulin for 30mins or synthetic peptide or protein composition for 3 hours respectively, L6-GLUT4myc cells were fixed via incubation with 3% paraformaldehyde (PFA). A 0.1 M glycine solution was then added to quench PFA and cells were blocked with 5% goat serum. The myotube monolayer was exposed to anti-myc antibody and then incubated with peroxidase conjugated donkey anti-mouse IgG. 1mL of o-phenylenediamine dihydrochloride (OPD) reagent was added to each well and this reaction was stopped by adding 250 $\mu$ l/well of 3 M HCL. To determine GLUT4 translocation to cell surface, a measured aliquot of each condition was determined spectrophotometrically on a plate reader using absorbance at 492nm. Preferably the peptide or fragment is capable of increasing GLUT4 translocation compared with an untreated control by at least 50% (i.e a relative unit increase in GLUT4 translocation of 1% to 1.5%).

In this specification, the term “composition” should be understood to mean something made by the hand of man, and not excludes naturally occurring compositions.

“Anti-inflammatory” as applied to a peptide, variant or fragment means a peptide, variant or fragment that is capable of significantly reducing the secretion of TNF $\alpha$  by LPS-stimulated J774.2 macrophages (compared with untreated LPS-stimulated J774.2 macrophages) when the macrophages are treated with 100 $\mu$ M of the peptide, variant or fragment. J774.2 macrophages were treated with 100 $\mu$ M of synthetic peptide for 24 hours and then stimulated with (A) LPS

(10ng/ml) for five hours or (B) LPS (10ng/ml) for 5 hours followed by ATP (5mM) for one hour. Supernatant was collected and levels of TNF $\alpha$  were determined by ELISA.

“Cellular growth promoting” as applied to a peptide, variant or fragment means a peptide,  
5 variant or fragment that is capable of increasing elastin production or cellular proliferation of human skin treated with a 20 $\mu$ M solution of peptide, variant or fragment in the following assay. Skin explants were prepared from abdominal plastic surgery. Some explants were delipidated with alcohol to obtain a dehydrated skin. These explants were maintained in maintenance medium supplied by the provider Bioprédic International for 5 days. Test items are applied  
10 twice per day with 5 $\mu$ L per explant. At the end of the test, viabilities controls are realized with the MTT on two explants, the third explant is fixed in the formaldehyde 4% for histology and cell staining. For each time of analysis (D1 and D5), histologies on delipidated explants, treated explants with test items, the DMSO 0.3% control and water control, are performed.  
After receipt in the laboratory, each skin explant in the maintenance medium is delipidated  
15 with 5 $\mu$ L alcohol during 3 hours. After 3 hours, all skin explants are treated two per day with test items, and they are incubated at 37°C +/- 2°C, 5% CO<sub>2</sub> for 1 day or 5 days. Integrity of the system is realized at day 1 and day 5 with a viability control with MTT. Histology is realized by the laboratory *Gredeco* and the immunostaining to elastin and Ki67 are realized by the same laboratory. Immunostaining to filaggrin is realized by the laboratory *Intertek*. The detection of  
20 elastin (rabbit monoclonal antibody, clone P15502, LSBio) is performed using an immunoperoxidase technique two layers (ABC kit, Vector Laboratories) and revealed by AEC (3-amino-9 -éthylcarbazole). The immunohistochemical staining intensity in the elastic fibers is evaluated using a semi-quantitative histological score. Epithelial proliferation was analyzed by immunohistochemistry using anti-Ki67 antibody. Immunodetection was performed using  
25 an indirect immunoperoxidase technique three layers, amplified (DAKO kit) and revealed by AEC (3-Amino-9-ethylcarbazole). Counting the number of labeled cells (keratinocytes of the basal layer of the epidermis) is performed and provides the total number of basal cells to calculate the % of labeled cells. The specific staining of filaggrin is performed with an immunoperoxidase staining (ABC kit, Fisher). The intensity of immunohistochemical marker  
30 in the epidermis is evaluated relative to the negative control of the solvent (Water or DMSO 0.3%).

“Antibacterial” or “antibacterial activity” as applied to a peptide, variant or fragment means a peptide , variant or fragment that is capable of visibly inhibiting the growth of a bacteria in the

following agar-plate based growth inhibition assay: Peptide stock=5mg/mL dissolved in DMSO. Bacterial inoculums were adjusted to McFarland 0.5 standard and MHA plates swabbed. Blank disks were placed in the plates and 10  $\mu$ L of each compound (at 64  $\mu$ g/mL – maximum concentration tested) added. Plates were incubated at 37°C for 16-18 hours.

- 5 Appropriate controls (DMSO; Mueller-Hinton media alone; and two antibiotic discs – ciprofloxacin and tetracycline) were also performed.

The term “topical composition” refers to a composition that is formulation for topical administration. “Topical administration” refers to the application to the keratinous tissue, such as the skin, hair and nails. Topical delivery generally means delivery to the skin, but can also mean delivery to a body lumen lined with epithelial cells, for example the lungs or airways, the gastrointestinal tract, the buccal cavity. In particular, formulations for topical delivery are described in Topical drug delivery formulations edited by David Osborne and Antonio Aman, Taylor & Francis, the complete contents of which are incorporated herein by reference.

10 Compositions or formulations for delivery to the airways are described in O’Riordan et al (Respir Care, 2002, Nov. 47), EP2050437, WO2005023290, US2010098660, and US20070053845. Composition and formulations for delivering active agents to the iluem, especially the proximal iluem, include microparticles and microencapsulates where the active agent is encapsulated within a protecting matrix formed of polymer or dairy protein that is acid resistant but prone to dissolution in the more alkaline environment of the ileum. Examples of such delivery systems are described in EP1072600.2 and EP13171757.1. An alternative means of transdermal administration is by use of a skin patch. For example, the active ingredient can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. The active ingredient can also be incorporated, at a concentration of between

25 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required. Injectable forms may contain between 10-1000 mg, preferably between 10-250 mg, of active ingredient per dose. Compositions may be formulated in unit dosage form, i.e., in the form of discrete portions containing a unit dose, or a multiple or sub-unit of a unit dose.

30 The term “cosmetic composition” when used herein relates to a composition that can be used for cosmetic purposes, personal care and/or hygiene purposes. It will be appreciated that the composition may have more than one cosmetic purpose and may be used for more than one of

these purposes at the same time. A “cosmetic” when used herein can include but are not limited to, lipstick, mascara, rouge, foundation, blush, eyeliner, facial and body powder, sunscreen, sunblock, nail polish, compacts, solids, pencils.

“Pharmaceutical compositions”: A further aspect of the invention relates to a pharmaceutical composition comprising a peptide of the invention or a composition of peptides of the invention, admixed with one or more pharmaceutically acceptable diluents, excipients or carriers. Even though the peptides and compositions of the present invention can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier, excipient or diluent, particularly for human therapy. The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine. Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the “Handbook of Pharmaceutical Excipients, 2<sup>nd</sup> Edition, (1994), Edited by A Wade and PJ Weller. In particular, formulations for topical delivery are described in Topical drug delivery formulations edited by David Osborne and Antonio Aman, Taylor & Francis, the complete contents of which are incorporated herein by reference. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol and the like. Examples of suitable diluents include ethanol, glycerol and water. The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, or in addition to, the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s). Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol. Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Preservatives, stabilizers, dyes and even flavouring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of phydroxybenzoic acid. Antioxidants and suspending agents may be also used.

The term “mammal” should be understood to mean a higher mammal, especially a human.

However, the term also includes non-mammalian animals such as fish. The human may be an infant, toddler, child, adolescent, adult, or elderly human. In one embodiment of the invention, the human is an elderly person, for example aged 55 or more. In one embodiment, the human is an elderly person experiencing deterioration of lean tissue mass. In one embodiment, the human is a sportsperson. In one embodiment, the human is pregnant woman. In one embodiment, the human is suffering from lethargy or perceived lack of energy.

The term "dermatologically acceptable," as used herein, means that the topical composition(s) or component(s) of the composition(s) are suitable for use in contact with human skin or keratinous tissue without risk of toxicity, incompatibility, instability and/or allergic response, and similar.

The term "sustained release" is used in a conventional sense relating to a delivery system of a compound or active, which provides the gradual release of this compound or active during a period of time and preferably, although not necessarily, with relatively constant compound release levels over a period of time.

The term "peptide" used herein refers to a polymer composed of up to 50 amino acids, for example 5 to 50 amino acid monomers typically linked via peptide bond linkage. Peptides (including fragments and variants thereof) of and for use in the invention may be generated wholly or partly by chemical synthesis or by expression from nucleic acid. For example, the peptides of and for use in the present invention can be readily prepared according to well-established, standard liquid or, preferably, solid-phase peptide synthesis methods known in the art (see, for example, J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis, 2nd edition, Pierce Chemical Company, Rockford, Illinois (1984), in M. Bodanzsky and A. Bodanzsky, The Practice of Peptide Synthesis, Springer Verlag, New York (1984). When necessary, any of the peptides employed in the invention can be chemically modified to increase their stability. A chemically modified peptide or a peptide analog includes any functional chemical equivalent of the peptide characterized by its increased stability and/or efficacy in vivo or in vitro in respect of the practice of the invention. The term peptide analog also refers to any amino acid derivative of a peptide as described herein. A peptide analog can be produced by procedures that include, but are not limited to, modifications to side chains, incorporation of unnatural amino acids and/or their derivatives during peptide synthesis and the use of cross-linkers and other methods that impose conformational constraint on the peptides or their analogs. Examples of side chain modifications include modification of amino

groups, such as by reductive alkylation by reaction with an aldehyde followed by reduction with  $\text{NaBH}_4$ ; amidation with methylacetimidate; acetylation with acetic anhydride; carbamylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6, trinitrobenzene sulfonic acid (TNBS); alkylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxa-5'-phosphate followed by reduction with  $\text{NABH}_4$ . The guanidino group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal. The carboxyl group may be modified by carbodiimide activation via o-acylisourea formation followed by subsequent derivatization, for example, to a corresponding amide. Sulfhydryl groups may be modified by methods, such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of mixed disulphides with other thiol compounds; reaction with maleimide; maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulfonic acid, phenylmercury chloride, 2-chloromercuric-4-nitrophenol and other mercurials; carbamylation with cyanate at alkaline pH. Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphonyl halides. Tyrosine residues may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative. Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate. Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. Peptide structure modification includes the generation of retro-inverso peptides comprising the reversed sequence encoded by D-amino acids.

A "variant" of the peptide shall be taken to mean a peptide having an amino acid sequence that is substantially identical to SEQUENCE ID NO.1, but which is altered in respect of one or more amino acid residues. Preferably such alterations involve the insertion, addition, deletion and/or substitution of 11 or fewer amino acids, more preferably of 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, preferably 5 or fewer, 4 or fewer, even more preferably of 3 or fewer, most preferably of 1 or 2 amino acids only. Insertion, addition and substitution with natural and modified amino acids is envisaged. The variant may have conservative amino acid

changes, wherein the amino acid being introduced is similar structurally, chemically, or functionally to that being substituted. Generally, the variant will have at least 70% amino acid sequence identity, preferably at least 80% sequence identity, more preferably at least 90% sequence identity, and ideally at least 95%, 96%, 97%, 98% or 99% sequence identity with the parent sequence.

The term variant is also taken to encompass the term “fragment” and as such means a segment of amino acid SEQUENCE ID NO. 1. Typically, the fragment has between 3 and 13 contiguous amino acids in length. Generally, the fragment has a charge of -5 to +3. The charge of a peptide, fragment or region is determined using the method of Cameselle, J.C., Ribeiro, J.M., and Sillero, A. (1986). Derivation and use of a formula to calculate the net charge of acid-base compounds. Its application to amino acids, proteins and nucleotides. *Biochem. Educ.* 14, 131–136.

In this specification, the term “sequence identity” should be understood to comprise both sequence identity and similarity, *i.e.* a variant (or homolog) that shares 70% sequence identity with a reference sequence is one in which any 70% of aligned residues of the variant (or homolog) are identical to, or conservative substitutions of, the corresponding residues in the reference sequence across the entire length of the sequence. Sequence identity is the amount of characters which match exactly between two different sequences. Hereby, gaps are not counted and the measurement is relational to the shorter of the two sequences.

In terms of “sequence homology”, the term should be understood to mean that a variant (or homolog) which shares a defined percent similarity or identity with a reference sequence when the percentage of aligned residues of the variant (or homolog) are either identical to, or conservative substitutions of, the corresponding residues in the reference sequence and where the variant (or homolog) shares the same function as the reference sequence.

This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example, one alignment program is BLAST, using default parameters. Details of these programs can be found at the following Internet address: <http://www.ncbi.nlm.nih.gov/blast/Blast.cgi>.

“Inflammatory disorder” means an immune-mediated inflammatory condition that affects humans and is generally characterised by dysregulated expression of one or more cytokines. Examples of inflammatory disorders include skin inflammatory disorders, inflammatory disorders of the joints, inflammatory disorders of the cardiovascular system, certain autoimmune diseases, lung and airway inflammatory disorders, intestinal inflammatory disorders. Examples of skin inflammatory disorders include dermatitis, for example atopic dermatitis and contact dermatitis, acne vulgaris, and psoriasis. Examples of inflammatory disorders of the joints include rheumatoid arthritis. Examples of inflammatory disorders of the cardiovascular system are cardiovascular disease and atherosclerosis. Examples of autoimmune diseases include Type 1 diabetes, Graves disease, Guillain-Barre disease, Lupus, Psoriatic arthritis, and Ulcerative colitis. Examples of lung and airway inflammatory disorders include asthma, cystic fibrosis, COPD, emphysema, and acute respiratory distress syndrome. Examples of intestinal inflammatory disorders include colitis and inflammatory bowel disease. Other inflammatory disorders include cancer, hay fever, periodontitis, allergies, hypersensitivity, ischemia, depression, systemic diseases, post infection inflammation and bronchitis. The peptides and compositions of the invention may also be employed in the non-therapeutic treatment of inflammation. Examples of non-therapeutic treatment of inflammation include use to relieve normal, non-pathological, inflammation, for example inflammation in the muscles and joints following exercise.

In this specification, the term “Metabolic disorder” should be understood to include pre-diabetes, diabetes; Type-1 diabetes; Type-2 diabetes; metabolic syndrome; obesity; diabetic dyslipidemia; hyperlipidemia; hypertension; hypertriglyceridemia; hyperfattyacidemia; hypercholesterolemia; hyperinsulinemia, and MODY.

“Ani-ageing” means inhibiting or slowing the appearance of ageing of a human’s skin and/or reversing the appearance of ageing. “Slowing or inhibiting ageing of the skin” means slowing or inhibiting the ageing process in the skin, and/or reversing the appearance of ageing.

“Disease or condition characterised by damaged dermal or epithelial cells or tissue” means any condition or disease that results in damaged dermal or epithelial tissue or cells or organs. One example is trauma which often results in damaged skin. Another example is an inflammatory skin condition such as psoriasis or eczema which often results in damaged skin. Another example is an inflammatory disorder of the lower intestines which can result in damaged

epithelial cells/tissue lining the lower intestines. Another example is damaged epithelial cells/tissue lining the lower intestines caused by ingestion of a toxic or damaging substance, for example toxic chemicals or drugs. Another example is cancer, for example bowel cancer, which can result in damaged epithelial tissue in the bowel. Another condition is a peripheral  
5 inflammatory disorder such as atopic dermatitis which can result in damage to the skin in humans.

“Disease or condition characterised by bacterial infection” means any condition or disease characterised having a pathology caused by growth of bacteria or by bacterial infection,  
10 including for example MRSA, salmonella, listeria, bacterial pneumonia, Staphylococcal food poisoning, bacterial meningitis. Specific examples are provided in [https://en.wikipedia.org/wiki/List\\_of\\_infectious\\_diseases](https://en.wikipedia.org/wiki/List_of_infectious_diseases).

“Man-made” as applied to comestible products should be understood to mean made by a human  
15 being and not existing in nature.

“Improving muscle status” means improving the muscle health, for example promoting skeletal muscle protein synthesis, skeletal glucose absorption, improving lean tissue mass in therapeutic or non-therapeutic context, promoting muscle recovery generally after activity exercise, or  
20 improving muscle performance. The methods or uses may be therapeutic or non-therapeutic. The term “improving lean tissue mass status” should be understood to mean increasing lean tissue mass, or inhibiting or preventing the rate of lean tissue mass degradation.

“Promoting muscle recovery” means causing an increase in absorption of glucose in skeletal  
25 muscle compared with untreated skeletal muscle.

“Disease or condition characterised by lethargy or low energy levels” means any condition or disease characterised by a feeling of tiredness or low energy. Examples include allergies, asthma, anemia, cancer and its treatments, chronic pain, heart disease, infection, depression,  
30 eating disorders, grief, sleeping disorders, thyroid problems, medication side effects, alcohol use, or drug use.

“Maintaining or restoring muscle health” means helping retain or restore mammalian muscle health resulting from damage incurred during exercise. By promoting glucose transport in skeletal muscle the peptides promote recovery from exercise, and relieve muscle soreness/pain and injury connected with exercise. They can also be used to decrease and prevent muscle cramping, and to allow a faster recovery from muscle cramping. Cramping can result from physical stress, mental stress, and or Repetitive Strain Injury stress. By promoting glucose transport the peptides help reduce Myopathy of the muscle, and help prevent Sarcopenia in mammals, promote recovery from injuries during exercise, and relieve muscle soreness/pain and injury connected with exercise. The invention also relates to a peptide or composition of the invention for use in maintaining or restoring muscle health in a mammal.

In this specification, the term “personal care product” should be understood to mean a composition formulated for use by humans in cleaning or treating the human body, particularly the skin, teeth, nails, feet and hair. Examples include shampoo, conditioner, skin creams and lotions, powders, dentifrice, shower gel or creams, bath or shower gel, hair dye, soap, body scrub, exfoliant, anti-dandruff solutions body lotion, shaving solutions, moisturisers, cleaners, masks, oils, serums, and rinses, deodorant, and anti-perspirant.

The term “skin aging” is used in the sense in which it is generally and widely used in the art of cosmetic and personal care products. Signs of skin aging include wrinkles, lines, crevices, bumps, red spots, large pores, roughness, dullness, loss of elasticity, sagging, loss of tightness, discoloration, blotching, hyperpigmentation, freckles, keratosis, inflammation, collagen breakdown and other histological changes in the skin layers including underlying tissue.

The term “cosmetically or pharmaceutically acceptable salts” means a salt recognized for its use in animals and more specifically in human beings, and includes salts used to form base addition salts, either they are inorganic, such as and not restricted to, lithium, sodium, potassium, calcium, magnesium, manganese, copper, zinc or aluminium among others, either they are organic, such as and not restricted to, ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, arginine, lysine, histidine or piperazine among others, or acid addition salts, either they are organic, such as and not restricted to, acetate, citrate, lactate, malonate, maleate, tartrate, fumarate, benzoate, aspartate, glutamate, succinate, oleate, trifluoroacetate, oxalate, pamoate or gluconate among others, or inorganic, such as and not restricted to, chloride, sulfate, borate or carbonate, among others. The nature of the salt is not critical, provided that it is cosmetically or pharmaceutically acceptable. The cosmetically or

pharmaceutically acceptable salts of the peptides of the invention can be obtained by the conventional methods, well known in the prior art [Berge S. M. et al., "Pharmaceutical Salts", J. Pharm. Sci., (1977), 66, 1-19].

The term "natural" as applied to a peptide means a peptide that includes (a) a fragment of a plant protein, typically rice or pea protein, or variants of pea protein including lentil, sweet pea, or chick pea or variants of rice protein including oat, grass, corn, wild rice and bananas, or (b) a variant of the fragment of a plant protein, for example a glucose transport promoting fragment of a homolog of the plant protein. The peptides or fragments of the invention may be isolated from plant protein composition or made synthetically using methods known to a person skilled in the art and described herein.

"C-terminal domain" as applied to a fragment means the first three amino acids at the c-terminus of the fragment.

"N-terminal domain" as applied to a fragment means the last three amino acids at the n-terminus of the fragment.

"Homolog" of a reference protein should be understood to mean a protein from a different species of plant having at least 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence homology with the reference protein. Thus, for example, homologs of pea protein P13918 include:

hydro

>gi|137584|sp|P08438.1|VCL\_VICFA RecName: Full=Vicilin; Flags: Precursor [Vicia faba]

>gi|22057|emb|CAA68559.1| vicilin [Vicia faba var. minor] >gi|383931031|gb|AFH56916.1|

vicilin [**Vicia faba**] **SEQ ID 81**

>gi|502105533|ref|XP\_004492829.1| PREDICTED: vicilin-like isoform X1 [**Cicer arietinum**] **ChickPea SEQ ID 82**

>gi|29539109|emb|CAD87730.1| allergen Len c 1.0101 [**Lens culinaris**] **Lentil SEQ ID 83**

In the specification the terms "comprise, comprises, comprised and comprising" or any variation thereof and the terms "include, includes, included and including" or any variation thereof are considered to be totally interchangeable and they should all be afforded the widest possible interpretation and vice versa.

**Brief Description of the Drawings**

The invention will be more clearly understood from the following description of an embodiment thereof, given by way of example only, with reference to the accompanying drawings, in which: -

5

**Figure 1** illustrates the effect of SP2 on GLUT4 translocation in L6-GLUT4myc skeletal muscle cells. L6-GLUT4myc cells were serum starved for 3 hours and then treated with either 200, 20, 2 and 0.2  $\mu$ M of each synthetic peptide for 3 hours or 100 nM of insulin for 30 minutes. Data are presented as average of triplicates.

10

**Figure 2** illustrates the effect of SEQ ID No. 1 on glucose uptake.

**Detailed Description of the Drawings**

In the broadest sense, the first aspect of the invention provides a topical cosmetic or pharmaceutical composition (hereafter “topical composition of the invention”) comprising a cosmetically or pharmaceutically effective amount of a peptide comprising an amino acid sequence of SEQUENCE ID NO. 1 or a variant thereof (hereafter “peptide of the invention”).

**SEQUENCE ID NO.1**

20 VLDLAIPVNRPGQL

The specific pea protein from which the natural (glucose transport promoting fragment) peptide of the invention is derived is provided in SEQUENCE ID NO: 2 (Pea Protein 1 – P13918). Homologs of Pea Protein 1 (SEQUENCE ID NO: 2) include *Vicia fabia*, *Cicer arietinum* and

25

*Lens culinaris* homologs (SEQ ID NO:81 to 83).

>gi|137584|sp|P08438.1|VCL\_VICFA RecName: Full=Vicilin; Flags: Precursor [Vicia faba]  
>gi|22057|emb|CAA68559.1| vicilin [Vicia faba var. minor] >gi|383931031|gb|AFH56916.1|  
vicilin [Vicia faba]

30

**SEQUENCE ID NO. 81**

MAATTLKDSFPLLTLGLIAFLASVCLSSRSQDNPVFVESNRFQTLFENENGHIRLLQK  
FDQHSKLLLENLQNYRLLEYKSKPHTIFLPQQTDADFILVVLSGKAILTVLLPNDRNSFS  
LERGDTIKLPAGTIGYLVNRDDEEDLRVLDLVIPVNRPGEPQSFLSGNQNPQSILSGF

SKNILEASFNTDYKEIEKVLLEEKGKEKYHRRGLKDRRQRGQEEENVIVKISRKQIEEL  
 NKNAKSSSKKSTSSSEPFNLRSREPIYSNKFGEFFETPKRNPQLQDLNIFVNYVEINE  
 GSLLPHYNSRAIVIVTVNEGKGDFELVGQRNENQQGLREEYDEEKEQGEEEEIRKQV  
 QNYKAKLSPGDVLVIPAGYPVAIKASSNLNLVGFGINAENNQRYFLAGEEDNVISQIH  
 5 KPVKELAFPGSAQEVDTLLENQKQSHFANAQPRERERGSQEIKDHLYSILGSF [SEQ  
 ID 81]

>gi|502105533|ref|XP\_004492829.1| PREDICTED: vicilin-like isoform X1 [*Cicer  
 arietinum*] **ChickPea**

10 **SEQUENCE ID NO. 82**

MAIKARFPLLVLGIVFLASVCAKSDKENPFFFKSNNCQTLFENENGHVRLQLRFDK  
 RSQLFENLQNYRLMEYNSKPHTLFLPQHNDADFILVVLGRRAILTVLNPNDNRNTFKL  
 ERGDTIKLPAGTIAYLANRDDNEDLRVLDLAIPVNRPGQFQSFLSGNENQQSYFQGF  
 SKKILEASFNSDYEEIERVLLLEEQEKEQKPEQRRGHKGRQQSQETDVIVKISREQIEELSK  
 15 NAKSNCKKSVSSESEPFNLRSRSPISNRFGNFFETPEKNPQLKDLDIFVNSVEIKEGS  
 LLLPHFNSRATVILVVNEGKGGEVELVGLRNENEQENKKEDEEEEEEDRNVQVQRFQS  
 KLSSGDVVPVASHPFSINASSDLFLLGFGINAQNNQRNFLAGEEDNVISQIQRPVKEV  
 AFPGSAEEVDRLKNQRQSHFANAQPQQKRKGSQRIRSPF [SEQ ID 82]

20 >gi|29539109|emb|CAD87730.1| allergen Len c 1.0101 [*Lens culinaris*] **Lentil**

**SEQUENCE ID NO. 83**

SRSDQENPFIFKSNRFQTIYENENGHIRLLQRFDKRSKIFENLQNYRLLEYKSKPHTIFL  
 PQFTDADFILVVLGKAILTVLNSNDRNSFNLERGDTIKLPAGTIAYLANRDDNEDLR  
 VLDLAIPVNRPGQLQSFLSGTQNQPSFLSGFSKNILEAAFNTEYEEIEKVLLEEQEKEQK  
 25 SQHRRSLRDKRQEITNEDVIVKVSREQIEELSKNAKSSSKKSVSSESEPFNLRSRNPIS  
 NKFGEFFETPEKNPQLQDLDFVNSVEIKEGSLLLPNYNSRAIVIVTVNEGKGDFELV  
 GQRNENQQEQREENDEEEGQEEETTKQVQRYRARLSPGDVLVIPAGHPVAINASSDL  
 NLIGFGINAKNNQRNFLAGEEDNVISQIQRPVKELAFPGSSREVDRLLTNQQSHFAN  
 AQLQIE [SEQ ID 83]

30

**SEQUENCE ID NO. 2**

MAATTMKASFLLMLMGISFLASVCVSSRSDPQNPFFKSNKFQTLFENENGHIRLLQKFDQRSKIFENLQ  
 35 NYRLLEYKSKPHTIFLPQHTDADYILVVLGKAILTVLKPDDRNSFNLERGDTIKLPAGTIAYLNRDDNEEL  
 RVLDLAIPVNRPGQLQSFLSGNQNNQNYLSGFSKNILEASFNTDYEEIEKVLLEEHEKETQHRRSLKDKR  
 QQSQEENVIVKLSRGQIEELSKNAKSTSKKSVSSESEPFNLRSRGPISNEFGKFFETPEKNPQLQDLDFV  
 NSVEIKEGSLLLPHYNSRAIVIVTVNEGKGDFELVGQRNENQQEQRKEDDEEEQGEEINKQVQNYKAK  
 LSSGDVFPVAGHPVAVKASSNLDLLGFGINAENNQRNFLAGDEDNVISQIQRPVKELAFPGSAQEVDRL  
 40 ENQKQSHFADAQPQQRERGSRETRDRLSSV

In one embodiment of the invention, the peptide or variant is bioactive. In one embodiment, the peptide or variant has glucose transport promoting activity. In an embodiment, the peptide or variant has anti-inflammatory activity. In one embodiment, the peptide or variant has cellular

growth promoting activity. In one embodiment, the peptide or variant has anti-aging activity. It will be appreciated that the peptide or variant may have two or three of anti-inflammatory activity, glucose transport promoting activity, cellular growth promoting activity and anti-aging activity. The peptide or variant may have anti-inflammatory activity, glucose transport promoting activity, cellular growth promoting activity and anti-aging activity.

In an embodiment of the invention the peptide comprises from about 3 to 50 amino acids in length, about 14 to about 50 amino acids in length, preferably about, 15, 20, 25, 30, 35, 40, 45, or 49 amino acids in length, preferably about 14, 15, 16, 17, 18, 19, or 20 amino acids in length.

In an embodiment of the invention the variant comprises from about 3 to about 14 amino acids in length, preferably about, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids in length.

In one embodiment, the variant has 1 to 5 amino acid changes compared to SEQUENCE ID NO: 1. In one embodiment, the variant has 1 to 4 amino acid changes compared to SEQUENCE ID NO: 1. In one embodiment, the variant has 1 to 3 amino acid changes compared to SEQUENCE ID NO: 1. In one embodiment, the variant has 1 to 2 amino acid changes compared to SEQUENCE ID NO: 1. In one embodiment, the amino acid change is an amino acid substitution. In one embodiment, the amino acid substitution is a conservative substitution. In one embodiment, the amino acid change is an amino acid addition. In one embodiment, the amino acid change is an amino acid deletion.

The variants of the invention include:-

#### 25 Variants of SEQUENCE ID NO: 1 (peptide E64 SP2)

Variants of SEQUENCE ID NO: 1 (VLDLAIPVNRPGQL) including variants having 1,2 or 3 conservative amino acid substitutions, 1, 2 to 3 non-conservative amino acid substitutions, 1-2 amino acid additions, 1, 2 or 3 amino acid deletions, are provided below:

30 One conservative amino acid substitution:

ILDLAIPVNRPGQL (SEQ ID 3); VLELAIPVNRPGQL (SEQ ID 4); VLDLAVPVNRPGQL (SEQ ID 5); VLDLAIPINRPGQL (SEQ ID 6); VLDLAIPVKNKPGQL (SEQ ID 7); VLDLAIPVEKPGQL (SEQ ID 8); VLDLAIPVKNKPGEL (SEQ ID 9)

Two conservative amino acid substitutions:

ILELAIPVNRPGQL (SEQ ID 10); ILDLAVPVNRPGQL (SEQ ID 11);  
 VLELAVPVNRPGQL (SEQ ID 12); VLELAIPVNKPGQL (SEQ ID 13);  
 ILDLAIPVNKPGQL (SEQ ID 14); VLDLAVPVNKPGL (SEQ ID 15);  
 5 VLDLAIPVEKPGEL (SEQ ID 16); ILDLAIPVNKPGEL (SEQ ID 17); VLELAIPVEKPGQL  
 (SEQ ID 18).

Three conservative amino acid substitutions:

ILELAVPVNRPGQL (SEQ ID 19); ILELAIPVNKPGQL (SEQ ID 20);  
 10 VLELAVPVNKPGL (SEQ ID 21); ILELAIPVNRPGEL (SEQ ID 22); ILDLAIPVNKPGEL  
 (SEQ ID 23); VLDLAVPVEKPGQL (SEQ ID 24); VLDLAVPVERPGL (SEQ ID 25);  
 VLELAIPVERPGL (SEQ ID 26).

One non-conservative amino acid substitution

15 KLDLAIPVNRPGQL (SEQ ID 27); VLDLAIPVNRPGQK (SEQ ID 28);  
 VLDLAIPVNRPGQL (SEQ ID 29); VLDLAIPVNRPGQL (SEQ ID 30);  
 VLDLAIPVNRPGQL (SEQ ID 31); VLDLWIPVNRPGQL (SEQ ID 32);  
 VLDLAIPVNRPGQL (SEQ ID 33); VLYLAIPVNRPGQL (SEQ ID 34).

20 Two non-conservative amino acid substitution

VLDLYIPVGRPGQL (SEQ ID 35); VKDLAIPVNRPGQL (SEQ ID 36);  
 VLDLAIPVNRPGQL (SEQ ID 37); VLDLAGGVNRPGQL (SEQ ID 38);  
 VLDLAIPKNEPGQL (SEQ ID 39); PLDLAIPVNDPGQL (SEQ ID 40);  
 VLDLAIPVNRPIQL (SEQ ID 41); VLDHAIPVNRPGQL (SEQ ID 42)

25

Three non-conservative amino acid substitution

VLDLAIPVNRPGGG (SEQ ID 43); VLDLHIPGNEPGQL (SEQ ID 44);  
 VYKLAIPVNEPGQL (SEQ ID 45); VLDLAIPVNRPYPG (SEQ ID 46);  
 VLDYAIPKNDPGQL (SEQ ID 47); VLDLAIPVNRPGQL (SEQ ID 48);  
 30 RRRLAIPVNRPGQL (SEQ ID 49); VLDLAIGVNRGPQL (SEQ ID 50)

One or two amino acid additions

VLDLAIPVNRPGFQL (SEQ ID 51); VLDLADIPVNRPGQL (SEQ ID 52);  
 VLDLAIPVGNRPGQL (SEQ ID 53); VLQQDLAIPVNRPGQL (SEQ ID 54);

VLDLAIPVNRGPGQKL (SEQ ID 55); VLDGLPLAIPVNRPGQL (SEQ ID 56);  
VLDLAIPVNRPGQLLL (SEQ ID 57); VLDLFLGAIPVNRPGQL (SEQ ID 58)

One, two or three amino acid deletions

- 5 VLDLAIPVNRGQL (SEQ ID 59); VLDLAPVNRPGQL (SEQ ID 60); LDLAIPVNRPGQL  
(SEQ ID 61); VLDLAIPVNRPGQ (SEQ ID 62); DLAI PVNRPGQL (SEQ ID 63);  
VLDLAIPVNRPG (SEQ ID 64); VLDLAINRPGQL (SEQ ID 65); VLDAIVNPGQL (SEQ  
ID 66)
- 10 The variant may be a bioactive variant. In one embodiment, the variant is a glucose transport  
promoting variant. In one embodiment, the variant is an anti-inflammatory variant. In one  
embodiment, the variant is an anti-aging variants. In one embodiment, the variant has cellular  
growth promoting activity. It will be appreciated that in one embodiment the bioactive variant  
15 is two or more of glucose transport promoting variant, an anti-inflammatory variant, cellular  
growth promoting variant and an anti-aging variant. In one embodiment, the bioactive variant  
is a glucose transport promoting variant, cellular growth promoting variant, an anti-  
inflammatory variant and an anti-aging variant.

20 The invention also provides fragments of SEQ ID NO No. 1, and peptides comprising one or  
more of these fragments.

These fragment may be a bioactive fragment. In one embodiment, the fragment is a glucose  
transport promoting fragment. In one embodiment, the fragment is an anti-inflammatory  
fragment. In one embodiment, the fragment has cellular growth promoting activity. In one  
25 embodiment, the fragment is an anti-aging fragment. It will be appreciated that in one  
embodiment the bioactive fragment is two or more of glucose transport promoting fragment,  
an anti-inflammatory fragment, cellular growth promoting fragment and an anti-aging  
fragment. In one embodiment, the bioactive fragment is a glucose transport promoting  
fragment, an anti-inflammatory fragment, cellular growth promoting fragment and an anti-  
30 aging fragment.

In one embodiment, the fragments are glucose transport promoting fragments.

Examples of fragments of SEQ ID NO: 1 are provided below:

VLDLAIPVNRPGQ (SEQ ID 67); VLDLAIPVNRPG (SEQ ID 68); VLDLAIPVNRP (SEQ ID 69); LDLAIPVNRPGQL (SEQ ID 70); DLAIPVNRPGQL (SEQ ID 71); LAIPVNRPGQL (SEQ ID 72); LDLAIPVNRPGQ (SEQ ID 73); DLAIPVNRPG (SEQ ID 74); LAIPVNRP (SEQ ID 75); VLDLAIPVN (SEQ ID 76); AIPVNRPGQL (SEQ ID 77); VNRPGQL (SEQ ID 78); VLDLAIPV (SEQ ID 79), and VLDLAIPVNR (SEQ ID 80).

Examples of peptides of the invention are as follows:

VLDLAIPVNRPGQLQ (SEQ ID 84); VLDLAIPVNRPGQLQSF (SEQ ID 85),  
 10 VLDLAIPVNRPGQLQSF (SEQ ID 86); VLDLAIPVNRPGQLQ (SEQ ID 87);  
 VLDLAIPVNR (SEQ ID 88); VLDLAIPVNR (SEQ ID 89); VLDLAIPVNR (SEQ ID 90);  
 LAIPVNRPGQLQSFL (SEQ ID 91); LAIPVNRPGQ (SEQ ID 92); DLAIPVNRPGQLQSF  
 (SEQ ID 93); LAIPVNRPGQLQSF (SEQ ID 94); LAIPVNRPGQLQS (SEQ ID 95);  
 VLDLAIPVNRPGQLQ (SEQ ID 96); DLAIPVNRPGQLQ (SEQ ID 97); LAIPVNRPGQLQ  
 15 (SEQ ID 98); LAIPVNRPGQL (SEQ ID 99); DLAIPVNRPGQL (SEQ ID 100);  
 DLAIPVNRPGQLQS (SEQ ID 101); LAIPVNRPGQLQSFLLSG (SEQ ID 102);  
 LAIPVNRPGQLQSFLLSGNQ (SEQ ID 103); LDLAIPVNRPGQL (SEQ ID 104);  
 LAIPVNRPGQLQSFL (SEQ ID 105); LAIPVNRPGQLQSFLLS (SEQ ID 106);  
 VLDLAIPVNRPGQLQSF (SEQ ID 107); VLDLAIPVNR (SEQ ID 108);  
 20 LAIPVNRPGQLQSFLLSG (SEQ ID 109); LDLAIPVNRPGQL (SEQ ID 110);  
 VLDLAIPVNRPGQLQ (SEQ ID 111); LAIPVNRPGQLQSFLLSGNQ (SEQ ID 112);  
 AIPVNRPGQLQSF (SEQ ID 113); AIPVNRPGQLQS (SEQ ID 114).

It will be appreciated that the topical composition may comprise a plurality of peptides,  
 25 fragments and/or variants. In one embodiment, the topical composition comprises substantially  
 all the peptides. In one embodiment, the topical composition comprises substantially all the  
 variants.

In one embodiment, the topical or cosmetic composition is substantially free of other  
 30 peptides.

The topical composition of the invention may be presented in a formulation selected from the  
 group comprising creams, multiple emulsions, anhydrous compositions, aqueous dispersions,  
 oils, milks, balsams, foams, lotions, gels, cream gels, hydro-alcoholic solutions, hydro-glycolic

solutions, cosmetic, personal care product, hydrogels, liniments, sera, soaps, dusting powder, paste, semi solid formulations, liniments, serums, shampoo, conditioner, ointments, any rinse off formulation, talc, mousses, powders, sprays, aerosols, solutions, suspensions, emulsions, syrups, elixirs, polysaccharide films, patches, gel patches, bandages, an adhesive system,  
5 water-in-oil emulsions, oil-in-water emulsions, and silicone emulsions.

In an embodiment of the current invention, the emulsion contains a lipid or oil. The emulsion may be, but is not limited to, oil-in-water, water-in-oil, water-in-oil-in-water and oil-in-water-in-silicone emulsions. The emulsion may contain a humectant. The emulsion may contain an anti-foaming agent, such as silicone. The emulsion may have any suitable viscosity. Emulsions  
10 may further contain an emulsifier and/or an anti-foaming agent. Methods of preparing an emulsion are known to a person skilled in the art.

The topical composition of the invention may be incorporated into a medical device for administration. Such a device can include but is not limited to a fabric, patch, bandage, gauge, sock, tight, underwear, dressing, glove, mask, adhesive patches, non-adhesive patches,  
15 occlusive patches and microelectric patches or suitable adhesive system. In such an embodiment, the device is in direct contact with the keratinous layer such as the skin, thus releasing the peptides of the invention. It will be understood that the topical composition may be incorporated in any suitable form as detailed herein. For example, the topical composition or peptides of the invention can be incorporated into the device or be present on the surface of  
20 the device or can be in a cream, gel or wax formulation or any suitable formulation defined herein and incorporated into the device or on the surface of the device.

The device may be adapted for adhesion or attachment to the skin.

In one embodiment the device is adapted to release a constant quantity of the composition or the peptides of the invention. It will be understood that the amount of the composition  
25 contained in the sustained release system will depend, for example, on where the composition is to be administered, the kinetics and duration of the release of the composition of the invention, as well as the nature of the condition, disorder and/or disease to be treated and/or cared for. The device may be such that the composition is released by biodegradation of the device, or by friction between the device and the body, due to bodily moisture, the skin's pH  
30 or body temperature.

In an embodiment of the invention the topical composition may further comprise at least one cosmetically or pharmaceutically acceptable excipient. Excipient may be used interchangeably

with functional ingredient or additive. It will be understood that although the topical compositions of the current invention can be administered alone, they will generally be administered in admixture with a cosmetic or pharmaceutical excipient. Cosmetically or pharmaceutically acceptable excipient are well known in the art and any known excipient, may  
5 be used provided that it is suitable for topical administration and is dermatologically acceptable without undue toxicity, incompatibility and/or allergic reaction.

Preferably any excipient included is present in trace amounts. The amount of excipient included will depend on numerous factors, including the type of excipient used, the nature of the excipient, the component(s) of the topical composition, the amount of active or peptide in the  
10 topical composition and/or the intended use of the topical composition. The nature and amount of any excipient should not unacceptably alter the benefits of the peptides of this invention.

In an embodiment of the invention the excipient may be a suitable diluent, carrier, binder, lubricant, suspending agent, coating agent, preservative, stabilisers, dyes, vehicle, solubilising agent, base, emollient, emulsifying agent, fragrance, humectant, and/or surfactants.

15 Examples of suitable diluents include, but are not limited to, any diluent disclosed in disclosed in US2014120131 or US2004132667. Examples include ethanol, glycerol and water.

Examples of suitable carriers include, but are not limited to, lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol and any suitable carrier disclosed in US2014120131 or US2004132667.

20 Examples of suitable binders include, but are not limited to, starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol and any suitable binder disclosed in US2014120131 or US2004132667.

25 Examples of suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, and sodium chloride and any suitable lubricant disclosed in US2014120131 or US2004132667.

The carrier may be any suitable carried known in the art or disclosed in US2014120131 or US2004132667. In some embodiments, the carrier may include, but is not limited to, a liquid, such as water, oils or surfactants, including those of petroleum, animal, plant or synthetic  
30 origin, polymer, oil, such as peanut oil, mineral oil, castor oil, soybean oil, alcohol, polysorbates, sorbitan esters, ether sulfates, sulfates, betaines, glycosides, maltosides, fatty

alcohols, nonoxynols, poloxamers, polyoxyethylenes, polyethylene glycols, dextrose, glycerol, or digitonin. It will be understood that the carrier will be dermatologically acceptable. Preferred carriers contain an emulsion such as oil-in-water, water-in-oil, water-in-oil-in-water and oil-in-water-in-silicone emulsions. Emulsions may further contain an emulsifier and/or an anti-foaming agent.

In an embodiment of the invention, the topical composition may further comprise one or more additional ingredients. The topical composition of the invention may be administered consecutively, simultaneously or sequentially with the one or more other additional agents. Such additional ingredients may be those of benefit to include in a topical composition, or of benefit depending on the intended use of the topical composition. The additional ingredient may be active or functional or both.

Examples of such additional ingredients include, but are not limited to, one or more of cleaning agents, conditioning agents, sunscreen, pigment, moisturiser, thickening agents, gelling agents, essential oil, astringents, pigments, anti-caking agent, anti-foaming agent, binders, additives, buffers, chelating agents, external analgesics, film formers or materials, bulking agents, polymers, opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin bleaching and lightening agents, skin conditioning agents, aloe vera, healing agents, soothing agents, smoothing agents, pantothenic acid, treating agents, thickeners, vitamins, colourants, pharmaceuticals, antiseptic agents, antifoaming agents, buffering agents, astringents, polymers, pH adjuster, deodorant or any other dermatologically acceptable carrier or surfactant.

It is to be understood that additional ingredients listed may provide more than one benefit. The classification given herein is for clarity and convenience only and not intended to limit the additional ingredient to that particular application or category listed.

Any additional ingredients should be suitable for application to the skin without undue toxicity, incompatibility and/or allergic reaction.

In some embodiments, the additional ingredient has glucose transport activity or aids glucose transport activity. In some embodiments, the additional ingredient has anti-inflammatory activity or aids anti-inflammatory activity. In some embodiments, the additional ingredient has anti-aging activity or aids anti-aging activity. In some embodiments, the additional ingredient is for keratinous layer health and/or development, skin health and/or development, and/or muscle health, recovery and/or development. The active agent may be a pharmacological

enhancer. Such active agents are known and available on the market. In such cases, the topical composition of the invention may be administered consecutively, simultaneously or sequentially with the one or more other active agents.

In some embodiments, the additional ingredient may be farnesol ([2E, 6E], -3, 7, 11,-trimethyl-  
5 2, 6, 10, dodecatrien-1-ol), phytantriol (3, 7, 11, 15, tetramethylhexadecane-1, 2, 3, -triol),  
desquamation actives, enzymes, enzyme inhibitors, enzyme activators, botanical extracts and  
marine extracts, anti-acne actives, anti-wrinkle or anti atrophy actives, anti-oxidant/radical  
scavengers, chelators, flavonoids, anti-inflammatory agents, anti-cellulite agents, topical  
anaesthetics, tanning actives, skin lightening agents, skin healing agents, bisabolol,  
10 antimicrobial or antifungal active, sunscreen actives, particulate material, conditioning agents,  
structuring agents, thickening agent,

The desquamation active may be any suitable agent that enhances the skin appearance or texture of the skin and is as disclosed in US2014120131 or US2004132667.

Examples of anti-acne actives are as disclosed in US2014120131 or US2004132667 and  
15 include, resorcinol, salicylic acid, erythromycin, zine, sulfur, benzoyl peroxides.

Examples of thickening agents are as disclosed in US2014120131 or US2004132667 and include carboxylic acid polymers, crosslinked polyacrylate polymers, polyacrylamide polymers, polysaccharides.

Examples of conditioning agents are as disclosed in US2014120131 or US2004132667 and  
20 include humectants, moisturiser or skin conditioner.

Examples of structuring agents are as disclosed in US2014120131 or US2004132667 and include any agent that provide rheological characteristics to the composition and contributes to the stability of the composition.

Any suitable antimicrobial or antifungal active may be used and examples are as disclosed in  
25 US2014120131 or US2004132667. Such actives are capable of destroying microbes, preventing growth or action of microbes. Examples include but are not limited to  $\beta$ -lactam drugs, quinolone drugs, tetracycline, erythromycin, streptomycin sulfate, salicylic acid, benzoyl peroxide.

Examples of a particulate material include metallic oxide.

30 Examples of anti-cellulite agents include xanthine agents.

Examples of tanning actives includes 1, 3-dihydroxy-2-propanone and those disclosed in US2014120131 or US2004132667.

Examples of topical anaesthetics include benzocaine, lidocaine and bupivacaine and those disclosed in US2014120131 or US2004132667.

- 5    Examples of skin lightening agents include any agent known in the art such as kojic acid, ascorbic acid and those disclosed in US2014120131 or US2004132667.

Examples of sunscreen actives include any suitable organic or inorganic sunscreen active. Examples include metallic oxides, 2-ethylhexyl-p-methoxycinnamate and those disclosed in US2014120131 or US2004132667.

- 10   Examples of skin healing agents includes panthenoic acid as disclosed in US2014120131 or US2004132667.

Examples of anti-inflammatory agents include any agent that enhances the skin appearance, tone or colour and include but are not limited to corticosteroids, hydrocortisone, non-steroidal agents such as ibuprofen and aspirin and those disclosed in US2014120131 or US2004132667.

- 15   Examples of flavonoids includes flavanones, methoxy flavonones, unsubstituted chalcone and mixtures thereof and those disclosed in US2014120131 or US2004132667.

- Examples of enzymes include lipases, proteases, catalase, super oxide-dismutase, amylase, peroxidase, glucuronidase, ceramidases, hyaluronidases. Examples of enzyme inhibitors include trypsin inhibitors, Bowman Birk inhibitors, chymotrypsin inhibitors, botanical  
20   extracts, flavonoids, quercetin chalcone and those disclosed in US2014120131 or US2004132667 and mixtures thereof. Examples of enzyme activators include coenzyme A, Q10 (ubiquinone), glycyrrhizin, berberine, chrysin and those disclosed in US2014120131 or US2004132667 and mixtures thereof

- Examples of anti-wrinkle or anti atrophy actives include sulfur containing D and L amino acids, particular, N-acyl derivatives such as N-acetyl-L-cysteine, hydroxyl acids, phytic acid, lipoic  
25   acid, lysophosphatidic acid, skin peel agents, vitamin B<sub>3</sub>, retinoids and those disclosed in US2014120131 or US2004132667 and mixtures thereof.

- The anti-oxidant/radical scavenger agent may be any agent that is useful for providing protection against UV radiation or other environmental agents which may cause skin damage  
30   such as those disclosed in US2014120131 or US2004132667. Examples of anti-oxidant/radical

scavengers include ascorbic acid, its salts and derivatives (vitamin C), tocopherol its salts and derivatives (vitamin E), butylated hydroxyl benzoic acids and their salts, peroxides, gallic acids and alkyl esters, sorbic acid, lipoic acid, amines, lysine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide  
5     dismutase, silymarin, tea extracts and mixtures thereof.

Examples of chelators include EDTA, NTA, hydroxamic acids, phytic acid, lactoferrin and those disclosed in US2014120131 or US2004132667 and mixtures thereof. A chelator means an agent capable of removing a metal ion by forming a complex so that the metal ion cannot participate in or catalyse chemical reactions. A chelator is useful for protection against UV  
10    radiation or other environmental agents that can cause skin damage.

It will be appreciated that a plurality of additional ingredients may be added. The amount of the additional ingredient may be from about 0.001% to about 50% weight of the composition, preferably, about 0.01% to about 20%, preferably about 0.1% to about 10%, about 0.5% to about 10%, about 1% to about 5%, preferably 2% weight of the composition. The amount of  
15    additional ingredient included will depend on numerous factors, including the type of additional ingredient used, the nature of the additional ingredient, the component(s) of the topical composition, the amount of active or peptide in the topical composition and/or the intended use of the topical composition. The nature and amount of any additional ingredient should not unacceptably alter the benefits of the peptides of this invention.

20    The topical composition may be alcohol free.

In some embodiments of the invention, the composition further comprises one or more additional active agents, in addition to the peptide of the invention (also known as the active of the composition). In addition, or alternatively, the composition may be administered with one or more other additional active agents. Typical said additional active agent is present in  
25    trace amounts only. In some embodiments, there may be no additional active agent present in the composition. The amount of additional active agent included will depend on numerous factors, including the type of additional active agent used, the nature of the additional active agent, the component(s) of the topical composition, the amount of active or peptide in the topical composition and/or the intended use of the topical composition. The nature and amount  
30    of any additional active agent should not unacceptably alter the benefits of the peptides of this invention.

It is to be understood that an ingredient that is considered to be an “active” ingredient in one product may be a “functional” or “excipient” ingredient in another and vice versa. It will also be appreciated that some ingredients play a dual role as both an active ingredient and as a functional or excipient ingredient.

- 5 Examples of the additional active agents include glucose transport promoting drugs, skin supplement, agent for treatment and/or care of the skin, anti-inflammatory agent, an anti-aging agent, a cellular growth promoting agent and pharmacological enhancers. Such agents are well known in the art and it will be appreciated that any suitable additional active agent may be used. Additional active agents for treatment and/or care of the skin may include collagen  
10 synthesis agents, retinoids, exfoliating agents, anti-cellulite agents, elastase inhibiting agents, melanin synthesis stimulating or inhibiting agents, self-tanning agents, antiaging agents, antimicrobial agents, antifungal agents, fungistatic agents, bactericidal agents, and healing agents. Active agents also include anti-inflammatory agents.

- Any additional active agent should be suitable for application to the skin without undue  
15 toxicity, incompatibility and/or allergic reaction.

It will be understood that the classification given herein is for clarity and convenience only and not intended to limit the additional ingredient, excipient, or active to that particular application or category listed.

- In a particularly preferred embodiment, the methods and uses of the invention involve  
20 administration of a peptide or composition of the invention in combination with one or more other active agents, for example, existing growth promoting drugs or pharmacological enhancers available on the market. In such cases, the compounds of the invention may be administered consecutively, simultaneously or sequentially with the one or more other active agents.

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- The effect of the current invention is accomplished by topical application or administration of the topical composition of the invention described herein to a person, animal or a patient in need of treatment or care. Topical delivery preferably means delivery to a keratinous layer such as the skin, hair and/or nails, but can also mean delivery to a body lumen lined with epithelial  
30 cells, for example the lungs or airways, the gastrointestinal tract, the buccal cavity. The effect may be confined to the surface of the skin or may be within the skin or a combination of both.

The topical composition of the invention is administered in a cosmetically or pharmaceutically effective amount. In other words, in an amount that is non-toxic but sufficient amount to provide the desired effect. It will be appreciated that a person skilled in the art would be capable of determining an appropriate dose of the topical compositions of the invention to administer without undue experimentation. Alternatively, a physician will determine the actual dose that is most suitable for a patient depending on the particular condition, disease or disorder to be treated or cared for and the age, body weight and/or health of the person. It will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For example, the composition may be administered at a dose of from 0.01 to 50 mg/kg body weight, such as from 0.1 to 30 mg/kg, more preferably from 0.1 to 20 mg/kg body weight, more preferably from 0.1 to 10 mg/kg body weight, preferably 0.1 to 5mg/kg body weight. In an exemplary embodiment, one or more doses of 10 to 300 mg/day or more preferably, 10 to 150 mg/day, will be administered to the patient. The amount and the frequency is as best suited to the purpose. The frequency of application or administration can vary greatly, depending on the needs of each subject, with a recommendation of an application or administration range from once a month to ten times a day, preferably from once a week to four times a day, more preferably from three times a week to three times a day, even more preferably once or twice a day.

In preferred embodiments, repeated use of the topical composition is provided.

The topical composition may be applied by, but not limited to, rubbing, or massaging into the keratinous tissue, skin or area of the body to be treated or cared for. In some embodiments, the composition is left on or not removed from the area of the body. In other embodiments, the composition is removed after a period of time, such as, but not limited to, from about 2 minutes to 60 minutes, from about 5 minutes to about 30 minutes, preferably from about 10 minutes to about 20 minutes. The composition may be removed immediately after application. In some embodiments of the current invention, the composition of the invention may be applied to an area to be treated by means to achieve a greater penetration of the composition and/or peptide of the invention, such as, but not limited to, iontophoresis, sonophoresis, electroporation, microelectric patches, mechanical pressure, osmotic pressure gradient, occlusive cure,

microinjections or needle-free injections by means of pressure, such as injections by oxygen pressure, or any combination thereof.

The peptides of the invention are used in the topical cosmetic or pharmaceutical composition of this invention at cosmetically or pharmaceutically effective concentrations to achieve the desired effect; in a preferred form with regards to the total weight of the composition, between 0.00000001% (in weight) and 20% (in weight); preferably between 0.000001% (in weight) and 15% (in weight), more preferably between 0.0001% (in weight) and 10% (in weight) and even more preferably between 0.0001% (in weight) and 5% (in weight). Ideally, the peptides of the present invention are preferably used from about 0.00001% w/w to about 0.5% w/w, and more preferably from 0.00005 w/w to about 0.05 w/w, and most preferably from about 0.0001 w/w to about 0.01 w/w of the composition. Ideally, the peptides of the present invention are preferably used from about 0.0001% w/w to about 0.004% w/w of the composition.

In some embodiments of the current invention, the composition may be delivered via any one of liposomes, mixed liposomes, oleosomes, niosomes, ethosomes, millicapsules, capsules, macrocapsules, nanocapsules, nanostructured lipid carriers, sponges, cyclodextrins, vesicles, micelles, mixed micelles of surfactants, surfactant-phospholipid mixed micelles, millispheres, spheres, lipospheres, particles, nanospheres, nanoparticles, milliparticles, solid nanoparticiles as well as microemulsions including water-in-oil microemulsions with an internal structure of reverse micelle and nanoemulsions microspheres, microparticles.

A variety of methods are available for preparing liposomes. See, e.g., Szoka et al., *Ann. Rev. Biophys. Bioeng.* 9:467 (1980), U.S. Pat. Nos. 4,186,183, 4,217,344, 4,235,871, 4,261,975, 4,485,054, 4,501,728, 4,774,085, 4,837,028, 4,235,871, 4,261,975, 4,485,054, 4,501,728, 4,774,085, 4,837,028, 4,946,787, PCT Publication No. WO 91/17424, Deamer & Bangham, *Biochim. Biophys. Acta* 443:629-634 (1976); Fraley, et al., *PNAS* 76:3348-3352 (1979); Hope et al., *Biochim. Biophys. Acta* 812:55-65 (1985); Mayer et al., *Biochim. Biophys. Acta* 858:161-168 (1986); Williams et al., *PNAS* 85:242-246 (1988); Liposomes (Ostro (ed.), 1983, Chapter 1); Hope et al., *Chem. Phys. Lip.* 40:89 (1986); Gregoriadis, *Liposome Technology* (1984) and Lasic, *Liposomes: from Physics to Applications* (1993)). Suitable methods include, for example, sonication, extrusion, high pressure/homogenization, microfluidization, detergent dialysis, calcium-induced fusion of small liposome vehicles and ether fusion methods, all of which are well known in the art.

These delivery systems may be adapted to achieve a greater penetration of the compound and/or peptides of the invention. This may improve pharmacokinetic and pharmacodynamics properties. The delivery system may be a sustained release system wherein the compound or peptide of the invention is gradually released during a period of time and preferably with a constant release rate over a period of time. The delivery systems are prepared by methods known in the art. The amount of peptide contained in the sustained release system will depend on where the composition is to be delivered and the duration of the release as well as the type of the condition, disease and/or disorder to be treated or cared for.

The topical composition of the invention may be for human or animal usage in human and veterinary medicine.

The topical composition of the invention may be used for pharmaceutical, personal care and/or cosmetic uses.

The composition can be used to treat or care for any disease, disorder or condition of the skin, including but not limited to, psoriasis, dermatitis, allergic dermatitis, eczema, spongiosis, edema, skin cancer, ulcers, acne, scars, cellulitis, elastosis, keratosis, rosacea, varicose veins, inflammatory disorders.

The topical composition may be used to for treating or caring for visible signs of aging including but not limited to wrinkles, stretch marks and dark circles, dryness, fine lines, age spots, red blotches, sagging skin, and conditions caused by sun exposure including sunburn, stress, pollution and/diet. The topical composition may also be used for delaying, slowing or inhibiting the skins or the onset of aging. The composition may be administered by a medical device, such as a plaster or a patch as described herein.

The topical composition may be used to treat or care for a wound in a mammal. In another embodiment, the topical composition is for use in the treatment or prevention of a disease or condition characterised by damaged epithelial cells or tissue, and/or damaged dermal or epithelial cells or tissue. The disease may be but is not limited to cancer and trauma.

The topical composition may be used to treat or care for any muscle condition, to improve, muscle status in a mammal, to promote recovery of muscle, typically following exercise, to maintain or restore muscle health (for example lean tissue mass) in a mammal, to enhance physical performance, in treatment or prevention of a disease or condition characterised by lethargy or low energy levels.

The topical composition may be used to promote growth of a tissue, promote growth of epithelial tissue, promote growth of skin, promote growth of an organ, promote growth of an organism. The skin can have a normal pathology and/or an abnormal pathology.

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The topical composition may also be used to treat or care for any inflammatory disorder.

In one embodiment the inflammatory disorder is an inflammatory disorder of the joints. In one embodiment the inflammatory disorder is an inflammatory disorder of the cardiovascular system. In one embodiment the inflammatory disorder is an autoimmune disease. In one embodiment the inflammatory disorder is a lung and airway inflammatory disorder. In one embodiment the inflammatory disorder is an intestinal inflammatory disorder. In one embodiment the inflammatory disorder is dermatitis. In one embodiment the inflammatory disorder is acne vulgaris. In one embodiment the inflammatory disorder is psoriasis. In one embodiment the inflammatory disorder is rheumatoid arthritis. In one embodiment the inflammatory disorder is cardiovascular disease. In one embodiment the inflammatory disorder is atherosclerosis. In one embodiment the inflammatory disorder is Type I diabetes.

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In one embodiment the inflammatory disorder is Graves disease. In one embodiment the inflammatory disorder is Guillain-Barre disease. In one embodiment the inflammatory disorder is Lupus. In one embodiment the inflammatory disorder is Psoriatic arthritis. In one embodiment the inflammatory disorder is Ulcerative colitis. In one embodiment the inflammatory disorder is asthma. In one embodiment the inflammatory disorder is cystic fibrosis. In one embodiment the inflammatory disorder is COPD. In one embodiment the inflammatory disorder is emphysema. In one embodiment the inflammatory disorder is acute respiratory distress syndrome. In one embodiment the inflammatory disorder is colitis. In one embodiment the inflammatory disorder is inflammatory bowel disease.

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The topical composition may also be used to treat or care for a metabolic disorder.

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In one embodiment, the metabolic disorder is pre-diabetes. In one embodiment, the metabolic disorder is diabetes. In one embodiment, the metabolic disorder is Type-1 diabetes. In one embodiment, the metabolic disorder is Type-2 diabetes. In one embodiment, the metabolic disorder is metabolic syndrome. In one embodiment, the metabolic disorder is obesity. In one

embodiment, the metabolic disorder is diabetic dyslipidemia. In one embodiment, the metabolic disorder is hyperlipidemia. In one embodiment, the metabolic disorder is hypertension. In one embodiment, the metabolic disorder is hypertriglyceridemia. In one embodiment, the metabolic disorder is hyperfattyacidemia. In one embodiment, the metabolic disorder is hypercholerterolemia. In one embodiment, the metabolic disorder is hyperinsulinemia. In one embodiment, the metabolic disorder is MODY

In an embodiment of the invention the composition is for use in maintaining or restoring gut health.

10 In an embodiment of the invention the composition is for use in treatment or prevention of pain.

The topical composition has a used as a person care product, a supplement, a cosmetic, a pharmaceutical product.

15

A method of treating, preventing or caring for any one of the diseases, disorders or conditions described herein is also provided, said method comprising a step of administering the topical composition of the invention. The composition may be administered to the skin, hair, the nails. The composition may be administered in any dose or frequency as disclosed herein by any method of topical application.

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In one embodiment the topical composition is a cosmetic composition. In one embodiment the topical composition is a pharmaceutical composition. It will be appreciated that the composition may have a dual function and be both a cosmetic and pharmaceutical composition.

25 It will be appreciated that the topical composition may be a therapeutic composition or may be a non-therapeutic composition. The topical composition may have a dual role.

In an embodiment of the invention the peptide may be a modified peptide. The term "modified peptide" is used interchangeably with the term derivative of the peptide. The modified peptide includes but is not limited to a peptide which has been substituted with one or more groups as defined herein.

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In one embodiment, the modification may be any modification that provides the peptides and or the composition of the invention with an increased ability to penetrate a cell. In one

embodiment, the modification may be any modification that increases the half-life of the composition or peptides of the invention. In one embodiment, the modification may be any modification that increases activity of the composition or peptides of the invention. In one embodiment, the modification may be any modification that increases selectivity of the composition or peptides of the invention.

In one embodiment, the group is a protecting group. The protecting group may be an N-terminal protecting group, a C-terminal protecting group or a side-chain protecting group. The peptide may have one or more of these protecting groups.

The person skilled in the art is aware of suitable techniques to react amino acids with these protecting groups. These groups can be added by preparation methods known in the art, for example the methods as outlined in paragraphs [0104] to [0107] of US2014120141. The groups may remain on the peptide or may be removed. The protecting group may be added during synthesis.

In an embodiment of the invention the peptides may be substituted with a group selected from one or more straight chain or branched chain, long or short chain, saturated, or unsaturated, substituted with a hydroxyl, amino, amino acyl, sulfate or sulphide group or unsubstituted having from 1 to 29 carbon atoms. N-acyl derivatives include acyl groups derived from acetic acid, capric acid, lauric acid, myristic acid, octanoic acid, palmitic acid, stearic acid, behenic acid, linoleic acid, linolenic acid, lipoic acid, oleic acid, isosteric acid, elaidic acid, 2-ethylhexanoic acid, coconut oil fatty acid, tallow fatty acid, hardened tallow fatty acid, palm kernel fatty acid, lanolin fatty acid or similar acids. These may be substituted or unsubstituted. When substituted they are preferably substituted with hydroxyl, or sulphur containing groups such as but not limited to  $\text{SO}_3\text{H}$ ,  $\text{SH}$ , or  $\text{S-S}$ .

In an embodiment of the current invention, the peptide is  $\text{R}_1\text{-X- R}_2$ .

$\text{R}_1$  and/or  $\text{R}_2$  groups respectively bound to the amino-terminal (N-terminal) and carboxyl-terminal (C-terminal) of the peptide sequence.

In one embodiment, the peptide is  $\text{R}_1\text{-X}$ . Alternatively, the peptide is  $\text{X- R}_2$ .

Preferably,  $R_1$  is H,  $C_{1-4}$  alkyl, acetyl, benzoyl or trifluoroacetyl;  
X is the peptide of the invention;

$R_2$  is OH or  $NH_2$ .

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In an embodiment,  $R_1$  is selected from the group formed by H, a non-cyclic substituted or unsubstituted aliphatic group, substituted or unsubstituted alicyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, Tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc) and  $R_5-CO-$ , wherein  $R_5$  is selected from the group formed by H, a non-cyclic substituted or unsubstituted aliphatic group, substituted or unsubstituted alicyclyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heterocyclyl and substituted or unsubstituted heteroarylalkyl;  $R_2$  is selected from the group formed by  $-NR_3R_4$ ,  $-OR_3$  and  $-SR_3$ , wherein  $R_3$  and  $R_4$  are independently selected from the group formed by H, a non-cyclic substituted or unsubstituted aliphatic group, substituted or unsubstituted alicyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted aralkyl; and with the condition that  $R_1$  and  $R_2$  are not  $\alpha$ -amino acids.

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In accordance with another preferred embodiment,  $R_2$  is  $-NR_3R_4$ ,  $-OR_3$  or  $-SR_3$  wherein  $R_3$  and  $R_4$  are independently selected from the group formed by H, substituted or unsubstituted  $C_{1-C_{24}}$  alkyl, substituted or unsubstituted  $C_2-C_{24}$  alkenyl, Tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), substituted or unsubstituted  $C_2-C_{24}$  alkynyl, substituted or unsubstituted  $C_3-C_{24}$  cycloalkyl, substituted or unsubstituted  $C_5-C_{24}$  cycloalkenyl, substituted or unsubstituted  $C_8-C_{24}$  cycloalkynyl, substituted or unsubstituted  $C_6-C_{30}$  aryl, substituted or unsubstituted  $C_7-C_{24}$  aralkyl, substituted or unsubstituted heterocyclyl ring of 3-10 members, and substituted or unsubstituted heteroarylalkyl of 2 to 24 carbon atoms and 1 to 3 atoms other than carbon wherein the alkyl chain is of 1 to 6 carbon atoms. Optionally,  $R_3$  and  $R_4$  can be bound by a saturated or unsaturated carbon-carbon bond, forming a cycle with the nitrogen atom. More preferably  $R_2$  is  $-NR_3R_4$  or  $-OR_3$ , wherein  $R_3$  and  $R_4$  are independently selected from the group formed by H, substituted or unsubstituted  $C_{1-C_{24}}$  alkyl, substituted or unsubstituted  $C_2-C_{24}$  alkenyl, substituted or unsubstituted  $C_2-C_{24}$  alkynyl, substituted or unsubstituted  $C_3-C_{10}$  cycloalkyl, substituted or unsubstituted  $C_6-C_{15}$  aryl and

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substituted or unsubstituted heterocyclyl of 3-10 members, substituted or unsubstituted heteroarylalkyl with a ring of 3 to 10 members and an alkyl chain of 1 to 6 carbon atoms. More preferably  $R_3$  and  $R_4$  are selected from the group formed by H, methyl, ethyl, hexyl, dodecyl, or hexadecyl. Even more preferably  $R_3$  is H and  $R_4$  is selected from the group formed by H, methyl, ethyl, hexyl, dodecyl, or hexadecyl. In accordance with an even more preferred embodiment,  $R_2$  is selected from -OH and -NH<sub>2</sub>.

In accordance with another embodiment of this invention  $R_1$  is selected from the group formed by H, acetyl, lauroyl, myristoyl or palmitoyl, and  $R_2$  is -NR<sub>3</sub>R<sub>4</sub> or -OR<sub>3</sub> wherein  $R_3$  and  $R_4$  are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, preferably  $R_2$  is -OH or -NH<sub>2</sub>. More preferably,  $R_1$  is acetyl or palmitoyl and  $R_2$  is -NH<sub>2</sub>.

In a preferred embodiment, the acyl group is bound to the N-terminal end of at least one amino acid of the peptide.

In an embodiment of the invention, the peptide is modified to comprise a side chain protecting group. The side chain protecting group may be one or more of the group comprising benzyl or benzyl based groups, t-butyl-based groups, benzyloxy-carbonyl (Z) group, and allyloxycarbonyl (alloc) protecting group. The side chain protecting group may be derived from an achiral amino acid such as achiral glycine. The use of an achiral amino acid helps to stabilise the resultant peptide and also facilitate the facile synthesis route of the present invention. Preferably, the peptide further comprises a modified C-terminus, preferably an amidated C-terminus. The achiral residue may be alpha-aminoisobutyric acid (methylalaine). It will be appreciated that the specific side chain protecting groups used will depend on the sequence of the peptide and the type of N-terminal protecting group used.

In one embodiment of the invention the peptide is conjugated, linked or fused to one or more polyethylene glycol polymers or other compounds, such as molecular weight increasing compounds. The molecular weight increasing compound is any compound that will increase the molecular weight, typically by 10% to 90%, or 20% to 50% of the resulting conjugate and may have a molecular weight of between 200 and 20,000, preferably between 500 and 10,000. The molecular weight increasing compound may be PEG, any water-soluble (amphiphilic or hydrophilic) polymer moiety, homo or co-polymers of PEG, a monomethyl-substituted polymer of PEG (mPEG) and polyoxyethylene glycerol (POG), polyamino acids such as poly-

lysine, poly-glutamic acid, poly-aspartic acid, particular those of L conformation, pharmacologically inactive proteins such as albumin, gelatin, a fatty acid, polysaccharide, a lipid amino acid and dextran. The polymer moiety may be straight chained or branched and it may have a molecular weight of 500 to 40000Da, 5000 to 10000 Da, 10000 to 5000, Da. The compound may be any suitable cell penetrating compound, such as tat peptide, penetratin, pep-1. The compound may be an antibody molecule. The compound may be a lipophilic moiety or a polymeric moiety.

The lipophilic substituent and polymeric substituents are known in the art. The lipophilic substituent includes an acyl group, a sulphonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulphonyl ester, thioester, amide or sulphonamide. The lipophilic moiety may include a hydrocarbon chain having 4 to 30 C atoms, preferably between 8 and 12 C atoms. It may be linear or branched, saturated or unsaturated. The hydrocarbon chain may be further substituted. It may be cycloalkane or heterocycloalkane.

The peptide may be modified at the N-terminal, C-terminal or both. The polymer or compound is preferably linked to an amino, carboxyl or thio group and may be linked by N-termini or C-termini of side chains of any amino acid residue. The polymer or compound may be conjugated to the side chain of any suitable residue.

The polymer or compound may be conjugated via a spacer. The spacer may be a natural or unnatural amino acid, succinic acid, lysyl, glutamyl, asparagyl, glycyl, beta-alanyl, gamma-amino butanoyl.

The polymer or compound may be conjugated via an ester, a sulphonyl ester, a thioester, an amide, a carbamate, a urea, a sulphonamide.

A person skilled in the art is aware of suitable means to prepare the described conjugate.

Compositions may be formulated in unit dosage form, i.e., in the form of discrete portions containing a unit dose, or a multiple or sub-unit of a unit dose.

In a particularly preferred embodiment, the methods and uses of the invention involve administration of a peptide or composition of the invention in combination with one or more other active agents available on the market. In such cases, the compounds of the invention may be administered consecutively, simultaneously or sequentially with the one or more other active agents

**EXAMPLES****EXAMPLE 1 to 9: Formulations**

5 In a preferred embodiment, the composition is formulated as a cosmetic as defined herein. In one embodiment the cosmetic is an emulsion or cream or a rub, such as a muscle rub.

In an embodiment the cream comprises an excipient or diluent, a suspending agent, a preservative and an amount of at least one peptide of the invention.

In an embodiment the cream comprises an alcohol, a carbomer, a sorbate, water and at least one peptide of the invention.

10 Preferably the alcohol is butylene glycol (1,3-butanediol). The alcohol may be present in an amount of between 1 and 10 % of the composition, preferably between 2 and 6%, preferably 4%. The sorbate may be polysorbate-20. The sorbate may be present in an amount of between .01 to 1% of the composition, preferably between .05 and .5%, preferably 0.10%. Water is present in an amount of between 10% and 90%, preferably 30% to 75%. The carbomer may be  
15 present in an amount of from 0.05% to 1%, preferably, 0.1% to 0.5%, preferably, 0.15%. The carbomer may be Ultrez 10.

The peptide of the invention may be present in an amount of from 0.5% to 10%, preferably, 1% to 5%, preferably 3%.

20 The composition may further comprise one or more of sugar alcohol such as glycerine, parabens, silicon, such as cyclohexasiloxane, a fatty alcohol or phosphoric acid or a mixture of fatty alcohol and phosphoric acid, such as cetearyl alcohol, dicetyl phosphate and Cereth 10 phosphate or combinations thereof, a polyoxyethylene stearyl ethers, such as Steareth 2 and 10, and a fragrance.

An exemplary rub or emulsion is follows in Example 1.

| Ingredient                                                 | Exemplary (w/w)% |
|------------------------------------------------------------|------------------|
| <b>Phase A</b>                                             |                  |
| Water                                                      | 70.95            |
| Carbomer                                                   | 0.15             |
| <b>Phase B</b>                                             |                  |
| Glycerin                                                   | 3.5              |
| <b>Phase C</b>                                             |                  |
| Steareth 2                                                 | 0.40             |
| Cetearyl alcohol dicetyl phosphate and Ceteth 10 phosphate | 4                |
| Cyclohexsiloxane                                           | 2                |
| Dioctyl succinate                                          | 7                |
| Steareth 10                                                | 1.2              |
| Mixed parabens                                             | 0.30             |
| <b>Phase D</b>                                             |                  |
| Sorbate                                                    | 0.10             |
| <b>Phase E</b>                                             |                  |
| Water                                                      | 2.50             |
| Sodium hydroxide                                           | 0.30             |
| <b>Phase F</b>                                             |                  |
| Fragrance                                                  | 0.10             |
| <b>Phase G</b>                                             |                  |
| Peptide(s) of the invention                                | 3                |

The resulting emulsion is suited as a rub. In addition, the rub is suitable for fragile aged skin.

- 5 The emulsion is suitable for improving fine lines, wrinkles, dryness reducing redness and irritation.

Percentages are examples only and it will be appreciated that any suitable percentage may be used depending on the use.

- 10 The emulsion is prepared in the following way: Phase A: disperse Ultrez 10 (carbomer) in water and let it swell for 20 minutes, then add phase B; heat to 75°C. Heat Phase C separately to 75°C. Mix the two phases under stirring, homogenise, add Phase D, neutralise with Phase E, cool until reaching 30°C, then add Phase F and Phase G; adjust to pH to 6 with ~NaOH. It will be understood that this is an example only and any suitable method known in the art may be used.

In a further embodiment, the composition may comprise one or more of water, a carbomer, a sorbate such as potassium sorbate, a sugar alcohol, such as glycerine, an alcohol such as 2-(2-Ethoxyethoxy)ethanol, a polyoxyethylene stearyl ethers, such as Steareth 2, a fatty alcohol or phosphoric acid or a mixture of fatty alcohol and phosphoric acid, such as cetearyl alcohol, dicetyl phosphate and Cereth 10 phosphate or combinations thereof, a siloxane, such as cyclomethicone, a Caprylic Capric Triglycerides, a sorbitan Stearate, Parabens, Sodium hydroxide, an active agent such as a skin lightening agent, such as a mixture of lycerin (and) Butylene Glycol (and) Arcostaphylus Uva Ursi Leaf Extract (and) Mitracarpus Scaber Extract (ETIOLINE®), or a muscle health agent and peptide of the invention.

10 The following composition in Example 2 is an example of an emulsion or cream or a rub.

| Ingredient                                                                        | Exemplary (w/w)% |
|-----------------------------------------------------------------------------------|------------------|
| Water Deionised                                                                   | qs 100           |
| Carbomer                                                                          | 0.10             |
| Potassium Sorbate                                                                 | 0.10             |
| Transcutol                                                                        | 3.00             |
| Glycerin                                                                          | 8.00             |
| Volpo S2 [Steareth 2]                                                             | 0.60             |
| Crodafos CES [Cetearyl Alcohol (and) Dicetyl Phosphate (and) Ceteth 10 Phosphate] | 4.00             |
| DC 344 [Cyclomethicone]                                                           | 2.00             |
| Crodamol GTCC [Caprylic/Capric triglyceride]                                      | 10.00            |
| Crill 3 [Sorbitan Stearate]                                                       | 1.60             |
| Mixed Parabens                                                                    | 0.30             |
| Sodium Hydroxide 30%                                                              | 0.35             |
| Water Deionised                                                                   | 3.50             |
| Peptide                                                                           | 3.00             |
| Active                                                                            | 3.00             |
|                                                                                   | .                |

The active can be ETIOLINE (R) [Glycerine (and) Etylene Glycol (and) Arcostaphylus uva leaf extract and Mitracarpus Scaber extract] ETIOLINE ® is a skin lightening ingredient sold by SEDERMA (WO 98/05299 of Nov. 19, 1996).

It will be understood that ETIOLINE can be replaced with any active agent, such as an agent that aids muscle health, development or recovery.

This formulation can be made according to the procedures generally outlined in Example 1.

The composition may be an emulsion or cream or rub comprising one or more of water, a carbomer, such as Ultrez 10, a sugar alcohol, such as glycerine, an alcohol such as phenova (phenoxyethanol and mixed parabens), a fatty acid ester such as ethylhexyl palmitate, a fatty alcohol such as cetearyl alcohol, a lactic acid ester such as myristyl lactate, a sorbate such as polysorbate 20 and/or potassium sorbate, a polymeric emulsifier such as Acrylate (C10 -30 alkyl acrylate) and a cross polymer, a siloxane, such as cyclomethicone, sodium hydroxide, at least one active agent, such as a muscle health agent or an agent for the treatment of stretch marks, such as siegesbeckia Orientalis extract (Darutoside) and a peptide.

The following composition in Example 3 is an example of an emulsion or cream. In an embodiment, the emulsion or cream is an anti-stretch mark cream.

| Ingredient                                                        | Exemplary (w/w)% |
|-------------------------------------------------------------------|------------------|
| <b>Part A</b>                                                     |                  |
| Water Deionised                                                   | qs 100           |
| Ultrez 10 [Carbomer]                                              | 0.40             |
| <b>Part B</b>                                                     |                  |
| Glycerin                                                          | 5.00             |
| Phenova [Phenoxyethanol (and) Mixed Parabens]                     | 0.80             |
| <b>Part C</b>                                                     |                  |
| Crodamol OP [Ethylhexyl Palmitate]                                |                  |
| Crodacol CS90 [Cetearyl alcohol]                                  | 4.00             |
| Crodamol ML [Myristyl Lactate]                                    | 0.50             |
| Crillet 1 [Polysorbate 20]                                        | 0.30             |
|                                                                   | 1.00             |
| <b>Part D</b>                                                     |                  |
| Pemulen TR2 [Acrylates/C 10-30 Alkyl Acrylate (and) Crosspolymer] | 0.20             |
| DC 345 [Cyclomethicone]                                           | 2.00             |
| <b>Part E</b>                                                     |                  |
| Potassium Sorbate                                                 | 0.10             |
| <b>Part F</b>                                                     |                  |
| Water                                                             |                  |
| Sodium Hydroxide 38%                                              | 6.00             |
|                                                                   | 0.60             |
| <b>Part G</b>                                                     |                  |
| peptide                                                           |                  |
| Active                                                            | 3.00             |
|                                                                   | 2.00             |

The active can be Darutoside (*Siegesbeckia Orientalis* Extract). Darutoside is a molecule sold by SEDERMA for the treatment of stretch marks. It will be understood Darutoside can be replaced with any active agent, such as any agent that aids muscle health, development or recovery.

This emulsion or rub is prepared in the following way: Phase A disperse Ultrez 10 (carbomer) in water and let it swell for 20 minutes, then add phase B; heat to 75°C. Heat Phase C separately to 75°C. Mix the two phases under stirring, homogenise, add Phase D, neutralise with Phase E, cool until reaching 30°C., then add Phase F and Phase G, adjust pH to -6 with NaOH.

In an embodiment of the invention the composition may be an emulsion, cream or a gel, preferably a gel, comprising one or more of water, a carbomer, such as Ultrez 10, a sugar alcohol, such as glycerine, an alcohol such as phenova (phenoxyethanol and mixed parabens), a sorbate such as polysorbate 20 and/or potassium sorbate, a polymeric emulsifier such as Acrylate (C10 -30 alkyl acrylate), a siloxane, such as cyclomethicone, sodium hydroxide, a peptide and at least one agent such as an agent for muscle health, recovery or development, or a suitable moisturising agent, such as an agent comprising *Imperata Cylindrica* (root) extract, water, glycerine, PEG-8, and carbomer (MOIST 24). In an embodiment, the gel is a moisturising gel.

The following composition in Example 4 is an example of a gel. In an embodiment, the gel is a moisturising gel.

| Ingredient                                                                                  | Exemplary (w/w)% |
|---------------------------------------------------------------------------------------------|------------------|
| <b>Part A</b>                                                                               |                  |
| Ultrez 10 [Carbomer]                                                                        | 0.20             |
| Water Deionised                                                                             | qs 100           |
| <b>Part B</b>                                                                               |                  |
| Glycerin                                                                                    | 3.00             |
| Phenova [Phenoxyethanol (and) Mixed Parabens]                                               | 0.80             |
| <b>Part C</b>                                                                               |                  |
| Cirillet 1 [Polysorbate 20]                                                                 | 0.50             |
| <b>Part D</b>                                                                               |                  |
| Potassium Sorbate                                                                           | 0.10             |
| <b>Part E</b>                                                                               |                  |
| Pemulen TR1 [Acrylates/C10-30 Alkyl<br>Acrylate Crosspolymer]                               | 0.20             |
| DC 345 [Cyclomethicone]                                                                     | 3.00             |
|                                                                                             | 2.00             |
| <b>Part F</b>                                                                               |                  |
| Water                                                                                       | 4.00             |
| Sodium Hydroxide 38%                                                                        | 0.40             |
| <b>Part G</b>                                                                               |                  |
| Peptide<br>Active                                                                           | 3.00             |
| MOIST-24 is a moisturising plant extract sold by<br>SEDERMA (WO 01/62218 of Aug. 30, 2001). | 5.00             |

This formulation can be made according to the procedures generally outlined in Example 3

The active can be MOIST-24 (R) [Imperata Cylindrica (root) Extract (and) water (and) Glycerin (and) PEG-8 (and) Carbomer] . It will be understood that any agent can be used to replace MOIST-24. For example, any agent that aids muscle health, development or recovery.

In an embodiment of the invention the composition may be an emulsion, cream or rub comprising one or more of water, a carbomer, such as Ultrez 10, a sorbate such as polysorbate 20, polysorbate 60 and/or potassium sorbate, an alcohol such as phenova (phenoxyethanol and mixed parabens), butylene glycol (1,3-butanediol), lanolin alcohol, and/or cetearyl alcohol, sorbitan stearate, Polydimethylsiloxane such as dimethicone, an isotridetyl isononanoate, a caprylic/capric triglyceride, a cetyl ester, sodium hydroxide, water, an agent for muscle health, recovery and/or development, or an anti-aging agent, such as an agent comprising butylene

glycol, water, laureth-3, hydroxyethylcellulose and acetyl-dipeptide-1-cetylester (CALMOSENSINE®).

The following composition in Example 5 is an example of a cream or a rub.

| Ingredient                                                  | Exemplary (w/w)% |
|-------------------------------------------------------------|------------------|
| <u>Part A</u>                                               |                  |
| Water Deionised                                             | qs 100           |
| Ultrez 10 [Carbomer]                                        | 0.20             |
| <u>Part B</u>                                               |                  |
| Potassium Sorbate                                           | 0.10             |
| <u>Part C</u>                                               |                  |
| Butylene Glycol                                             | 2.00             |
| Phenova [Phenoxyethanol (and) Mixed Parabens]               | 0.80             |
| <u>Part D</u>                                               |                  |
| Crill 3 [Sorbitan Stearate]                                 | 1.00             |
| Crillet 3 [Polysorbate 60]                                  | 2.50             |
| DC 200 [Dimethicone]                                        | 2.50             |
| Crodamol TN [Isotridetyl Isononanoate]                      | 5.00             |
| Crodamol GTCC [Caprylic/Capric Triglyceride]                | 5.00             |
| Crodamol SS [Cetyl Esters]                                  | 1.00             |
| Super Hartolan [Lanolin Alcohol]                            | 0.50             |
| Super Sterol Ester [C10-C30 Cholesterol/ Lanosterol esters] | 0.30             |
| Crodacol CS90 [Cetearyl Alcohol]                            | 3.00             |
| <u>Part E</u>                                               |                  |
| Water Deionised                                             | 2.50             |
| Sodium Hydroxide 38%                                        | 0.25             |
| <u>Part F</u>                                               |                  |
| peptide                                                     | 3.00             |
| Active agent                                                | 4.00             |

5 This formulation can be made according to the procedures generally outlined in Example 3.

The active can be CALMOSENSINE (R) [Butylene Glycol (and) water (and) Laureth-3 (and)Hydroxyethylcellulose (and) Acetyl-Dipeptide-1-cetylester] Calmosensine(R) is an analgesic peptide offered by SEDERMA (WO 98/07744 of Feb. 26, 1998). It will be understood that any agent can be used to replace CALMOSENSINE. For example, any agent

10 that aids muscle health, development or recovery.

In an embodiment of the invention the composition may be an emulsion, cream or rub comprising one or more of water, a carbomer, such as Ultrez 10, a sugar alcohol, such as

- glycerine, a sorbate such as potassium sorbate, a steareth such as Steareth 10, a fatty alcohol or phosphoric acid or a mixture of fatty alcohol and phosphoric acid, such as cetearyl alcohol, dicetyl phosphate and Cereth 10 phosphate or combinations thereof, diethylhexyl succinate, mixed parabens, Sorbitan Stearate, Sodium Hydroxide, water, a peptide, and an active agent,
- 5 such as an agent for muscle health, recovery and/or development or an agent for mature skin, such as one comprising Trifolium Pratense(Clover) Flower Extract (and) Glycerin (and) Butylene Glycol (and) Lecithin (TEROCARE®).

The following composition in Example 6 is an example of a cream or a rub.

| Ingredient                                         | Exemplary (w/w)% |
|----------------------------------------------------|------------------|
| <u>Part A</u>                                      |                  |
| Ultrez 10 [Carbomer]                               | 0.20             |
| Water                                              | qs 100           |
| <u>Part B</u>                                      |                  |
| Glycerin                                           | 3.50             |
| <u>Part C</u>                                      |                  |
| Potassium Sorbate                                  | 0.10             |
| <u>Part D</u>                                      |                  |
| Volpo S10 [Steareth 10]                            | 1.50             |
| Crodafos CES [Ceterayl Alcohol]                    | 3.50             |
| Dicetyl Phosphate(and) Ceteth-10 Phosphate] DC 200 |                  |
| [Dimethicone]                                      | 2.00             |
| Diethylhexyl Succinate                             | 7.00             |
| Mixed Parabens                                     |                  |
|                                                    | 0.30             |
| Crill 3 [Sorbitan Stearate]                        |                  |
|                                                    | 0.40             |
| <u>Part E</u>                                      |                  |
| Sodium Hydroxide 38%                               |                  |
| Water                                              | 0.20             |
|                                                    | 4.00             |
| <u>Part F</u>                                      |                  |
| Active agent                                       | 3.00             |
| Peptide                                            | 3.00             |

This formulation can be made according to the procedures generally outlined in Example 3.

The active agent can be STEROCARE (TM) [Trifolium Pratense (Clover) Flower Extract (and) Glycerin (and) Butylene Glycol (and) Lecithin Sterocare(R) is offered by SEDERMA as an active ingredient for mature skin (FR 2769502 of Apr. 14, 2000, WO 99/18927 of Apr. 22, 1999). It will be understood that any agent can be used to replace STEROCARE®. For example, any agent that aids muscle health, development or recovery.

The following composition in Example 7 is an example of a rub or a tonic.

| Ingredient                                               | Exemplary (w/w)% |
|----------------------------------------------------------|------------------|
| <u>Part A</u><br>Water deionised                         | qs 100           |
| <u>Part B</u><br>Mixed Parabens<br>Butylene Glycol       | 0.14<br>2.00     |
| <u>Part C</u><br>Peptide<br>Ethanol                      | 0.0008<br>10.00  |
| <u>Part D</u><br>Crillet 1 (Polysorbate 20)<br>Fragrance | 1.50<br>0.10     |

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The following composition in Example 8 is an example of a cream or a rub.

| Ingredient                                                                  | Exemplary (w/w)% |
|-----------------------------------------------------------------------------|------------------|
| <u>Part A</u>                                                               |                  |
| Ultrez 10 [Carbomer]                                                        | 0.20             |
| Water Deionised                                                             | qs 100           |
| <u>Part B</u>                                                               |                  |
| Glycerin                                                                    | 3.00             |
| <u>Part C</u>                                                               |                  |
| Potassium Sorbate                                                           | 0.10             |
| <u>Part D</u>                                                               |                  |
| Volpo S10 [Steareth 10]                                                     | 1.50             |
| Crodafos CES [Ceterayl Alcohol Dicetyl Phosphate (and) Ceteth-10 Phosphate] | 3.00             |
| DC 200 [Dimethicone]                                                        | 2.00             |
| Crodamol OSU [Diethylhexyl Succinate]                                       | 5.00             |
| Mixed Parabens                                                              | 0.30             |
| Crill 3 [Sorbitan Stearate]                                                 | 0.40             |
| <u>Part E</u>                                                               |                  |
| Sodium Hydroxide 38%                                                        | 0.20             |
| Water Deionised                                                             | 4.00             |
| <u>Part F</u>                                                               |                  |
| Water                                                                       | 10.0             |
| Peptide                                                                     | 0.00075          |
| Agent                                                                       | 0.001            |
| Agent                                                                       | 0.002            |

The agent can be Deferoxamine and/or Berberine. These are used as skin thickeners.

- 5 Deferoxamine and Berberine can be replaced with another active agents, such as an agent for muscle health, recovery and development.

The following composition in Example 9 is an example of a gel or rub.

| Ingredient                                    | Exemplary (w/w)% |
|-----------------------------------------------|------------------|
| <u>Part A</u>                                 |                  |
| Water Deionised                               | qs 100           |
| <u>Part B</u>                                 |                  |
| Butylene Glycol                               | 5.00             |
| Phenova [Phenoxyethanol (and) Mixed Parabens] | 0.80             |
| <u>Part C</u>                                 |                  |
| Crill 3 [Sorbitan Stearate]                   |                  |
| Crillet 3 [Polysorbate 60]                    | 1.20             |
| DC 200 [Dimethicone]                          | 3.00             |
| Crodamol IPM [Isopropyl Myristate]            | 2.00             |
| Crodamol W [Stearyl Heptanoate]               | 5.00             |
| Crodamol GTCC [Caprylic/Capric Triglyceride]  | 0.30             |
| Crodacol CS90 [Cetearyl Alcohol]              | 5.00             |
|                                               | 2.00             |
| <u>Part D</u>                                 |                  |
| Carbopol 980 at 2% [Carbomer]                 | 10.00            |
| <u>Part E</u>                                 |                  |
| Potassium Sorbate                             | 0.10             |
| <u>Part F</u>                                 |                  |
| Water                                         | 2.00             |
| Sodium Hydroxide                              | 0.20             |
| <u>Part G</u>                                 |                  |
| Water                                         | 10.0             |
| Peptide                                       | 0.00045          |
| Active agent                                  | 0.1              |
| Active agent                                  | 0.0001           |

This gel can be prepared in the following way: Homogenize Part B and pour it into Part A. Heat Part (A+B) to 75°C. Heat Part C and Part D to 75°C. Pour Part C into Part (A+B) with helix stirring; then, pour Part D into Part (A+B+C). Add Part F and Part E. Pour Part G at about 35°C.

The active can be Rutin and or Bowman Birk Inhibitor. These agents are used for tissue regeneration. Rutin and Bowman Birk Inhibitor can be replaced with another active agent, such as an agent for muscle health, recovery and development.

**Example 10****Glucose transport activity***Study Description*

Skeletal muscle is the predominant site of glucose disposal (80%) under insulin-stimulated or post-prandial conditions. Under these conditions, transport of glucose into skeletal muscle is facilitated principally by the insulin-responsive glucose transport protein GLUT4, which translocates to the cell surface upon insulin or contractile stimulation.

The effect of six synthetic peptides (SP1-6) on *in vitro* GLUT4 translocation using the L6 rat skeletal muscle cell line was determined. A clone of the L6 cell line containing overexpression of GLUT4 tagged with a c-myc epitope (courtesy of Prof. Amira Klip, Hospital for Sick Children, Toronto) was used to investigate the efficacy of each SP and protein composition for effects on GLUT4 translocation in a dose-response design.

SP2 [SEQ ID 1] is a peptide of the invention, whereas peptides SP1 and SP3-SP6 are comparative peptides.

SP1 (E\_685two\_BE) DTFYNAAWDPSNR [SEQ ID 115]

SP2 (E\_64two\_BE) VLDLAIPVNRPGQL [SEQ ID 1]

SP3 (E\_93\_BE) YQHQQGGKQEQENEGNNIFSGFK [SEQ ID 116]

SP4 (I\_641\_BE) ALDWAIANLLR [SEQ ID 117]

SP5 (I\_1021\_BE) YDYENV DAGA AK [SEQ ID 118]

SP6 (I\_24\_BE) EVQDSPLDACR [SEQ ID 119]

**Methodology**

*Cell culture*

L6-GLUT4myc cells were grown in 10% FBS and 2 µg/ml blasticidin. Cells were grown for 48-72 hours before being seeded in 24-well plates at 15,000 cells per well in 2% FBS and allowed to differentiate for 6 to 8 days prior to experimentation.

*Experimental design*

L6-GLUT4myc cells were serum-starved for three hours prior to incubation with 100 nM of insulin for 30mins, or 200, 20, 2.0 and 0.2  $\mu$ M of SP, and 2, 1, 0.5 and .25mg/ml of composition for 3 hours respectively. A 3 hour incubation period was selected based on previous findings identifying that incubation with branch chain amino acid containing di-peptides for 3 hours increases glucose uptake in L6 myotubes 1. Treatments were staggered in order to determine GLUT4myc translocation at the same time point.

*Measurement of GLUT4myc translocation in L6 myotubes*

The quantity of myc-tagged GLUT4 at the cell surface was measured by antibody-coupled colorimetric assay. Briefly, after incubation with either insulin for 30mins or synthetic peptide or protein composition for 3 hours respectively, L6-GLUT4myc cells were fixed via incubation with 3% paraformaldehyde (PFA). A 0.1 M glycine solution was then added to quench PFA and cells were blocked with 5% goat serum. The myotube monolayer was exposed to anti-myc antibody and then incubated with peroxidase conjugated donkey anti-mouse IgG. 1mL of o-phenylenediamine dihydrochloride (OPD) reagent was added to each well and this reaction was stopped by adding 250 $\mu$ l/well of 3 M HCL. To determine GLUT4 translocation to cell surface, a measured aliquot of each condition was determined spectrophotometrically on a plate reader using absorbance at 492nm.

*Synthetic peptides*

Peptides were first diluted in a suitable solvent. Dimethyl sulfoxide (DMSO) was the solvent of choice for peptides with poor predicted water solubility. Final concentration of DMSO in each well at 200, 20, 2 and .2  $\mu$ M for each synthetic peptide are shown in Table 2

Table 1. Concentration of DMSO per well for each synthetic peptide

| Peptide           | Concentration of DMSO per well (%) |            |           |             |
|-------------------|------------------------------------|------------|-----------|-------------|
|                   | 200 $\mu$ M                        | 20 $\mu$ M | 2 $\mu$ M | 0.2 $\mu$ M |
| SP1 (E_685two_BE) | 4.0                                | 0.4        | 0.04      | 0.004       |
| SP2 (E_64two_BE)  | 0.9                                | 0.09       | 0.009     | 0.0009      |
| SP3 (E_93_BE)     | 0.8                                | 0.08       | 0.008     | 0.0008      |
| SP4 (I_641_BE)    | 0.2                                | 0.02       | 0.002     | 0.0002      |
| SP5 (I_1021_BE)   | 3.0                                | 0.3        | 0.03      | 0.003       |
| SP6 (I_24_BE)     | 0.0                                | 0.0        | 0.0       | 0.0         |

## Results

### 5 Synthetic peptides

In addition to an untreated control, 100 nM insulin was utilised to stimulate a maximal GLUT4 translocation response i.e. a positive control in each experiment. The average increase in cell surface GLUT4 translocation in response to 100 nM insulin was 1.72-fold when compared to untreated control (Figure 1). Treatments were staggered so that all conditions (untreated, insulin and sample) were processed at the same time-point. There was a trend for SP2 to increase GLUT4 translocation at a concentration ranging from 0.2 – 2  $\mu$ M. SP1 at 200  $\mu$ M tended to decrease translocation due to poor cell viability.

### Conclusion of the experiment

15 SP2 displayed a trend for stimulatory effect on skeletal muscle GLUT4 translocation and its ability to facilitate glucose transport in skeletal muscle.

**EXAMPLE 11****Glucose uptake assay**

*In vitro* model: HsKMc – Human skeletal muscle cells (Sigma – 150-05a)

5 Glucose detection assay: PrismColor Glucose Uptake Assay Kit (Molecutools, Dublin 15)

*Principle*

10 Measuring glucose uptake using 2-deoxyglucose (2-DG) is a widely accepted method used to investigate glucose uptake in skeletal muscle cells. 2-DG is taken up by glucose transporters and metabolized to 2-DG-6-phosphate (2-DG6P). The amount of accumulated non-metabolized 2-DG6P is proportional to glucose uptake by cells.

*Method*

- 15 1. Human skeletal myoblasts were seeded in a 96 well plate at 10,000 cells per well in Skeletal Muscle Differentiation medium and allowed to differentiated for 72h prior to experimentation.
2. The differentiated cells were serum starved for 24h prior to stimulation with insulin or synthetic peptides. After starvation, the serum free media was removed, cells rinsed  
20 with Phosphate Buffered Saline (PBS) and media replaced with 100  $\mu$ l of Krebs-Ringer-Phosphate-HEPES (KRPH) and incubated for 1h.
3. The cells were then stimulated with 100nM insulin for 30 minutes or 5  $\mu$ g/ml, 0.5  $\mu$ g/ml or 0.05 $\mu$ g/ml synthetic peptide for 3h respectively.
4. Following stimulation the cells were incubated with 10  $\mu$ l/well of 2-DG solution for  
25 40 min and glucose uptake was measured using the 'PrismColor Glucose Uptake Assay Kit' (Molecutools), all steps were carried out according to the manufacturer's instructions.
5. Results were calculated as a percentage of the untreated control. An increase in  
30 optical density reading indicates greater incorporation of 2-DG6P and increase in glucose uptake.

*Results*

Treatment with SEQ ID NO.1 results in a significant increase in glucose uptake as illustrated by Figure 2. These results demonstrate the efficacy of SEQ No 1 to facilitate glucose transport  
5 in skeletal muscle.

The invention is not limited to the embodiments hereinbefore described which may be varied in construction and detail without departing from the spirit of the invention.

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## SEQUENCES

5 PEPTIDE : LQGQNDQRGEIIR [SEQ ID 120]  
PEPTIDE : PNVNPWHNPRQGGF [SEQ ID 121]  
PEPTIDE : FYNEGDAPVVALY [SEQ ID 122]  
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PEPTIDE : YDQYKDAWDTSVVAEIK[SEQ ID 412]  
PEPTIDE : SSFDFIDGYDTPVEGR[SEQ ID 413]  
PEPTIDE : GPDVGVDYKDNQM[SEQ ID 414]  
15 PEPTIDE : ILNLNNNPYFK[SEQ ID 415]  
PEPTIDE : VVGTPAYEE[SEQ ID 416]  
PEPTIDE : IDGYDTPVEGR[SEQ ID 417]  
PEPTIDE : VVGTPAYE[SEQ ID 418]  
PEPTIDE : IYGPDTGV DYK[SEQ ID 419]  
20 PEPTIDE : VAGSAPGIEGDE[SEQ ID 420]  
PEPTIDE : IYGPDTGV DYKDNQMR[SEQ ID 421]  
PEPTIDE : VVGTPAYEEMVR[SEQ ID 422]  
PEPTIDE : DFIDGYDTPVEGR[SEQ ID 423]  
PEPTIDE : LGLGVAGSAPGIEGDEIAPLAK[SEQ ID 424]  
25 PEPTIDE : FNAPLAHLIMAGADVLAVPSR[SEQ ID 425]  
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PEPTIDE : LGLGVAGSAPGIEGDEIAPL[SEQ ID 427]  
PEPTIDE : VLTVSPYYAEELISGIAR[SEQ ID 428]  
PEPTIDE : EALQAEAGLPVDR[SEQ ID 429]  
30 PEPTIDE : LGLGVAGSAPGIEGD[SEQ ID 430]  
PEPTIDE : IMAGADVLAVPSR[SEQ ID 431]  
PEPTIDE : GLGVAGSAPGIEGDE[SEQ ID 432]  
PEPTIDE : EALQAEAGLPVDRK[SEQ ID 433]  
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35 PEPTIDE : LEEQKGPDMVA[SEQ ID 435]  
PEPTIDE : LGVAGSAPGIEGDEIAPLAK[SEQ ID 436]  
PEPTIDE : GLGVAGSAPGIEGDEIAPLAK[SEQ ID 437]  
PEPTIDE : TGGLGDVLGGLPPAM[SEQ ID 438]  
PEPTIDE : NVLLGLGVAGSAPGIEGDE[SEQ ID 439]  
40 PEPTIDE : TVFDGVL RPQL[SEQ ID 440]  
PEPTIDE : RLQSQNDQRGEIHHVK[SEQ ID 441]  
PEPTIDE : EGYGEGQQQPGMTR[SEQ ID 442]  
PEPTIDE : GYGEGQQQPGMTR[SEQ ID 443]  
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45 PEPTIDE : YGGEGSSSEQGYGEGSS[SEQ ID 445]  
PEPTIDE : YGGEGSSSEQGYGEGSS[SEQ ID 446]  
PEPTIDE : SSEEGYGEGQQQPGMTR[SEQ ID 447]  
PEPTIDE : SEEGYGEGQQQPGMTR[SEQ ID 448]  
PEPTIDE : QGYGEGSSEE[SEQ ID 449]  
50 PEPTIDE : YGGEGSSSEQGYGEGSSEEGY[SEQ ID 450]  
PEPTIDE : YGEGQQQPGMTR[SEQ ID 451]  
PEPTIDE : YGEGQQQPGMTR[SEQ ID 452]  
PEPTIDE : SYEESMPMPLEQGWSSSSSE[SEQ ID 453]  
PEPTIDE : YGEGSSEEGYGEGQQQPGMTR[SEQ ID 454]  
55 PEPTIDE : QQQQPGMTRV[SEQ ID 455]  
PEPTIDE : GEQQQPGMTR[SEQ ID 456]  
PEPTIDE : SYEESMPMPLEQGWSSSSSEY[SEQ ID 457]  
PEPTIDE : YGGEGSSSEQGYGEGSSEEGY[SEQ ID 458]

5 PEPTIDE : YGEQQQQPGMTRVR[SEQ ID 459]  
PEPTIDE : GEGSSEEGYYGEQQQQPGMTR[SEQ ID 460]  
PEPTIDE : YGEGSSEEGYYGEQQQQPGMTR[SEQ ID 461]  
PEPTIDE : QQQQPGMTRVR[SEQ ID 462]  
PEPTIDE : QYAAQLPSMCRVEPQQCSIFAAGQY[SEQ ID 463]  
PEPTIDE : TVFNGVLRPGQL[SEQ ID 464]  
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PEPTIDE : YSNTPGMVY[SEQ ID 471]  
15 PEPTIDE : LVPRYSNTPGM[SEQ ID 472]  
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PEPTIDE : FYNEGDAPVVAL[SEQ ID 474]  
PEPTIDE : FEPLRRVRSEAGVTE[SEQ ID 475]  
PEPTIDE : FYNEGDAPVVVALY[SEQ ID 476]  
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PEPTIDE : VEERSQNIFSGF[SEQ ID 479]  
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PEPTIDE : IYVTDLNNGANQLDPRQRDFL[SEQ ID 486]  
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PEPTIDE : YVTDLNNGANQLDPRQRDFL[SEQ ID 491]  
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PEPTIDE : SGFSTELLSEALGVSSQVAR[SEQ ID 495]  
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PEPTIDE : DFLAGNK[SEQ ID 500]  
PEPTIDE : DVLANAYR[SEQ ID 501]  
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PEPTIDE : AFTPLQYK[SEQ ID 508]  
PEPTIDE : FGAFTPLQYKSYQD[SEQ ID 509]  
PEPTIDE : GDEFGAFTPLQYK[SEQ ID 510]  
PEPTIDE : FGAFTPLQYKSYQDV[SEQ ID 511]  
55 PEPTIDE : FGAFTPLQYK[SEQ ID 512]  
PEPTIDE : FGAFTPLQYKS[SEQ ID 513]  
PEPTIDE : VYIIQGRGITGPTF[SEQ ID 514]  
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5 PEPTIDE : KTNPNMSMVSHIAGK[SEQ ID 516]  
PEPTIDE : TNPNSMVSHIAGK[SEQ ID 517]  
PEPTIDE : PNSMVSHIAGKS[SEQ ID 518]  
PEPTIDE : NIDNPNRADTYNPRAGRVTN[SEQ ID 519]  
PEPTIDE : QRDFFLAGNKR[SEQ ID 520]  
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PEPTIDE : QRDFFLAGNK[SEQ ID 522]  
PEPTIDE : QEQEQGQMQR[SEQ ID 523]  
10 PEPTIDE : SLLQPYASLQEQE[SEQ ID 524]  
PEPTIDE : ASLQEQEQGQM[SEQ ID 525]  
PEPTIDE : ASLQEQEQGQMQR[SEQ ID 526]  
PEPTIDE : DFFLAGNKR[SEQ ID 527]  
PEPTIDE : QAFPIRSVRSQAGTTE[SEQ ID 528]  
15 PEPTIDE : KTNPNMSMVSHIAGKSSIF[SEQ ID 529]  
PEPTIDE : VRRVIEPRGLLPHYTNAGSL[SEQ ID 530]  
PEPTIDE : FGAFTPLQYKSYQDVYN[SEQ ID 531]  
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PEPTIDE : RVRQNIDNPNRADTYNPRAGRVTNL[SEQ ID 533]  
20 PEPTIDE : NIDNPNRADTYNPRAGRVTNL[SEQ ID 534]  
PEPTIDE : GAFTPLQYKSYQDVYN[SEQ ID 535]  
PEPTIDE : PNSMVSHIAGKSSIFR[SEQ ID 536]  
PEPTIDE : RLQAFPIRSVRSQAGTTE[SEQ ID 537]  
PEPTIDE : TNPNSMVSHIAGKSSIFR[SEQ ID 538]  
25 PEPTIDE : ELGAPDVGHM[SEQ ID 539]  
PEPTIDE : LGAPDVGHM[SEQ ID 540]  
PEPTIDE : ELGAPDVGHMSEVF[SEQ ID 541]  
PEPTIDE : ELGAPDVGHMSE[SEQ ID 542]  
PEPTIDE : ELGAPDVGHMSEVFR[SEQ ID 543]  
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PEPTIDE : ELGAPDVGHMSE[SEQ ID 545]  
PEPTIDE : LGAPDVGHMSE[SEQ ID 546]  
PEPTIDE : YRELGAPDVGHMSE[SEQ ID 547]  
PEPTIDE : LGAPDVGHMSEV[SEQ ID 548]  
35 PEPTIDE : RELGAPDVGHMSE[SEQ ID 549]  
PEPTIDE : APTGTFIASGVVVGKD[SEQ ID 550]  
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PEPTIDE : RHQITDTTNGHYAPVTYIQVE[SEQ ID 552]  
PEPTIDE : GDLAIVKFSPNEQNKHIGE[SEQ ID 553]  
40 PEPTIDE : NPDNPDNPNPDNPNPD[SEQ ID 554]  
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PEPTIDE : VLDLAIPVNRPGQLQSF [SEQ ID 556]  
PEPTIDE : SFLLSGNQNNYLS [SEQ ID 557]  
PEPTIDE : VLDLAIPVNR [SEQ ID 558]  
45 PEPTIDE : SFLLSGNQNNYLSGFS [SEQ ID 559]  
PEPTIDE : LAIPVNRPGQLQSFLLSG [SEQ ID 560]  
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PEPTIDE : LDLAIPVNRPGQL [SEQ ID 562]  
PEPTIDE : VLDLAIPVNRPGQLQ [SEQ ID 563]  
50 PEPTIDE : LAIPVNRPGQLQSFLLSGNQ [SEQ ID 564]  
PEPTIDE : SFLLSGNQNNYLSGFSKNILE [SEQ ID 565]  
PEPTIDE : GSLLLPHYN [SEQ ID 566]  
PEPTIDE : GSLLLPHYNS [SEQ ID 567]  
PEPTIDE : SSNLDLLGFG [SEQ ID 568]  
55 PEPTIDE : AFDLAKNKNQYLRGFS [SEQ ID 569]  
PEPTIDE : QYLRGFSKNILE [SEQ ID 570]  
PEPTIDE : NLLGFGINAE [SEQ ID 571]  
PEPTIDE : SNLNLGFG [SEQ ID 572]

5 PEPTIDE : LAKNKNQYLRGFSKN [SEQ ID 573]  
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 PEPTIDE : LRGFSKNILE [SEQ ID 575]  
 PEPTIDE : YSNKFGKLFE [SEQ ID 576]  
 PEPTIDE : AFDLAKNKNQYLRGF [SEQ ID 577]  
 PEPTIDE : AFDLAKNKNQYLRGFSK [SEQ ID 578]  
 PEPTIDE : NKNQYLRGFS [SEQ ID 579]  
 PEPTIDE : NKNQYLRGFSKNILE [SEQ ID 580]  
 10 PEPTIDE : SSNLNLLGFG [SEQ ID 581]  
 PEPTIDE : EYSNKGKLF [SEQ ID 582]  
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 PEPTIDE : LNLLGFGI [SEQ ID 584]  
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 15 PEPTIDE : VQPGRRWEREEDEEQVDE [SEQ ID 586]  
 PEPTIDE : RERWEREEDEEQVDE [SEQ ID 587]  
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 PEPTIDE : LAKNKNQYLRGFS [SEQ ID 589]  
 PEPTIDE : ELLGLKNE [SEQ ID 590]  
 20 PEPTIDE : ASSNLNLL [SEQ ID 591]  
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 PEPTIDE : LLGLKNEQQE [SEQ ID 593]  
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 30 PEPTIDE : FLLAGNNNR [SEQ ID 601]  
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 PEPTIDE : FLLAGNNNRAQQQQVYG [SEQ ID 605]  
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 PEPTIDE : GSLLPHYN [SEQ ID 615]  
 45 PEPTIDE : GSLLPHYNS [SEQ ID 616]  
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 PEPTIDE : ASSNLNLL [SEQ ID 620]  
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 PEPTIDE : SSNLNLLGFG [SEQ ID 622]  
 PEPTIDE : ASSNLNLLG [SEQ ID 623]  
 PEPTIDE : LLGLKNEQQE [SEQ ID 624]  
 PEPTIDE : LVVLSGKAIL [SEQ ID 625]  
 55 PEPTIDE : LNLLGFGI [SEQ ID 626]  
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 PEPTIDE : LQNYRLLE [SEQ ID 628]  
 PEPTIDE : LLSGTQNQPSLL [SEQ ID 629]

5 PEPTIDE : LLLPNYNSR [SEQ ID 630]  
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PEPTIDE : GSLLLPNYS [SEQ ID 632]  
PEPTIDE : NLQNYRLL [SEQ ID 633]  
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10 PEPTIDE : LQLLKPTLTQQE [SEQ ID 638]

15 PEPTIDE : LSEALGVNAL [SEQ ID 639]  
PEPTIDE : LNSQKFPILNLVQLSATR [SEQ ID 640]  
PEPTIDE : HGLSLLQPYA [SEQ ID 641]  
PEPTIDE : HGLSLLQPYASL [SEQ ID 642]  
PEPTIDE : HGLSLLQPY [SEQ ID 643]  
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PEPTIDE : DRKRRQQGEETDAIVK [SEQ ID 645]  
20 PEPTIDE : IGINGFGRIGRLVAR [SEQ ID 646]  
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PEPTIDE : INGFGRLVAR [SEQ ID 648]  
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PEPTIDE : LLLGIIFLASVV [SEQ ID 650]  
25 PEPTIDE : RLLQKFDQRSKIF [SEQ ID 651]  
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PEPTIDE : VIVKLSR [SEQ ID 654]  
PEPTIDE : HSPR [SEQ ID 655]  
30 PEPTIDE : HWF [SEQ ID 656]  
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PEPTIDE : DSINALEPDHR [SEQ ID 660]  
35 PEPTIDE : LDALEPDNRIESE [SEQ ID 661]  
PEPTIDE : EEGIQLVAEAIR [SEQ ID 662]  
PEPTIDE : TFAEETWGK [SEQ ID 663]  
PEPTIDE : LVSHPIAAHEGR [SEQ ID 664]  
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40 PEPTIDE : ILVDGSHDIER [SEQ ID 666]  
PEPTIDE : LDVTPLSLGL [SEQ ID 667]  
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45 PEPTIDE : HMPP [SEQ ID 671]  
PEPTIDE : HMPS [SEQ ID 672]  
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PEPTIDE : PRRF [SEQ ID 674]  
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PEPTIDE : FWM [SEQ ID 677]  
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PEPTIDE : HMPSS [SEQ ID 680]  
55 PEPTIDE : HRRS [SEQ ID 681]  
PEPTIDE : MPPS [SEQ ID 682]  
PEPTIDE : MPRR [SEQ ID 683]  
PEPTIDE : PHMPS [SEQ ID 684]

5 PEPTIDE : HGGEGGRPY [SEQ ID 685]  
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PEPTIDE : LQQAPPPQR [SEQ ID 687]  
PEPTIDE : VGWGEQPWSPY [SEQ ID 688]  
PEPTIDE : HPRPPKPDAPR [SEQ ID 689]  
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PEPTIDE : MRFR [SEQ ID 691]  
PEPTIDE : WHT [SEQ ID 692]  
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PEPTIDE : HRFR [SEQ ID 694]  
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PEPTIDE : MFRRP [SEQ ID 696]  
PEPTIDE : NMPS [SEQ ID 697]  
PEPTIDE : WMK [SEQ ID 698]  
15 PEPTIDE : YSLKPLVPR [SEQ ID 699]  
PEPTIDE : PVEMPTLLYP [SEQ ID 700]  
PEPTIDE : QSFLLSGNQ [SEQ ID 701]  
PEPTIDE : SLTLEDVPNHGTIR [SEQ ID 702]  
PEPTIDE : LSLTDLK [SEQ ID 703]  
20 PEPTIDE : THPMNFLNER [SEQ ID 704]  
PEPTIDE : LGLSPQDALK [SEQ ID 705]  
PEPTIDE : TRPPVPSTIPTK [SEQ ID 706]  
PEPTIDE : RGPQQYAEWQINE [SEQ ID 707]  
PEPTIDE : GIARLAGTSSVIN [SEQ ID 708]  
25 PEPTIDE : YLRGFS [SEQ ID 709]  
PEPTIDE : LRGFSK [SEQ ID 710]  
PEPTIDE : GALMLPHYNSR [SEQ ID 711]  
PEPTIDE : GALMLPHYN [SEQ ID 712]  
PEPTIDE : RSQNIF [SEQ ID 713]  
30 PEPTIDE : GHPM [SEQ ID 714]  
PEPTIDE : WDP [SEQ ID 715]  
PEPTIDE : WHN [SEQ ID 716]  
PEPTIDE : PMPL [SEQ ID 717]  
PEPTIDE : HNPR [SEQ ID 718]  
35 PEPTIDE : HPSF [SEQ ID 719]  
PEPTIDE : PNSM [SEQ ID 720]  
PEPTIDE : HPMS [SEQ ID 721]  
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PEPTIDE : VFDGVLRPG [SEQ ID 723]  
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PEPTIDE : LQSQND [SEQ ID 725]  
PEPTIDE : LEPDNR [SEQ ID 726]  
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PEPTIDE : RGEIIHVK [SEQ ID 728]  
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PEPTIDE : RLQSQNDQRGEIIH [SEQ ID 730]  
PEPTIDE : LQSQNDQRGEI [SEQ ID 731]  
PEPTIDE : FLPQHTD [SEQ ID 732]  
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PEPTIDE : QSFLLSGNQ [SEQ ID 735]  
PEPTIDE : PGQLQSFLLSGN [SEQ ID 736]  
PEPTIDE : PGQLQSFLLSGNQNNQNNYLSGF [SEQ ID 737]  
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55 PEPTIDE : QNQNNYLSGFSK [SEQ ID 739]  
PEPTIDE : GPQQYAEWQINEK [SEQ ID 740]  
PEPTIDE : RGPQQYA [SEQ ID 741]

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PEPTIDE: GKIKIGINGFGRIGRLVA [SEQ ID 743]  
PEPTIDE: MMAP [SEQ ID 744]  
PEPTIDE: MAPH [SEQ ID 745]  
5 PEPTIDE: ERGVLY [SEQ ID 746]  
PEPTIDE: RVLNGL [SEQ ID 747]  
PEPTIDE: SLLSGE [SEQ ID 748]  
PEPTIDE: LLSGED [SEQ ID 749]  
10 PEPTIDE: LSGEDA [SEQ ID 750]  
PEPTIDE: HRHA [SEQ ID 751]  
PEPTIDE: SRAIVITVNE [SEQ ID 752]  
PEPTIDE: AKLTPGDV [SEQ ID 753]  
PEPTIDE: IVIVTVNEGK [SEQ ID 754]  
15 PEPTIDE: LDALEPDNRISEGGGL (also in P02857) [SEQ ID 755]  
PEPTIDE: RPYYSNAPQE (also in P02857) [SEQ ID 756]  
PEPTIDE: LDALEPDNRISEGGLIETWNPNNK (also in P02857) [SEQ ID 757]  
PEPTIDE: AIVIVTVNEGK (also in P13918) [SEQ ID 758]  
PEPTIDE: LQVVNCNGNTVFDGEL [SEQ ID 759]  
20 PEPTIDE: QVVNCNGNTVFDGEL [SEQ ID 760]  
PEPTIDE: IIAVPTGIVF [SEQ ID 761]  
PEPTIDE: GRRYRDRHQKVNRFRE [SEQ ID 762]  
PEPTIDE: RPYYSNAPQEI [SEQ ID 763]  
PEPTIDE: RLDALPDNRIE [SEQ ID 764]  
25 PEPTIDE: RLDALPDNRIESE [SEQ ID 765]  
PEPTIDE: LDALEPDNRISEGGLIETW [SEQ ID 766]  
PEPTIDE: LDALEPDNRIE [SEQ ID 767]  
PEPTIDE: LDALEPDNRISEGGGLIE [SEQ ID 768]  
PEPTIDE: LDALEPDNRISEGGGL (also in P02855) [SEQ ID 769]  
30 PEPTIDE: RPYYSNAPQE (also in P02857) [SEQ ID 770]  
PEPTIDE: LDALEPDNRISEGGLIETWNPNNK (also in P02855) [SEQ ID 771]  
PEPTIDE: VEHGLSLLQPYASLQEQEQGVQSRER [SEQ ID 772]  
PEPTIDE: RSQNIFSGF [SEQ ID 773]  
PEPTIDE: GITGPTFPGCPEY [SEQ ID 774]  
35 PEPTIDE: CNGS [SEQ ID 775]  
PEPTIDE: SPREC [SEQ ID 776]  
PEPTIDE: PREC [SEQ ID 777]  
PEPTIDE: PRECR [SEQ ID 778]  
PEPTIDE: CPES [SEQ ID 779]  
40 PEPTIDE: SGCS [SEQ ID 780]  
PEPTIDE: CSNG [SEQ ID 781]  
PEPTIDE: RSQNIFSGFSTE [SEQ ID 782]  
PEPTIDE: VEEWSQNIFSGFST [SEQ ID 783]  
PEPTIDE: WSQNIFSGFSTEL [SEQ ID 784]  
45 PEPTIDE: WSQNIFSGFSTE [SEQ ID 785]  
PEPTIDE: STSQWQSSRR [SEQ ID 786]  
PEPTIDE: NRPI [SEQ ID 787]  
PEPTIDE: CDGS [SEQ ID 788]  
PEPTIDE: PRGC [SEQ ID 789]  
50 PEPTIDE: PRGCR [SEQ ID 790]  
PEPTIDE: RGCR [SEQ ID 791]  
PEPTIDE: GCRF [SEQ ID 792]  
PEPTIDE: PTFP [SEQ ID 793]  
PEPTIDE: PGCPE [SEQ ID 794]  
55 PEPTIDE: GCPE [SEQ ID 795]  
PEPTIDE: CPET [SEQ ID 796]  
PEPTIDE: AHCW [SEQ ID 797]  
PEPTIDE: HWCY [SEQ ID 798]

5 PEPTIDE : SGCP [SEQ ID 799]  
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PEPTIDE : GCPN [SEQ ID 801]  
PEPTIDE : CPNG [SEQ ID 802]  
PEPTIDE : TFCTM [SEQ ID 803]  
PEPTIDE : FCTM [SEQ ID 804]  
PEPTIDE : FCTMR [SEQ ID 805]  
PEPTIDE : CTMR [SEQ ID 806]  
10 PEPTIDE : EGCA [SEQ ID 807]  
PEPTIDE : SQNIFSGFSTELL [SEQ ID 808]  
PEPTIDE : SQNIFSGFSTE [SEQ ID 809]  
PEPTIDE : QNDQRGEIVR [SEQ ID 810]  
PEPTIDE : SQNIFSGFSTEL (also in P07730) [SEQ ID 811]  
PEPTIDE : QLQCQNDQRGEI (also in P07730) [SEQ ID 812]  
15 PEPTIDE : LGQSTSQWQSSR (also in P07730) [SEQ ID 813]  
PEPTIDE : QQLLGQSTSQWQSSR (also in P07730) [SEQ ID 814]  
PEPTIDE : LLGQSTSQWQSSR (also in P07730) [SEQ ID 815]  
PEPTIDE : NDQRGEIVR [SEQ ID 816]  
PEPTIDE : GQSTSQWQSSR [SEQ ID 817]  
20 PEPTIDE : STSQWQSSR [SEQ ID 818]  
PEPTIDE : GITGPTFPGPCPET [SEQ ID 819]  
PEPTIDE : GITGPTFPGPCETY [SEQ ID 820]  
PEPTIDE : SQNIFSGFSTEL (also in P07728) [SEQ ID 821]  
PEPTIDE : QLQCQNDQRGEI (also in P07728) [SEQ ID 822]  
25 PEPTIDE : LGQSTSQWQSSR (also in P07728) [SEQ ID 823]  
PEPTIDE : QQLLGQSTSQWQSSR (also in P07728) [SEQ ID 824]  
PEPTIDE : LLGQSTSQWQSSR (also in P07728) [SEQ ID 825]  
  
30 PEPTIDE : IFFANQTYL [SEQ ID 826]  
PEPTIDE : EHLEPNLEGLTVEE [SEQ ID 827]  
PEPTIDE : IFFANQTYLPSETPAPLVHYREEELNNLRGDTGER [SEQ ID 828]  
PEPTIDE : IHFEWDDDMGIPGAFYIK [SEQ ID 829]  
PEPTIDE : IFFANQTYLPSETPAPLVHYREEELNNLR [SEQ ID 830]  
PEPTIDE : TEQALPADLIK [SEQ ID 831]  
35 PEPTIDE : EHLEPNLEGLTVEEAIQNK [SEQ ID 832]  
PEPTIDE : ISKEHLEPNLEGLTVEEAIQNK [SEQ ID 833]  
PEPTIDE : LSLPHPGDEHGAUSY [SEQ ID 834]  
PEPTIDE : ISKEHLEPNLEGLTVEEAIQNK [SEQ ID 835]  
PEPTIDE : EHLEPNLEGLTVEEAIQNK [SEQ ID 836]  
40 PEPTIDE : LSTGGNSGSPVFNEKNE [SEQ ID 837]  
PEPTIDE : QSFLSGNQNNQNYLSG [SEQ ID 838]  
PEPTIDE : VLDLAIPVNRPGQLQS [SEQ ID 839]  
PEPTIDE : VLDLAIPVNRPGQLQSFL [SEQ ID 840]  
PEPTIDE : FLLSGNQNNQNYLSG [SEQ ID 841]  
45 PEPTIDE : FLLSGNQNNQNYLSGFSK [SEQ ID 842]  
PEPTIDE : DPQNPFIKSNKFQTLFE [SEQ ID 843]  
PEPTIDE : ELAFPGSAQEVDRILENQK [SEQ ID 844]  
PEPTIDE : AIVIVTVNEGK (also in P02855) [SEQ ID 845]  
PEPTIDE : INAVAAKRLQSQNDQRGE [SEQ ID 846]  
50 PEPTIDE : NRAQQQVYGSSIE [SEQ ID 847]  
PEPTIDE : PSTNPWHSR [SEQ ID 848]  
PEPTIDE : CHGS [SEQ ID 849]  
PEPTIDE : CHGSM [SEQ ID 850]  
PEPTIDE : PWHS [SEQ ID 851]  
55 PEPTIDE : FREC [SEQ ID 852]  
PEPTIDE : RECR [SEQ ID 853]  
PEPTIDE : ECRF [SEQ ID 854]

PEPTIDE : CRFD [SEQ ID 855]  
PEPTIDE : CRFDR [SEQ ID 856]  
PEPTIDE : CTGT [SEQ ID 857]  
PEPTIDE : FPGC [SEQ ID 858]  
5 PEPTIDE : FPGCP [SEQ ID 859]  
PEPTIDE : PGCP [SEQ ID 860]  
PEPTIDE : PGCPA [SEQ ID 861]  
PEPTIDE : PGCPAT [SEQ ID 862]  
10 PEPTIDE : GCPA [SEQ ID 863]  
PEPTIDE : CPAT [SEQ ID 864]  
PEPTIDE : ENFC [SEQ ID 865]  
PEPTIDE : NFCT [SEQ ID 866]  
PEPTIDE : NFCTI [SEQ ID 867]  
PEPTIDE : FCTI [SEQ ID 868]  
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PEPTIDE : AQQQQVYGSSIEQHSGQNIFSGF [SEQ ID 870]  
PEPTIDE : AAKRLQSQNDQRGE [SEQ ID 871]  
PEPTIDE : QARSLKNNRGEE (also in P14614) [SEQ ID 872]  
PEPTIDE : FNPSTNPWHSPRQGS (also in Q0DEV5) [SEQ ID 873]  
20 PEPTIDE : QARSLKNNRGEE (also in P14323) [SEQ ID 874]  
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PEPTIDE : VAGSAPGIEGDEIAPLAK [SEQ ID 876]  
PEPTIDE : LGVAGSAPGIEGDEIAPLAKEN [SEQ ID 877]  
25 PEPTIDE : GSAPGIEGDEIAPLAKE [SEQ ID 878]  
PEPTIDE : VAGSAPGIEGDEIAP [SEQ ID 879]  
PEPTIDE : GVAGSAPGIEGDEIAPLAK [SEQ ID 880]  
PEPTIDE : GVAGSAPGIEGDEIAPLAKEN [SEQ ID 881]  
PEPTIDE : VAGSAPGIEGDEIAPLAKEN [SEQ ID 882]  
30 PEPTIDE : SAPGIEGDEIAPLAK [SEQ ID 883]  
PEPTIDE : GSAPGIEGDEIAPLAK [SEQ ID 884]  
PEPTIDE : SAPGIEGDEIAPLAKEN [SEQ ID 885]  
PEPTIDE : FNPSTNPWHSPRQGS (also in P14323) [SEQ ID 886]  
PEPTIDE : VDLVIPVNGPGK [SEQ ID 887]  
35 PEPTIDE : LVDLVIPVNGPGK [SEQ ID 888]  
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PEPTIDE : IKLPAGTTSYL [SEQ ID 890]  
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50 PEPTIDE : SQERRNPFLFKSNKFLTLFENE [SEQ ID 903]  
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PEPTIDE : ELTFPGSVQEINR [SEQ ID 905]  
PEPTIDE : KNPQLQDLDI [SEQ ID 906]  
PEPTIDE : GQSTSQQSSR [SEQ ID 907]  
55 PEPTIDE : QSTSQQSSR (also in P07728) [SEQ ID 908]  
PEPTIDE : QSTSQQSSR (also in P07730) [SEQ ID 909]  
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PEPTIDE : PSTNPWHSPR [SEQ ID 911]

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 5 PEPTIDE : GSMGLTFPGCPATY (also in P14614) [SEQ ID 916]  
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 PEPTIDE : LGAFTPRYQQ [SEQ ID 918]  
 PEPTIDE : ALGVNALVAKRLQGQN [SEQ ID 919]  
 PEPTIDE : LGAFTPRYQ [SEQ ID 920]  
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 PEPTIDE : GSMGLTFPGCPATY (also in P14323) [SEQ ID 922]  
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 PEPTIDE : CAGVFVIRR [SEQ ID 924]  
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 PEPTIDE : SFGGSPLQSPR [SEQ ID 927]  
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 PEPTIDE : GHIRLLQKFDKRSKIFE [SEQ ID 934]  
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 5 PEPTIDE : AKPHTIFLPQHIDADLILVVLSGKAILTVLSPNDR [SEQ ID 973]  
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 PEPTIDE : PRVPAQRERGRQEKEKEEKRHGEWRPS [SEQ ID 975]  
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 10 PEPTIDE : GSEPRVPAQRERGRQEKEKEEKRHGEWRP [SEQ ID 978]  
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 PEPTIDE : PAQRERGRQEKEKEEKRHGEWRPS [SEQ ID 1004]  
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 40 PEPTIDE : PAQRERGRQEKEKEEKRHGEWRPSY [SEQ ID 1007]  
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 45 PEPTIDE : GSEPRVPAQRERGRQEKEKEEKRHGEW [SEQ ID 1012]  
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5 PEPTIDE : GEKEEKRHGEWRPS [SEQ ID 1026]  
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 PEPTIDE : RLSSV [SEQ ID 1123]  
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 45 PEPTIDE : VKNGLKLLRPAF [SEQ ID 1126]  
 PEPTIDE : FLLAGNNR [SEQ ID 1127]  
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 PEPTIDE : LLRPAFAQQQE [SEQ ID 1130]  
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 PEPTIDE : NSFNLER [SEQ ID 1134]  
 PEPTIDE : VLDLAIPVNR [SEQ ID 1135]  
 55 PEPTIDE : DDNEELR [SEQ ID 1136]  
 PEPTIDE : LSSGDVFPAGHPVAVK [SEQ ID 1137]  
 PEPTIDE : EDDEEEQGEIEINK [SEQ ID 1138]  
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 PEPTIDE : QQQSQEENVIVK [SEQ ID 1143]  
 5 PEPTIDE : LSRGQIEELSK [SEQ ID 1144]  
 PEPTIDE : GQIEELSK [SEQ ID 1145]  
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 PEPTIDE : PHTIFLPQHTDADYILVVLGSK [SEQ ID 1148]  
 10 PEPTIDE : SNKFQTLFENENGHIR [SEQ ID 1149]  
 PEPTIDE : SKIFENLQNYR [SEQ ID 1150]  
 PEPTIDE : IFENLQNYR [SEQ ID 1151]  
 PEPTIDE : ILENQKQSHFADAQPQQR [SEQ ID 1152]  
 PEPTIDE : PGQLQSFLLSGNQNNQNYLSGFSK [SEQ ID 1153]  
 15 PEPTIDE : FFELTPEKNQQLQDLDFVNSVDLK [SEQ ID 1154]  
 PEPTIDE : QLEELSK [SEQ ID 1155]  
 PEPTIDE : QEEDEDEDEER [SEQ ID 1156]  
 PEPTIDE : YQHQQGGKQEQENEGNNIFSGFK [SEQ ID 1157]  
 PEPTIDE : GDTIKLPAGTTSYLVNQDDEEDLR [SEQ ID 1158]  
 20 PEPTIDE : RQQGEETDAIVK [SEQ ID 1159]  
 PEPTIDE : VLLEEQEKDRK [SEQ ID 1160]  
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 PEPTIDE : FEAFDLAK [SEQ ID 1162]  
 PEPTIDE : EQIEELKK [SEQ ID 1163]  
 25 PEPTIDE : EQIEELK [SEQ ID 1164]  
 PEPTIDE : NKNQYLR [SEQ ID 1165]  
 PEPTIDE : LSPGDVVIIPAGHPVAITASSNLNLLGFGINAENNER [SEQ ID 1166]  
 PEPTIDE : PSYEKQEDDEEEKQK [SEQ ID 1167]  
 PEPTIDE : EEDEEEGQR [SEQ ID 1168]  
 30 PEPTIDE : TLFLPQYTDADFILVVLGSK [SEQ ID 1169]  
 PEPTIDE : LVDLVIPVNGPGKFEAFDLAK [SEQ ID 1170]  
 PEPTIDE : KNPQLQDLDFVNYVEIK [SEQ ID 1171]  
 PEPTIDE : GYVGLTFPGCPATHQQQFQLFEQR [SEQ ID 1172]  
 PEPTIDE : RGPQQYAEWQINEK [SEQ ID 1173]  
 35 PEPTIDE : DEHQKIHQFR [SEQ ID 1174]  
 PEPTIDE : FRDEHQK [SEQ ID 1175]  
 PEPTIDE : FPILNLIQMSATR [SEQ ID 1176]  
 PEPTIDE : TNANAFVSHLAGK [SEQ ID 1177]  
 PEPTIDE : ALPVDVVANAYR [SEQ ID 1178]  
 40 PEPTIDE : YVYDVNNNANQLEPRQKEFL [SEQ ID 1179]  
 PEPTIDE : VYVYDVNNNANQLEPRQKEFL [SEQ ID 1180]  
 PEPTIDE : ADSYNPR [SEQ ID 1181]  
 PEPTIDE : KPTLTQQQEQAQAQDQ [SEQ ID 1182]  
 PEPTIDE : QAQAQDQYQQVQY [SEQ ID 1183]  
 45 PEPTIDE : QAQDQYQQVQY [SEQ ID 1184]  
 PEPTIDE : LQAFEPLR [SEQ ID 1185]  
 PEPTIDE : SRVQVVSNGFK [SEQ ID 1186]  
 PEPTIDE : WNVNAHSLVY [SEQ ID 1187]  
 PEPTIDE : NVNAHSLVY [SEQ ID 1188]  
 50 PEPTIDE : IQGRSRVQVVSNGFK [SEQ ID 1189]  
 PEPTIDE : GKTVFDGVLPGQL [SEQ ID 1190]  
 PEPTIDE : FGKTVFDGVLPGQL [SEQ ID 1191]  
 PEPTIDE : FQQQYYPGLSNESESETSE [SEQ ID 1192]  
 PEPTIDE : QQYYPGLSN [SEQ ID 1193]  
 55 PEPTIDE : QQQYYPGLSN [SEQ ID 1194]  
 PEPTIDE : VTNLNTQNFILSLVQMSAVK [SEQ ID 1195]  
 PEPTIDE : ITQGRARVQVNNNGKTVF [SEQ ID 1196]

5 PEPTIDE : ITQGRARVQVVNNNGKTVFNGE [SEQ ID 1197]  
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PEPTIDE : RALPNDVLANAYRISREE [SEQ ID 1200]  
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PEPTIDE : SIFRALPNDVLANAY [SEQ ID 1202]  
PEPTIDE : SIFRALPNDVLAN [SEQ ID 1203]  
PEPTIDE : SSIFRALPNDVLANAYR [SEQ ID 1204]  
10 PEPTIDE : SIFRALPNDVLANAYRISREE [SEQ ID 1205]  
PEPTIDE : SIFRALPND [SEQ ID 1206]  
PEPTIDE : IYVTDLNNGANQLDPRQRD [SEQ ID 1207]  
PEPTIDE : VTNLNSQNFILNLVQMSAVK [SEQ ID 1208]  
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15 PEPTIDE : NIDNPNRADTYNPRAGRVTNL [SEQ ID 1211]  
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PEPTIDE : HNRGDEFGAFTPLQYK [SEQ ID 1214]  
PEPTIDE : SYQDVYNVAESS [SEQ ID 1215]  
20 PEPTIDE : ISREEAQR [SEQ ID 1216]  
PEPTIDE : SIFRALPTDVLANAYRISREE [SEQ ID 1217]  
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PEPTIDE : YRISREEAQLKHNRGDE [SEQ ID 1219]  
PEPTIDE : FKDEHQKIHR [SEQ ID 1220]  
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PEPTIDE : TVFNGELRR [SEQ ID 1222]  
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PEPTIDE : GEIVRVER [SEQ ID 1229]  
PEPTIDE : RGLSLLQPYASLQ [SEQ ID 1230]  
35 PEPTIDE : RGLSLLQPYASLQEQ [SEQ ID 1231]  
PEPTIDE : RGLSLLQPYASLQEQE [SEQ ID 1232]  
PEPTIDE : RGLSLLQPYASLQE [SEQ ID 1233]  
PEPTIDE : RNPQAYR [SEQ ID 1234]  
PEPTIDE : FLLAGNKRNPQAY [SEQ ID 1235]  
40 PEPTIDE : EVEEWSQNIF [SEQ ID 1236]  
PEPTIDE : LAGNKRNPQAYR [SEQ ID 1237]  
PEPTIDE : FLLAGNKRNPQA [SEQ ID 1238]  
PEPTIDE : ELGAPDVGHMSE [SEQ ID 1239]  
PEPTIDE : IVQGHARVQVVSNLGK [SEQ ID 1240]  
45 PEPTIDE : IVQGHARVQVVSNL [SEQ ID 1241]  
PEPTIDE : IVQGHARVQVVS [SEQ ID 1242]  
PEPTIDE : NNRGEELGAFTPR [SEQ ID 1243]  
PEPTIDE : GEELGAFTPR [SEQ ID 1244]  
PEPTIDE : FPILNLVQLSATR [SEQ ID 1245]  
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PEPTIDE : LQGQNDQR [SEQ ID 1247]  
PEPTIDE : SGFNNELLSEALGVNALVAK [SEQ ID 1248]  
PEPTIDE : PAFAQQEQEAQQEQEAQAQY [SEQ ID 1249]  
PEPTIDE : VAKRLQGQNDQRGEI [SEQ ID 1250]  
55 PEPTIDE : ALVAKRLQGQNDQRGEI [SEQ ID 1251]

**Claims**

1. A topical, cosmetic or pharmaceutical, composition comprising a cosmetically or pharmaceutically effective amount of a peptide comprising an amino acid sequence of SEQUENCE ID NO. 1 or a variant thereof.
2. The topical composition of Claim 1, wherein said peptide is a bioactive peptide.
3. The topical composition of Claim 1, wherein said variant is a bioactive variant.
4. The topical composition of any one of the preceding Claims comprising a plurality of peptides.
5. The topical composition of any one of the preceding Claims, wherein the composition further comprises at least one cosmetically or pharmaceutically acceptable excipient or additive.
6. The topical composition of any one of the preceding Claims, wherein composition further comprises at least one cosmetically or pharmaceutically acceptable active.
7. The topical composition of any one of the preceding Claims, wherein said variant or bioactive variant has from about 70% to about 99% sequence identity with SEQUENCE ID NO. 1.
8. The topical composition of any one of the preceding Claims, wherein said variant or bioactive variant has an amino acid sequence comprising any one of SEQUENCE ID NO. 3 to 80 and 84 to 114.
9. The topical composition of any one of the preceding Claims wherein the peptide comprises from about 3 to about 50 amino acids in length.
10. The topical composition of any one of the preceding Claims, wherein the peptide or variant has one or more of or more of anti-inflammatory activity, cellular growth promoting activity, anti-aging activity and glucose transport-promoting activity.
11. The topical composition of any one of the preceding Claims for use in improving muscle status in a mammal.
12. The topical composition of Claim 11, wherein the muscle status is promoting recovery of muscle, typically following exercise, maintaining or restoring muscle health (for example lean tissue mass) in a mammal, and/or enhancing physical performance.

13. The topical composition of any one of the preceding Claims for use in the treatment or prevention of a disease or condition characterised by lethargy or low energy levels.
14. The topical composition of any one of the preceding Claims for use in promoting growth of tissue.
15. The topical composition of Claim 14, wherein the growth of tissue is in promoting growth of epithelial tissue, promoting growth of skin, promoting growth of an organ, and/or promoting growth of an organism.
16. The topical composition of any of the preceding Claims for use in slowing or inhibiting, or preventing aging of human skin, for use in the treatment of a skin condition, and/or for treatment of a wound.
17. The topical composition of any one of the preceding claims for use in treatment or prevention of an inflammatory disorder and/or inflammation in a mammal and/or a metabolic disorder.
18. The topical composition of the invention wherein the composition in a formulation selected from the group comprising creams, multiple emulsions, anhydrous compositions, aqueous dispersions, oils, milks, balsams, foams, lotions, gels, cream gels, hydro-alcoholic solutions, hydro-glycolic solutions, cosmetic, personal care product, hydrogels, liniments, sera, soaps, dusting powder, paste, semi solid formulations, liniments, serums, shampoo, conditioner, ointments, any rinse off formulation, talc, mousses, powders, sprays, aerosols, solutions, suspensions, emulsions, syrups, elixirs, polysaccharide films, patches, gel patches, bandages, an adhesive system, water-in-oil emulsions, oil-in-water emulsions, and silicone emulsions.
19. A medical device comprising the topical composition of the invention.

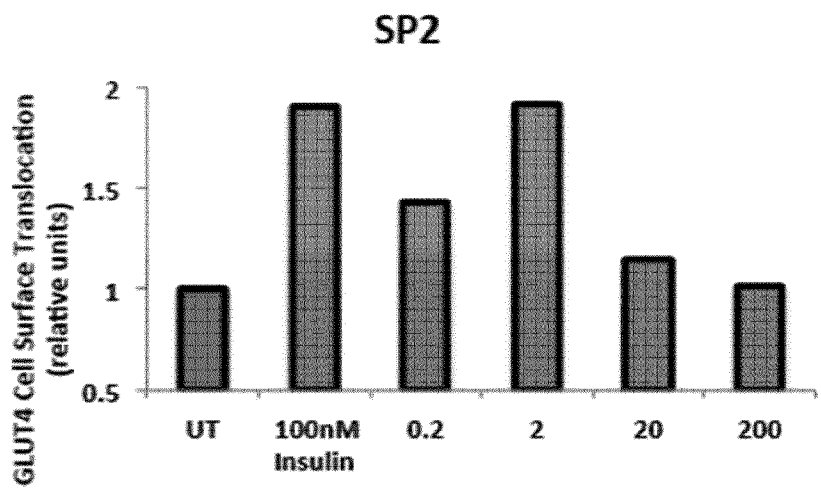


Figure 1

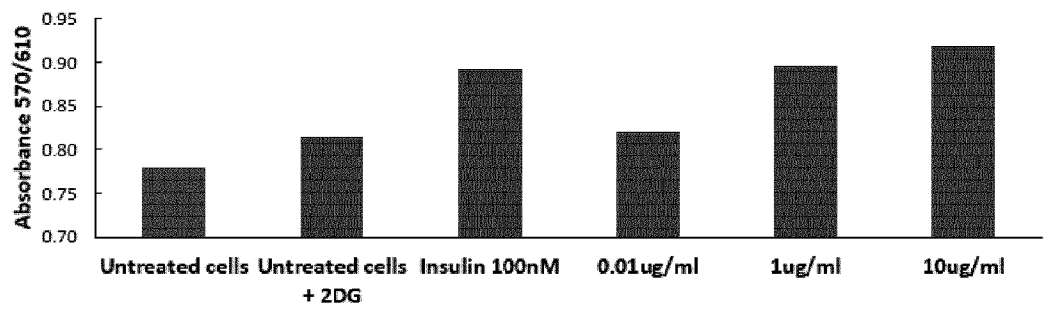


Figure 2

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2016/067094

| A. CLASSIFICATION OF SUBJECT MATTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                       |                                                    |
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| INV.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | A61K38/04<br>A61Q19/08                                                                                                                                                                                                                                                                                                | A61P21/00<br>A61K8/97                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | C07K7/04<br>A23L33/18                                                                                                                                                                                                                                                                                                 | C07K14/415<br>A61K8/64                             |
| ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                       |                                                    |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                    |
| B. FIELDS SEARCHED                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                       |                                                    |
| Minimum documentation searched (classification system followed by classification symbols)<br>A61K A23L C07K A61Q                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                       |                                                    |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                       |                                                    |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, BIOSIS, Sequence Search, EMBASE, FSTA, WPI Data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                       |                                                    |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                       |                                                    |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                    | Relevant to claim No.                              |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>DATABASE UniProt [Online]</p> <p>1 January 1990 (1990-01-01),<br/>"RecName: Full=Vicilin; Flags:<br/>Precursor;",<br/>XP002752386,<br/>retrieved from EBI accession no.<br/>UNIPROT:P13918<br/>Database accession no. P13918<br/>cited in the application<br/>sequence</p> <p style="text-align: center;">-/--</p> | 1-19                                               |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                       |                                                    |
| <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> |                                                                                                                                                                                                                                                                                                                       |                                                    |
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| 30 November 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                       | 15/12/2016                                         |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                       | Authorized officer<br><br>Madruga, Jaime           |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/067094

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International application No

PCT/EP2016/067094

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