

[19] Patents Registry [11] 1245664 B
The Hong Kong Special Administrative Region
香港特別行政區
專利註冊處

[12] **STANDARD PATENT (R) SPECIFICATION**
轉錄標準專利說明書

[21] Application no. 申請編號	[51] Int. Cl.
18105412.9	A61K 38/17 (2006.01) A61P 17/08 (2006.01)
[22] Date of filing 提交日期	A61P 17/10 (2006.01) A61K 8/00 (2006.01)
25.04.2018	A61K 8/64 (2006.01) C07K 14/705 (2006.01)
	A61Q 19/00 (2006.01)

[54] POLYPEPTIDES TO TREAT SKIN CONDITIONS ASSOCIATED WITH OVERPRODUCTION OF SEBUM
用於治療與皮脂分泌過多有關的皮膚問題的多肽

[30] Priority 優先權	29.05.2015 US 62/168,374	[73] Proprietor 專利所有人
[43] Date of publication of application 申請發表日期	31.08.2018	Taghibiglou, Changiz 1901-320 Fifth Avenue North Saskatoon, Saskatchewan S7K 2P5 CANADA
[45] Date of publication of grant of patent 批予專利的發表日期	26.06.2020	Wang, Yu Tian 406-6015 Iona Drive Vancouver, British Columbia V6T 2J4 CANADA
[86] International application no. 國際申請編號	PCT/CA2016/050605	[72] Inventor 發明人
[87] International publication no. and date 國際申請發表編號及日期	WO2016/191864 08.12.2016	Taghibiglou, Changiz Wang, Yu Tian
EP Application no. & date 歐洲專利申請編號及日期	EP 16802284.6 27.05.2016	[74] Agent and / or address for service 代理人及/或送達地址
EP Publication no. & date 歐洲專利申請發表編號及日期	EP 3307317 18.04.2018	WILKINSON & GRIST 6th Floor, Prince's Building Chater Road HONG KONG
Date of grant in designated patent office 指定專利當局批予專利日期	04.09.2019	.



(11)

EP 3 307 317 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
04.09.2019 Bulletin 2019/36

(51) Int Cl.:
A61K 38/17 (2006.01) **A61P 17/08 (2006.01)**
A61P 17/10 (2006.01) **A61K 8/00 (2006.01)**
A61K 8/64 (2006.01) **C07K 14/705 (2006.01)**
A61Q 19/00 (2006.01)

(21) Application number: **16802284.6**(22) Date of filing: **27.05.2016**

(86) International application number:
PCT/CA2016/050605

(87) International publication number:
WO 2016/191864 (08.12.2016 Gazette 2016/49)

(54) **POLYPEPTIDES TO TREAT SKIN CONDITIONS ASSOCIATED WITH OVERPRODUCTION OF SEBUM**

POLYPEPTIDE ZUR BEHANDLUNG VON HAUTLEIDEN IM ZUSAMMENHANG MIT DER ÜBERPRODUKTION VON SEBUM

POLYPEPTIDES POUR TRAITER DES AFFECTIONS CUTANÉES ASSOCIÉES À UNE SURPRODUCTION DE SÉBUM

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**

(30) Priority: **29.05.2015 US 201562168374 P**

(43) Date of publication of application:
18.04.2018 Bulletin 2018/16

(73) Proprietors:

- Taghibiglou, Changiz
Saskatoon, Saskatchewan S7K 2P5 (CA)
- Wang, Yu Tian
Vancouver, British Columbia V6T 2J4 (CA)

(72) Inventors:

- Taghibiglou, Changiz
Saskatoon, Saskatchewan S7K 2P5 (CA)
- Wang, Yu Tian
Vancouver, British Columbia V6T 2J4 (CA)

(74) Representative: **Jostarndt Patentanwalts-AG
Philipsstrasse 8
52068 Aachen (DE)**

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Description**FIELD**

5 [0001] The present application relates generally to lipid metabolism, and more specifically to the use of lipid metabolism mediators to treat skin conditions.

BACKGROUND

10 [0002] Sterol regulatory element binding proteins (SREBPs) are endoplasmic reticulum (ER) membrane bound transcription factors best known for their role in activating genes required for cholesterol, fatty acid, triglyceride and phospholipid biosynthesis. SREBP-1 is mostly implicated in regulation of genes involved in fatty acid, phospholipid and triglyceride synthesis, while SREBP-2 is responsible for regulating genes in the cholesterol biosynthesis pathway (Goldstein et al. 2006). In the ER membrane, immature SREBPs exist in a tight association with SREBP cleavage activating protein (SCAP) (Nohturfft et al. 1998). SCAP determines the fate of SREBP based on cellular cholesterol levels or cellular stress. In the case of sterol depletion/cellular stress, SCAP interacts with a member of COPII coat proteins and escorts immature SREBPs (full-length) to the Golgi where they are proteolytically processed and N-terminal released as active (mature) transcription factors. When the cellular cholesterol level is high (or there is no cellular stress), SCAP binds to another ER membrane resident protein called Insig (there are two isoforms, Insig-1 and -2) (Flury et al. 2005) which retains the SREBP-SCAP complex in the ER membrane (Yang et al. 2002; Sun et al. 2005). In cholesterol-depleted cells, Insig-1 protein is rapidly ubiquitinated on lysine-156 and lysine-158 and degraded by proteasomes (Gong et al. 2006; Lee et al. 2006a; Lee et al. 2006b). Cellular stresses such as hypotonic shock and ER stress also activate SREBP via rapid turnover of Insig-1 (Lee and Ye 2004). The degradation of Insig1 in the ER is an essential determining step in release of immature SREBP-1 and its subsequent proteolytic activation in Golgi.

25 [0003] The present application is directed generally to the use of polypeptide inhibitors of ubiquitination of Insig-1 as defined in the claims, and to the use of compositions comprising the polypeptide inhibitors, to treat skin disorders associated with excess sebum production.

30 [0004] Human Insig-1 (EntrezGene ID: 3638) is targeted for degradation by ubiquitination on lysine-156 and lysine-158. Polypeptides of the disclosure comprise amino acid sequences derived from the ubiquitination site of human Insig-1, including amino acid residues lysine-156 and lysine-158 flanked by at least one N-terminal amino acid residue and one C-terminal amino acid residue. Upon application to a sebocyte, these polypeptides may compete with the native Insig-1 protein as a target for ubiquitination, thereby reducing, preventing, or inhibiting ubiquitination of Insig-1; leading to reduction, prevention, or inhibition of Insig-1 within the sebocyte and interfering with the SREBP-1 pathway. Polypeptides of the disclosure have been demonstrated to inhibit the production of sebaceous lipids from sebocytes, in both the presence and absence of linoleic acid and/or testosterone.

35 [0005] An embodiment of the disclosure is a composition for use to treat a skin disease or condition associated with overproduction of sebum, being seborrheic dermatitis said composition comprising a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 21 or a conservatively substituted amino acid sequence of SEQ ID NO: 21 that retains the lysine residues at amino acid positions 2 and 4 of SEQ ID NO: 21 and a pharmaceutically or cosmetically acceptable carrier. In an embodiment, the pharmaceutically or cosmetically acceptable carrier is a topically acceptable carrier. In a further embodiment the composition additionally comprises a skin penetration enhancer.

40 [0006] In an embodiment, the polypeptide further comprises a linker.

45 [0007] In another embodiment, the composition comprises a cell penetrating peptide joined to the polypeptide. In an embodiment, the cell penetrating peptide is joined to the N-terminal end of the polypeptide, optionally by a linker. In another embodiment the cell penetrating polypeptide is joined to the C-terminal end of the polypeptide, optionally by a linker.

50 [0008] In an embodiment, the composition comprises a polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1 to 20 or a conservatively substituted amino acid sequence of any one of SEQ ID NOs: 1 to 20.

55 [0009] In an embodiment, the polypeptide is up to 25 amino acids residues in length. In another embodiment, the polypeptide is up to 40 amino acids in length. In another embodiment, the polypeptide is up to 6, up to 7, up to 8, up to 9, up to 10, up to 11, up to 12, up to 13, up to 14, up to 15, up to 16, up to 17, up to 18, up to 19, up to 20, up to 21, up to 22, up to 23, up to 24, up to 25, up to 26, up to 27, up to 28, up to 29, up to 30, up to 31, up to 32, up to 33, up to 34, up to 35, up to 36, up to 37, up to 38, up to 39, or up to 40 amino acids in length. In another embodiment, the polypeptide is between 5 and 21 amino acids in length. In another embodiment, the polypeptide is at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at

least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, or greater than 25 amino acids in length.

[0010] In an embodiment, the polypeptide comprises an amino acid sequence of any one of SEQ ID NOs: 1, 7-12, 14, 15, and 18-21 flanked at the N and/or C terminus by one or more amino acids that are not native to the sequence flanking the N and/or C terminus of the corresponding portion of human Insig-1. In an embodiment, the polypeptide comprises an amino acid sequence of any one of SEQ ID NOs: 1, 7-12, 14, 15, and 18-21 flanked at the N and/or C terminus by at least one, two, or three amino acids that are not native to the sequence flanking the N and/or C terminus of the corresponding portion of human Insig-1.

[0011] In an embodiment, the polypeptide comprises an amino acid having at least 80% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 2 or having at least 80% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

[0012] In an embodiment, the polypeptide comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 2 or having at least 90% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

[0013] In an embodiment, the polypeptide comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 2 or having at least 95% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:2.

[0014] In an embodiment, the polypeptide comprises an amino acid sequence having an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion or having a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion, and the polypeptide is capable of inhibiting ubiquitination of Insig-1.

[0015] In an embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[0016] In an embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[0017] In an embodiment, the polypeptide has an amino acid sequence consisting of SEQ ID NO: 1 or SEQ ID NO: 2.

[0018] Another embodiment is a topical composition for use to treat a skin disease or condition associated with over-production of sebum being seborrheic dermatitis comprising a polypeptide of the disclosure.

[0019] Yet another embodiment is a method of treating a skin condition associated with overproduction of sebum, being acne the method comprising administering a polypeptide of the disclosure to a subject in need of treatment. In an embodiment the skin condition is acne or seborrheic dermatitis. In another embodiment the skin condition is acne. In an embodiment, the administration is topical administration.

[0020] A still further embodiment is use of a polypeptide of the disclosure to cosmetically treat a skin condition associated with overproduction of sebum being acne.

[0021] Another embodiment is a method of altering lipid production by a sebocyte cell by administering to the cell a polypeptide of the disclosure. The administration is in vitro administration. In an embodiment, the alteration is a reduction in lipid production relative to a control sebocyte cell.

[0022] In other aspects, there is provided an in vitro method for preventing, inhibiting or reducing SREBP-1 in a sebaceous lipid producing cell, the method comprising contacting the cell with a polypeptide having an amino acid composition substantially similar to SEQ ID NO: 1 or SEQ ID NO: 2. The sebaceous lipid producing cell is a sebocyte.

DESCRIPTION OF FIGURES

[0023] **Figures 1A, 1B, and 1C. Effect of an INDIP peptide (SEQ ID NO: 2) on sebaceous lipid production.** Increasing amounts of the INDIP peptide were applied to SZ95 sebocytes either in the absence (A) of linoleic acid and testosterone, or in the presence (B and C) of different amounts of linoleic acid and testosterone.

DETAILED DESCRIPTION

[0024] Any terms not directly defined herein shall be understood to have the meanings commonly associated with them as understood within the art. As employed throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

[0025] As used herein "a", "an" and/or "the" includes one and/or more than one.

[0026] As used herein the term "about" means than the value or range of values can be greater than or lesser than the stated value or range of values by 10%, but is not intended to limit any value or range of values to only this broader definition. Each value or range of values preceded by the term "about" is also intended to encompass the stated absolute value or range of values.

[0027] As used herein the term "subject" refers to an animal, such as a bird or a mammal. Specific animals include rat, mouse, dog, cat, cow, sheep, horse, pig or primate. A subject may further be a human, alternatively referred to as

a patient. A subject may further be a transgenic animal. A subject may further be a rodent, such as a mouse or a rat.

[0028] The term "SCAP" refers to SREBP cleavage activating protein, which is encoded by the gene corresponding to EntrezGene ID: 22937. SREBP cleavage-activating protein (SCAP) is a regulatory protein that is required for the proteolytic cleavage of the sterol regulatory element binding protein (SREBP). SCAP is an integral membrane protein located in the endoplasmic reticulum (ER). One of the cytosolic regions of SCAP contains a hexapeptide amino acid sequence, MELADL, that functions to detect cellular cholesterol. When cholesterol is present, SCAP undergoes a conformational change that prevents it from activating SREBP and cholesterol synthesis does not occur. SCAP has 8 transmembrane domains and both the N-terminal and C-terminal face the cytoplasm. Also, it binds SREBP by a series of consecutive WD repeats on its C-terminus.

[0029] The term "SREBP1" refers to sterol regulatory element binding protein 1, which may alternately be referred to as SREBF-1 or SREBP-1. The gene which encodes this protein corresponds to EntrezGene ID: 6720. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the endoplasmic reticulum membrane. In cells with low levels of sterols, SREBPs are cleaved to a water soluble N-terminal domain which is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences which upregulate the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feedback loop, as described herein.

[0030] The term "Insig-1" refers to the protein product of insulin-induced gene 1 (EntrezGene ID: 3638). The polypeptide is 277 amino acids in length. This protein binds to the sterol-sensing domains of SREBP cleavage-activating protein (SCAP) and HMG CoA reductase, and is essential for the sterol-mediated trafficking of the two proteins. Alternatively spliced transcript variants encoding distinct isoforms have been observed. Degradation of Insig-1 by ubiquitin-mediated pathways is essential for SCAP/SREBP regulation, as described herein. Human Insig-1 is targeted for degradation by ubiquitination on lysine-156 and lysine-158. The present application provides various compositions and methods for modulating ubiquitination of Insig-1.

The terms "peptide", "polypeptide" and "protein" may be used interchangeably, and refer to a compound comprised of at least two amino acid residues covalently linked by peptide bonds or modified peptide bonds, for example peptide isosteres (modified peptide bonds) that may provide additional desired properties to the peptide, such as increased half-life. A peptide may comprise at least two amino acids. The amino acids comprising a peptide or protein described herein may also be modified either by natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Modifications can occur anywhere in a peptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It is understood that the same type of modification may be present in the same or varying degrees at several sites in a given peptide. Examples of modifications to peptides may include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, Proteins-Structure and Molecular Properties, 2nd ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993 and Wold F, Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in Posttranslational Covalent Modification of Proteins, B.C. Johnson, ed., Academic Press, New York, 1983; Seifter et al., Analysis for protein modifications and nonprotein cofactors, *Meth. Enzymol.* (1990) 182: 626-646 and Rattan et al. (1992), Protein Synthesis: Posttranslational Modifications and Aging, " *Ann NY Acad Sci* 663: 48-62.

[0031] As used herein, the term "cell-penetrating peptide", also referred to as a "protein transduction domain", refers to a peptide that is capable of carrying a large macromolecule, such as a peptide, across a cellular membrane, for example as described in Nasrollahi et al (2012), *Chem Biol Drug Des* 80: 639-646. Cell penetrating peptides are relatively short (up to 30 amino acids in length), water soluble, cationic and/or amphipathic peptides that may be joined to polypeptides, for example through recombinant expression, covalent linkage, or peptide synthesis, to improve the ability of the polypeptide to pass through cell membranes. The cell penetrating peptide may be joined to either the N-terminal end of the polypeptide or the C-terminal end of the polypeptide, optionally by a linker. Cell penetrating peptides have also been shown to facilitate skin penetration. As used herein the term "cell penetrating peptide" is also intended to include skin penetrating peptides, for example as described in Menegatti et al (2016), *Advanced Healthcare Materials*, 5(5):602-609 and Kumar et al (2015) *Journal of Controlled Release* 199:168-178. Cell penetrating and skin penetrating peptides are known in the art and include Penetratin, Tat, Transportan, MAP, KALA, P1, MPG, Pep-1, polyarginine, polylysine, hCT, SPACE, and TD-1.

[0032] As used herein the term "linker" is intended to include peptide linkers and chemical cross-linkers. Peptide linkers are relatively short amino acid sequences used to join one polypeptide sequence to another. Typically a peptide linker

will be between about 1 to about 30 amino acids in length. The peptide linker may be a flexible linker having a glycine-rich sequence. For example, the linker may comprise a series of one to five, or more, glycine residues. Chemical cross-linkers for covalently joining polypeptides are well known in the art and include but are not limited to amine-to-amine crosslinkers, sulfhydryl-to-sulfhydryl crosslinkers, amine-to-sulfhydryl crosslinkers, *in vivo* crosslinking reagents, and carboxyl-to-amine crosslinkers.

[0033] A "substantially similar" amino acid sequence is an amino acid sequence that differs from a reference sequence by one or more conservative substitutions, but which may, for example, be functionally homologous to another substantially similar sequence. It will be appreciated by a person of skill in the art the aspects of the individual amino acids in a peptide of the application that may be substituted.

[0034] Amino acid sequence similarity or identity may be computed by using the BLASTP and TBLASTN programs which employ the BLAST (basic local alignment search tool) 2.0 algorithm. Techniques for computing amino acid sequence similarity or identity are well known to those skilled in the art, and the use of the BLAST algorithm is described in ALTSCHUL et al. 1990, *J Mol. Biol.* 215: 403- 410 and ALTSCHUL et al. (1997), *Nucleic Acids Res.* 25: 3389-3402.

[0035] Amino acids may be described as, for example, polar, non-polar, acidic, basic, aromatic or neutral. A polar amino acid is an amino acid that may interact with water by hydrogen bonding at biological or near-neutral pH. The polarity of an amino acid is an indicator of the degree of hydrogen bonding at biological or near-neutral pH. Examples of polar amino acids include serine, proline, threonine, cysteine, asparagine, glutamine, lysine, histidine, arginine, aspartate, tyrosine and glutamate. Examples of non-polar amino acids include glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, and tryptophan. Acidic amino acids have a net negative charge at a neutral pH. Examples of acidic amino acids include aspartate and glutamate. Basic amino acids have a net positive charge at a neutral pH. Examples of basic amino acids include arginine, lysine and histidine. Aromatic amino acids are generally nonpolar, and may participate in hydrophobic interactions. Examples of aromatic amino acids include phenylalanine, tyrosine and tryptophan. Tyrosine may also participate in hydrogen bonding through the hydroxyl group on the aromatic side chain. Neutral, aliphatic amino acids are generally nonpolar and hydrophobic. Examples of neutral amino acids include alanine, valine, leucine, isoleucine and methionine. An amino acid may be described by more than one descriptive category. Amino acids sharing a common descriptive category may be substitutable for each other in a peptide.

[0036] Nomenclature used to describe the peptide compounds of the present application follows the conventional practice where the amino group is presented to the left and the carboxyl group to the right of each amino acid residue. In the sequences representing selected specific embodiments of the present application, the amino- and carboxy-terminal groups, although not specifically shown, will be understood to be in the form they would assume at physiologic pH values, unless otherwise specified. In the amino acid structure formulae, each residue may be generally represented by a one-letter or three-letter designation, corresponding to the trivial name of the amino acid, in accordance with the following Table 1:

Table 1: Nomenclature and abbreviations of the 20 standard L-amino acids commonly found in naturally occurring peptides.

Full name	Three-letter abbreviation	One-letter abbreviation
Alanine	Ala	A
Cysteine	Cys	C
Aspartic acid	Asp	D
Glutamic acid	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
Asparagine	Asp	N
Proline	Pro	P
Glutamine	Gln	Q

(continued)

Full name	Three-letter abbreviation	One-letter abbreviation
5 Arginine	Arg	R
Serine	Ser	S
Threonine	Thr	T
10 Valine	Val	V
Tryptophan	Trp	W
Tyrosine	Tyr	T

15 [0037] The hydropathy index of an amino acid is a scale indicating the tendency of an amino acid to seek out an aqueous environment (negative value) or a hydrophobic environment (positive value) (KYTE & DOOLITTLE 1982. *J Mol Biol* 157:105-132). Hydropathy indices of the standard amino acids include alanine (1.8), arginine (-4.5), asparagine (-3.5), aspartic acid (-3.5), cysteine (2.5), glutamine (-3.5), glutamic acid (-3.5), glycine (-0.4), histidine (-3.2), isoleucine (4.5), leucine (3.8), lysine (-3.9), methionine (1.9), phenylalanine (2.8), proline (-1.6), serine (-0.8), threonine (-0.7), tryptophan (-0.9), tyrosine (-1.3), and valine (4.2). Amino acids with similar hydropathy indices may be substitutable for each other in a peptide.

20 [0038] Amino acids contained within the peptides described herein will be understood to be in the L- or D- configuration. In peptides and peptidomimetics of the present application, D-amino acids may be substitutable for L-amino acids. Amino acids contained within the peptides of the present application, and particularly at the carboxy- or amino-terminus, may be modified by methylation, amidation, acetylation or substitution with other chemical groups which may change the 25 circulating half-life of the peptide without adversely affecting their biological activity. Additionally, a disulfide linkage may be present or absent in the peptides of the application.

30 [0039] Nonstandard amino acids may occur in nature, and may or may not be genetically encoded. Examples of genetically encoded nonstandard amino acids include selenocysteine, sometimes incorporated into some proteins at a UGA codon, which may normally be a stop codon, or pyrrolysine, sometimes incorporated into some proteins at a UAG codon, which may normally be a stop codon. Some nonstandard amino acids that are not genetically encoded may 35 result from modification of standard amino acids already incorporated in a peptide, or may be metabolic intermediates or precursors, for example. Examples of nonstandard amino acids include 4-hydroxyproline, 5-hydroxylysine, 6-N-methyllysine, gamma-carboxyglutamate, desmosine, selenocysteine, ornithine, citrulline, lanthionine, 1-aminocyclopropane-1-carboxylic acid, gamma-aminobutyric acid, carnitine, sarcosine, or N-formylmethionine. Synthetic variants of standard 40 and non-standard amino acids are also known and may include chemically derivatized amino acids, amino acids labeled for identification or tracking, or amino acids with a variety of side groups on the alpha carbon. Examples of such side groups are known in the art and may include aliphatic, single aromatic, polycyclic aromatic, heterocyclic, heteronuclear, amino, alkylamino, carboxyl, carboxamide, carboxyl ester, guanidine, amidine, hydroxyl, alkoxy, mercapto-, alkylmercapto-, or other heteroatom-containing side chains. Other synthetic amino acids may include alpha-imino acids, non-alpha amino acids such as beta-amino acids, des- carboxy or des-amino acids. Synthetic variants of amino acids may be synthesized using general methods known in the art, or may be purchased from commercial suppliers, for example RSP Amino Acids LLC (Shirley, MA).

45 [0040] The polypeptides of the present application may be in isolation, or may be linked to or in combination with tracer compounds, protein transduction domains or sequences, liposomes, carbohydrate carriers, polymeric carriers or other agents or excipients as will be apparent to one of skill in the art. In an alternate embodiment, such peptides may comprise a medicament, wherein such peptides may be present in a pharmacologically effective amount.

50 [0041] Conservative substitutions: It will be understood by one skilled in the art that conservative substitutions may be made in the amino acid sequence of a polypeptide without disrupting the three-dimensional structure or function of the polypeptide. Accordingly, the present application includes polypeptides comprising conservatively substituted amino acid sequences of SEQ ID NO:1 and SEQ ID NO: 2. Conservative substitutions are accomplished by the skilled artisan by substituting amino acids with similar hydrophobicity, polarity, and R chain length for one another. Additionally, by comparing aligned sequences of homologous proteins from different species, conservative substitutions may be identified by locating amino acid residues that have been mutated between species without altering the basic functions of the encoded proteins. Table 2 provides an exemplary list of conservative substitutions.

Table 2: Conservative Amino Acid Substitutions

Type of Amino Acid	Substitutable Amino Acids
Hydrophilic	Ala, Pro, Gly, Glu, Asp, Gln, Asn, Ser
Sulphydryl	Cys
Aliphatic	Val, Ile, Leu, Met
Basic	Lys, Arg, His
Aromatic	Phe, Tyr, Trp

[0042] The term "medicament" as used herein, a "medicament" refers to a composition that may be administered to a patient or test subject and is capable of producing an effect in the patient or test subject. The effect may be chemical, biological or physical, and the patient or test subject may be human, or a non-human animal, such as a rodent or transgenic mouse, or a dog, cat, cow, sheep, horse, hamster, guinea pig, rabbit or pig. The medicament may be comprised of the effective chemical entity alone or in combination with a pharmaceutically acceptable excipient.

[0043] The term "pharmaceutically acceptable excipient" may include any and all solvents, dispersion media, coatings, antibacterial, antimicrobial or antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. An excipient may be suitable for intravenous, intraperitoneal, intramuscular, subcutaneous, intrathecal, topical or oral administration. An excipient may include sterile aqueous solutions or dispersions for extemporaneous preparation of sterile injectable solutions or dispersion. Use of such media for preparation of medicaments is known in the art.

[0044] The term "skin penetration enhancer" may include any and all skin penetration enhancers that are physiologically compatible. Examples of skin penetration enhancers include alcohols, amides, esters, ether alcohols, fatty acids, glycols, pyrrolidones, sulphoxides, surfactants, and terpenes. Use of such skin penetration enhancers for the formulation of topical delivery systems is known in the art.

[0045] As used herein, the term "skin disorder associated with overproduction of sebum" includes skin conditions believed to be caused or exacerbated by excessive sebum production by sebaceous glands. Sebum is produced by the sebaceous glands and is composed of keratin, fat, and cellular debris. Skin disorders associated with overproduction of sebum include acne and seborrhea; including seborrheic dermatitis (cradle cap, dandruff), seborrhea congestive, seborrheic blepharitis, and seborrheic keratosis.

[0046] The term "treatment or treating" as used herein means an approach for obtaining beneficial or desired results, including clinical results. Treatment includes therapeutic treatment and prophylactic treatment. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. The term "treatment or treating" in some embodiments means preventing disease at a subclinical stage.

[0047] The term a "therapeutically effective amount", "effective amount" or a "sufficient amount" of a composition of the present disclosure is a quantity sufficient to, when administered to the subject, including a mammal, for example a human, effect beneficial or desired results, including clinical results, and, as such, an "effective amount" or synonym thereto depends upon the context in which it is being applied. In the context of disease, therapeutically effective amounts of the agents are used to treat, modulate, attenuate, reverse, or affect disease, condition or disorder, such as the skin disorder associated with overproduction of sebum. An "effective amount" is intended to mean that amount of a composition that is sufficient to treat, prevent or inhibit such disorders, conditions or diseases. The amount of a given agent that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of condition, disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. As defined herein, a therapeutically effective amount of an agent may be readily determined by one of ordinary skill by routine methods known in the art.

[0048] Moreover, a "treatment" or "prevention" regime of a subject with a therapeutically effective amount of an agent may consist of a single administration, or alternatively comprise a series of applications. For example, the agent may be administered at least once a week. However, in another embodiment, the agent may be administered to the subject from about one time per week to about twice daily for a given treatment. The length of the treatment period depends on a variety of factors, such as the severity of the disease, the age of the subject, the concentration and the activity of the agent, or a combination thereof. It will also be appreciated that the effective dosage of the agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic

administration may be required.

[0049] The term "administering" is defined as any conventional route for administering an agent to a subject for use, for example, in treating a skin condition, disease or disorder, as is known to one skilled in the art. This may include, for example, topical administration. In other embodiments this may include parenteral (i.e. subcutaneous, intradermal, intramuscular, intravenous, etc.), oral, sublingual, or mucosal administration and the like. The dose of the agent may vary according to factors such as the severity of the skin condition and the health, age, weight and/or sex of the subject. The dosage regime may be adjusted to provide the optimum dose. One skilled in the art will appreciate that the dosage regime can be determined and/or optimized without undue experimentation.

[0050] As used herein "altering lipid production" of a sebocyte cell includes a change in lipid production by the sebocyte cell as compared to a control sebocyte cell to which a polypeptide of the disclosure has not been administered. The change in lipid production may, for example, be a change in the rate of lipid production, the amount of lipid production, or a change in the lipid profile produced by the cell. In some instances, the change will be a reduction in the rate and/or amount of lipid produced by the sebocyte cell.

[0051] Administering a composition to a cell includes in vivo, ex vivo and in vitro administration.

[0052] The polypeptides of the present disclosure may be administered as a sterile aqueous solution, or may be administered in a fat-soluble excipient, or in another solution, suspension, patch, tablet or paste format as is appropriate. A composition of the disclosure may be formulated for administration by inhalation. For instance, a polypeptide may be combined with an excipient to allow dispersion in an aerosol. Examples of inhalation formulations will be known to those skilled in the art. Other agents may be included in combination with the polypeptides of the present disclosure to aid uptake or metabolism, or delay dispersion within the host, such as in a controlled-release formulation. Examples of controlled release formulations will be known to those of skill in the art, and may include microencapsulation, embolism within a carbohydrate or polymer matrix, and the like. Other methods known in the art for making formulations are found in, for example, "Remington's Pharmaceutical Sciences", (19th edition), ed. A. Gennaro, 1995, Mack Publishing Company, Easton, Pa.

[0053] Polypeptides of the disclosure may be included in a cosmetic composition. For example, polypeptides of the disclosure may be included in cosmetic products such as beauty masks, make-up, cosmetic patches, and creams or lotions.

[0054] The term "pharmaceutically acceptable" means compatible with the treatment of humans and animals.

[0055] The term "cosmetically acceptable" means compatible with cosmetic application to humans and animal.

[0056] Delivery of bioactive molecules such as polypeptides, to a cell or cells in a reasonably efficient manner may require more than just applying the naked peptide onto the cell, or administering the naked peptide into the patient or test subject. Agents that enable delivery of bioactive molecules into cells in a suitable manner so as to provide an effective amount, such as a pharmacologically effective amount are known in the art, and are described in, for example, DIETZ et al 2004. Mol Cell. Neurosci 27:85-131. Examples of such agents include liposomes, antibodies or receptor ligands that may be coupled to the bioactive molecule, viral vectors, and protein transduction domains (PTD). Examples of PTDs include *Antennapedia* homeodomain (PEREZ et al 1992 J. Cell Sci 102:717-722), transportan (POOGA et al 1998 FASEB J 12: 67-77), the translocation domains of diphtheria toxin (STENMARK et al 1991 J Cell Biol 113:1025-1032; WIEDLOCHA et al 1994 Cell 76:1039-1051), anthrax toxin (BALLARD et al 1998 Infect. Immun 66:615-619; BLANKE et al 1996 Proc Natl Acad Sci 93: 8437-8442) and *Pseudomonas* exotoxin A (PRIOR et al 1992 Biochemistry 31:3555-3559), protegrin derivatives such as dermaseptin S4 (HARITON-GAZAL et al 2002 Biochemistry 41:9208-9214), HSV-1 VP22 (DILBER et al 1999 Gene Ther. 6:12-21), PEP-1 (MORRIS et al 2001 Nature Biotechnol 19:1173-1176), basic peptides such as poly-L and poly-D-lysine (WOLFERT et al 1996 Gene Ther. 3:269-273; RYSER et al 1980 Cancer 45:1207-1211; SHEN et al 1978 Proc Natl Acad Sci 75:1872-1876), HSP70 (FUJIHARA et al 1999 EMBO J 18:411-419) and HIV-TAT (DEMARCHI et al 1996 J Virol 70:4427-4437). Other examples and related details of such protein transduction domains are described in DIETZ, *supra* and references therein. In an embodiment, a composition of the disclosure may comprise a delivery agent.

[0057] The polypeptides and compositions of the disclosure may be capable of inhibiting ubiquitination of Insig-1, and thereby inhibiting SREBP-1. Examples of such polypeptides include polypeptides comprising the amino acid sequences set forth in Table 3, as well as conservatively substituted derivatives of the amino acid sequences set forth in Table 3, provided they comprise SEQ ID NO:21. Examples of such polypeptides also include polypeptides having single amino acid substitutions (conservative or non-conservative), deletions, or insertions of the amino acid sequences set forth in Table 3, provided that the resulting polypeptides retain the ability to inhibit ubiquitination of Insig-1. Examples of such polypeptides additionally include those described in WO2009121176A1,

Table 3: Sequence Listing

SEQ ID NO:	SEQUENCE
1	GEPHKFKREW

(continued)

SEQ ID NO:	SEQUENCE
2	YGRKKRQRRGEHKFKREW
3	GGEHKFKREW
4	GGGEPHKFKREW
5	GGGGEHKFKREW
6	GGGGGEHKFKREW
7	EPHKFKREW
8	GEPHKFKRE
9	EPHKFKRE
10	GEPHKFKRE
11	EPHKFKRE
12	PHKFKRE
13	PHKFKR
14	PHKFKK
15	DPHKFKREW
16	EPHKFKREF
17	DPHKFKREF
18	EPHKFKRDW
19	EPHKFKRD
20	PHKFKRD
21	HKFKR

[0058] Polypeptides of the disclosure may be capable of preventing or inhibiting ubiquitination of Insig-1, and thereby inhibiting SREBP-1. An example of such a polypeptide is illustrated below in working Example 1. Peptides derived from a peptide having substantial similarity to the ubiquitination region of the Insig-1 protein are referred to herein as INDIP peptides. The term "INDIP peptide" includes polypeptides comprising SEQ ID NOs 1 to 21 and polypeptides comprising conservatively substituted SEQ ID NOs 1 to 21. Generally speaking, INDIP peptides comprise a short fragment of the Insig-1 ubiquitination region and may be attached to a protein transduction domain such as the TAT protein transduction domain to produce a PTD-fused Insig-1 ubiquitination region peptide (for example, see SEQ ID NO: 2). INDIP peptides have been previously described (WO2009121176A1).

[0059] An embodiment of the disclosure is a composition for use to treat a skin disease or condition associated with overproduction of sebum, said composition comprising a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 21 or a conservatively substituted amino acid sequence of SEQ ID NO: 21 that retains the lysine residues at amino acid positions 2 and 4 of SEQ ID NO: 21 and a pharmaceutically or cosmetically acceptable carrier. In an embodiment, the pharmaceutically or cosmetically acceptable carrier is a topically acceptable carrier. In a further embodiment the composition additionally comprises a skin penetration enhancer.

[0060] In an embodiment, the polypeptide further comprises a linker.

[0061] In another embodiment, the composition comprises a cell penetrating peptide joined to the polypeptide. In an embodiment, the cell penetrating peptide is joined to the N-terminal end of the polypeptide, optionally by a linker. In another embodiment the cell penetrating polypeptide is joined to the C-terminal end of the polypeptide, optionally by a linker.

[0062] In an embodiment, the composition comprises a polypeptide comprising an amino acid sequence of any one of SEQ ID NOs: 1 to 20 or a conservatively substituted amino acid sequence of any one of SEQ ID NOs: 1 to 20.

[0063] In an embodiment, the polypeptide is up to 25 amino acids residues in length. In another embodiment, the polypeptide is up to 40 amino acids in length. In another embodiment, the polypeptide is up to 6, up to 7, up to 8, up to 9, up to 10, up to 11, up to 12, up to 13, up to 14, up to 15, up to 16, up to 17, up to 18, up to 19, up to 20, up to 21, up

to 22, up to 23, up to 24, up to 25, up to 26, up to 27, up to 28, up to 29, up to 30, up to 31, up to 32, up to 33, up to 34, up to 35, up to 36, up to 37, up to 38, up to 39, or up to 40 amino acids in length. In another embodiment, the polypeptide is between 5 and 21 amino acids in length. In another embodiment, the polypeptide is at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, or greater than 25 amino acids in length.

[0064] In an embodiment, the polypeptide comprises an amino acid sequence of any one of SEQ ID NOs: 1, 7-12, 14, 15, and 18-21 flanked at the N and/or C terminus by one or more amino acids that are not native to the sequence flanking the N and/or C terminus of the corresponding portion of human Insig-1. In an embodiment, the polypeptide comprises an amino acid sequence of any one of SEQ ID NOs: 1, 7-12, 14, 15, and 18-21 flanked at the N and/or C terminus by at least one, two, or three amino acids that are not native to the sequence flanking the N and/or C terminus of the corresponding portion of human Insig-1.

[0065] In an embodiment, the polypeptide comprises an amino acid having at least 80% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 2 or having at least 80% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

[0066] In an embodiment, the polypeptide comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 2 or having at least 90% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

[0067] In an embodiment, the polypeptide comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 2 or having at least 95% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:2.

[0068] In an embodiment, the polypeptide comprises an amino acid sequence having an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion or having a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion, and the polypeptide is capable of inhibiting ubiquitination of Insig-1.

[0069] In an embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[0070] In an embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[0071] In an embodiment, the polypeptide has an amino acid sequence consisting of SEQ ID NO: 1 or SEQ ID NO: 2.

[0072] Another embodiment is a topical composition for use to treat a skin disease or condition associated with over-production of sebum comprising a polypeptide of the disclosure.

[0073] The following non-limiting example is illustrative of the present disclosure:

EXAMPLE 1 - Application of an INDIP peptide (SEQ ID NO: 2) to SZ95 sebocytes in vitro causes significant reduction in lipid production

[0074] SZ95 is an immortalized human sebocyte cell line that is widely used as an in vitro human sebocyte model. Cultured SZ95 sebocytes have been shown to retain major characteristics of normal human sebocytes, including the expression of sebaceous gland protein markers and expected biological responses to androgens and retinoids (Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterization of an immortalized human sebaceous gland cell line (SZ95) J Invest Dermatol. 1999;113:1011-1020 and Wróbel A, Seltmann H, Fimmel S, Müller-Decker K, Tsukada M, Bogdano VB, et al. Differentiation and apoptosis in human immortalized sebocytes. J Invest Dermatol. 2003;120:175-181).

Methods

[0075] Cell Cultures. Immortalized human facial SZ95 sebocytes, which have been shown to conserve the major characteristics of normal sebocytes [Zouboulis, Ch. C., Seltmann, H., Neitzel, H. & Orfanos, C. E. (1999) J. Invest. Dermatol. 113, 1011-1020], were maintained in Sebomed Basal Medium (Biochrom, Berlin) supplemented with 5 ng/ml human epidermal growth factor (Sigma), 10% heat inactivated FCS (Biochrom GmbH, Berlin, Germany), 50 ug/ml gentamicin (GIBCO/BRL), and 1 mM Ca²⁺, in a humidified atmosphere of 5% CO₂ at 37°C. Shortly before the experiments were performed, BSA-medium [constituted of Sebomed Basal Medium supplemented with 1 mg/ml fatty acid-free BSA (Boehringer Mannheim), 1 mM Ca²⁺, and 10-6 M linoleic acid (Sigma)] or Sebomed Complete Medium (Biochrom) was added to the cells. The SZ95 human sebocytes used for the experiments were between passages 31 and 35. The cells were subcultured at 60-70% confluence. The cultures were maintained at 37°C in a humidified 5% CO₂ incubator and the medium was replaced every 2-3 days.

[0076] Detection of Lipids. The cells were cultured in 96-well tissue culture plates at a density of 2,000 cells per well for 2 days. The wells were then washed with PBS, and Sebomed Complete Medium was added. After 2 days, the medium

was harvested, and fresh medium without or with INDIP peptide (SEQ ID NO: 2) at a concentration of 0, 0.1, 1, 10, or 20 μ M in the presence and absence of Linoleic acid (5×10^{-5} and 10^{-4} M) and Testosterone (2×10^{-8} M) was given to the cells. The supernatants were harvested 24 or 48 h later; the wells were washed twice with PBS, and 100 μ l of a 10 μ g/ml nile red solution in PBS was added to each well. 10 μ M of scrambled INDIP peptide (i.e. a scrambled version of SEQ ID NO: 2) was used as the negative control peptide. The plates were then incubated at 37°C for 30 min, and the released fluorescence was read on a Molecular Devices SPECTRAmax Gemini spectrofluorometer. The results are presented as percentages of the absolute fluorescence units in comparison with the controls, using 485 nm excitation and 565 nm emission filters for neutral lipids and 540 nm excitation and 620 nm emission filters for polar lipids. Experiments were performed in triplicate, with 10 wells evaluated for each data point in each experiment.

[0077] Proliferation and Cell Number Analysis. Cells were cultured in 96-well tissue culture plates at a density of 2,000 cells per well for 2 days. The wells were then washed with PBS, and BSA-medium with or without active compounds was added. Cell proliferation was conducted using the 4-methylumbelliferyl heptanoate fluorescence assay and measured automatically, as previously described [Zouboulis, Ch. C., Garbe, C., Krasagakis, K., Kruger, S., Schroder, K. & Orfanos, C. E. (1991) Melanoma Res. 1, 91-95.]. Briefly, after removing the media, the cells were washed twice with PBS, and 100 μ l of a 100 μ g/ml 4-methylumbelliferyl heptanoate solution in PBS was added to each well. The plates were then incubated at 37°C for 30 min, and the released fluorescence, which is representative for cell numbers, was read on a Molecular Devices SPECTRAmax Gemini spectrofluorometer using 355 nm excitation and 460 nm emission filters. Relative cell numbers were plotted as "Cell Amount". Experiments were performed in quadruplicate, with 10 wells evaluated for each data point in each experiment.

Results

[0078] Figures 1A, 1B, and 1C show the results of addition of an INDIP peptide (SEQ ID NO: 2) to in vitro cell cultures of SZ95 sebocytes. Figure 1A shows the results of application of the INDIP peptide without the addition of stimulants linoleic acid and testosterone, while Figures 1B and 1C show the results of application of increasing concentrations of the INDIP peptide in the presence of different concentrations of linoleic acid and testosterone. At a 20 μ M, and occasionally at a 10 μ M concentration of the INDIP peptide, the production of neutral (sebaceous) lipids was significantly reduced over time, with a greater effect seen as time progressed (24 vs 48 hours). These results were seen either in the absence or in the presence of linoleic acid and testosterone. The concomitant reduction of polar lipids indicates a parallel reduction of membrane synthesis, i.e. a reduction of the synthetic activity of the cells. This indicates that the INDIP peptide (SEQ ID NO: 2) is able to reduce sebaceous differentiation in all conditions tested, with and without the stimulating effect of the combined linoleic acid and testosterone.

[0079] While the present disclosure has been described with reference to specific examples, it is to be understood that the disclosure is not limited to the disclosed examples.

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Claims

1. A composition for use in the treatment of a skin disease or condition associated with overproduction of sebum being seborrheic dermatitis, said composition comprising a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 21 or a conservatively substituted amino acid sequence of SEQ ID NO: 21 that retains the lysine residues at amino acid positions 2 and 4 of SEQ ID NO: 21 and a pharmaceutically or cosmetically acceptable carrier.
2. The composition for use according to claim 1, wherein the polypeptide further comprises a linker.
3. The composition for use according to claim 1 or 2, wherein the composition further comprises a cell penetrating peptide or skin penetrating peptide joined to the polypeptide.
4. A composition for use according to any one of the above claims, wherein the polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 21.
5. The composition for use according to any one of the above claims, wherein the polypeptide comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 2 or having at least 90% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.
6. The composition for use according to any one of claims 1 to 4, wherein the polypeptide comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 2 or having at least 95% sequence identity to a conservatively substituted amino acid sequence of SEQ ID NO:2.
7. The composition for use according to any one of claims 1 to 4, wherein the polypeptide comprises an amino acid sequence having an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion or having a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 with a single non-conservative amino acid substitution, deletion, or insertion and wherein the polypeptide inhibits ubiquitination of Insig-1.
8. The composition for use according to any one of claims 1 to 4, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or a conservatively substituted amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
- 55 9. The composition for use according to any one of claims 1 to 4, wherein the composition is a topical composition.
10. Use of a polypeptide as set forth in any one of claims 1 to 8 to cosmetically treat a skin condition associated with overproduction of sebum being acne.

11. A method of altering lipid production by a sebocyte cell, said method comprising administering to the cell a polypeptide as set forth in any one of claims 1 to 8, wherein the administration is carried out in vitro.

12. The method of claim 11, wherein the alteration is a reduction in lipid production relative to a control sebocyte cell.

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Patentansprüche

1. Zusammensetzung zur Verwendung bei der Behandlung einer Hautkrankheit oder einem Hautleiden in Zusammenhang mit der Überproduktion von Sebum, bei dem es sich um Seborrhoische Dermatitis handelt, wobei die Zusammensetzung ein Polypeptid aufweist, das eine Aminosäuresequenz gemäß der SEQ ID NO: 21 oder eine konservativ substituierte Aminosäuresequenz der SEQ ID NO: 21 aufweist, die die Lysinreste bei Aminosäuresequenzen 2 und 4 der SEQ ID NO: 21 hält, sowie einen pharmazeutisch oder kosmetisch akzeptablen Träger.

15. 2. Zusammensetzung zur Verwendung nach Anspruch 1, wobei das Polypeptid ferner einen Linker aufweist.

3. Zusammensetzung zur Verwendung nach Anspruch 1 oder 2, wobei die Zusammensetzung ferner ein hautdurchdringendes oder in Zellen eindringendes Peptid aufweist, das an das Polypeptid angelagert ist.

20. 4. Zusammensetzung zur Verwendung nach einem der vorstehenden Ansprüche, wobei das Polypeptid eine Aminosäuresequenz gemäß SEQ ID Nr. 21 aufweist.

25. 5. Zusammensetzung zur Verwendung nach einem der vorstehenden Ansprüche, wobei das Polypeptid eine Aminosäuresequenz mit zumindest 90 % Sequenzidentität zu SEQ ID Nr. 1 oder SEQ ID Nr. 2 oder zumindest 90 % Sequenzidentität zu einer konservativ substituierten Aminosäuresequenz der SEQ ID Nr. 1 oder SEQ ID Nr. 2 aufweist.

30. 6. Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Polypeptid eine Aminosäuresequenz mit zumindest 95 % Sequenzidentität zu SEQ ID Nr. 2 oder mit zumindest 95 % Sequenzidentität zu einer konservativ substituierten Aminosäuresequenz der SEQ ID Nr. 2 aufweist.

35. 7. Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Polypeptid eine Aminosäuresequenz mit einer Aminosäuresequenz der SEQ ID Nr. 1 oder SEQ ID Nr. 2 mit einer einzelnen nicht-konservativen Aminosäuresequenzsubstitution, -deletion, oder -insertion aufweist, oder mit einer konservativ substituierten Aminosäuresequenz der SEQ ID Nr. 1 oder SEQ ID Nr. 2 mit einer einzelnen, nicht-konservativen Aminosäuresubstitution, -deletion, oder -insertion aufweist, und wobei das Polypeptid die Ubiquitinierung von Insig-1 hemmt.

40. 8. Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Polypeptid eine Aminosäuresequenz der SEQ ID Nr. 1 oder SEQ ID Nr. 2 oder eine konservativ substituierte Aminosäuresequenz der SEQ ID NR. 1 oder SEQ ID Nr. 2 aufweist.

45. 9. Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei die Zusammensetzung eine topische Zusammensetzung ist.

10. 10. Verwendung eines Polypeptid nach einem der Ansprüche 1 bis 8, zur kosmetischen Behandlung einer Hautkrankheit in Zusammenhang mit der Überproduktion von Sebum, bei der es sich um Akne handelt.

50. 11. Verfahren zum Verändern der Lipidproduktion durch eine Talgdrüsenzelle, das Verfahren umfassend das Verabreichen einer Polypeptids nach einem der Ansprüche 1 bis 8 an die Zelle, wobei die Verabreichung in vitro erfolgt.

12. Verfahren nach Anspruch 11, wobei die Veränderung eine Verringerung der Lipidproduktion bezogen auf eine Talgdrüsen-Kontrollzelle ist.

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Revendications

1. Composition destinée à une utilisation dans le traitement d'une maladie de peau ou condition de peau associée à une surproduction de sébum telle que la parakératose séborrhéique, ladite composition comprenant un polypeptide

comportant une séquence d'acides aminés comme décrit dans SEQ ID NO : 21, ou une séquence d'acides aminés substituée de manière conservative de SEQ ID NO : 21, laquelle retient les résidus lysine sur des positions d'acides aminés 2 et 4 de la SEQ ID NO : 21, et un vecteur acceptable sur le plan pharmaceutique ou cosmétique.

5 2. Composition destinée à une utilisation selon la revendication 1, dans laquelle le polypeptide comprend en outre un lieu.

10 3. Composition destinée à une utilisation selon la revendication 1 ou 2, dans laquelle la composition comprend en outre un peptide pénétrant dans les cellules ou un peptide pénétrant dans la peau joint au polypeptide.

15 4. Composition destinée à une utilisation selon l'une quelconque des revendications précédentes, dans laquelle le polypeptide comprend une séquence d'acides aminés comme décrit dans SEQ ID NO : 21.

20 5. Composition destinée à une utilisation selon l'une quelconque des revendications précédentes, dans laquelle le polypeptide comprend une séquence d'acides aminés présentant une identité de séquence d'au moins 90 % avec SEQ ID NO : 1 ou SEQ ID NO : 2, ou présentant une identité de séquence d'au moins 90 % avec une séquence d'acides aminés substituée de manière conservative de SEQ ID NO : 1 ou SEQ ID NO : 2.

25 6. Composition destinée à une utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le polypeptide comprend une séquence d'acides aminés présentant une identité de séquence d'au moins 95 % avec SEQ ID NO : 2, ou présentant une identité de séquence d'au moins 95 % avec une séquence d'acides aminés substituée de manière conservative de SEQ ID NO : 2.

30 7. Composition destinée à une utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le polypeptide comprend une séquence d'acides aminés présentant une séquence d'acides aminés de SEQ ID NO : 1 ou SEQ ID NO : 2 avec une substitution, une suppression ou une introduction d'acides aminés non conservative et unique, ou présentant une séquence d'acides aminés substituée de manière conservative de SEQ ID NO : 1 ou SEQ ID NO : 2 avec une substitution, une suppression ou une introduction d'acides aminés non conservative et unique, et dans laquelle le polypeptide inhibe l'ubiquitination de Insig-1.

35 8. Composition destinée à une utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le polypeptide comprend une séquence d'acides aminés de SEQ ID NO : 1 ou SEQ ID NO : 2, ou une séquence d'acides aminés substituée de manière conservative de SEQ ID NO : 1 ou SEQ ID NO : 2.

40 9. Composition destinée à une utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle la composition est une composition topique.

45 10. Utilisation d'un polypeptide selon l'une quelconque des revendications 1 à 8, pour traiter sur le plan cosmétique une condition de peau associée à une surproduction de sébum de type acné.

11. Procédé de modification de la production de lipides par une cellule sébocyte, ledit procédé comprenant l'administration dans la cellule d'un polypeptide selon l'une quelconque des revendications 1 à 8, dans lequel l'administration est réalisée *in vitro*.

12. Procédé selon la revendication 11, dans lequel la modification est une réduction de la production de lipides par rapport à une cellule de contrôle sébocyte.

50

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FIGURE 1A

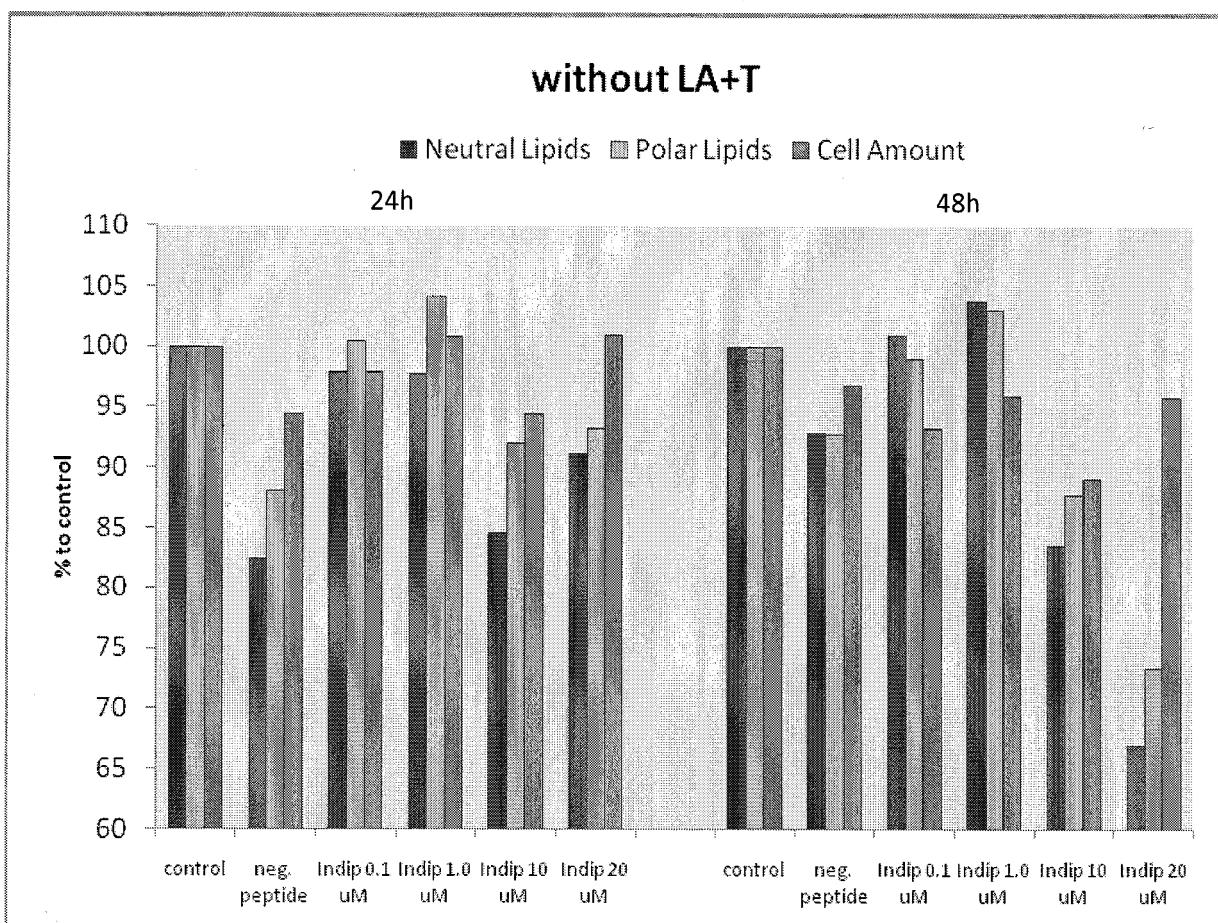


FIGURE 1B

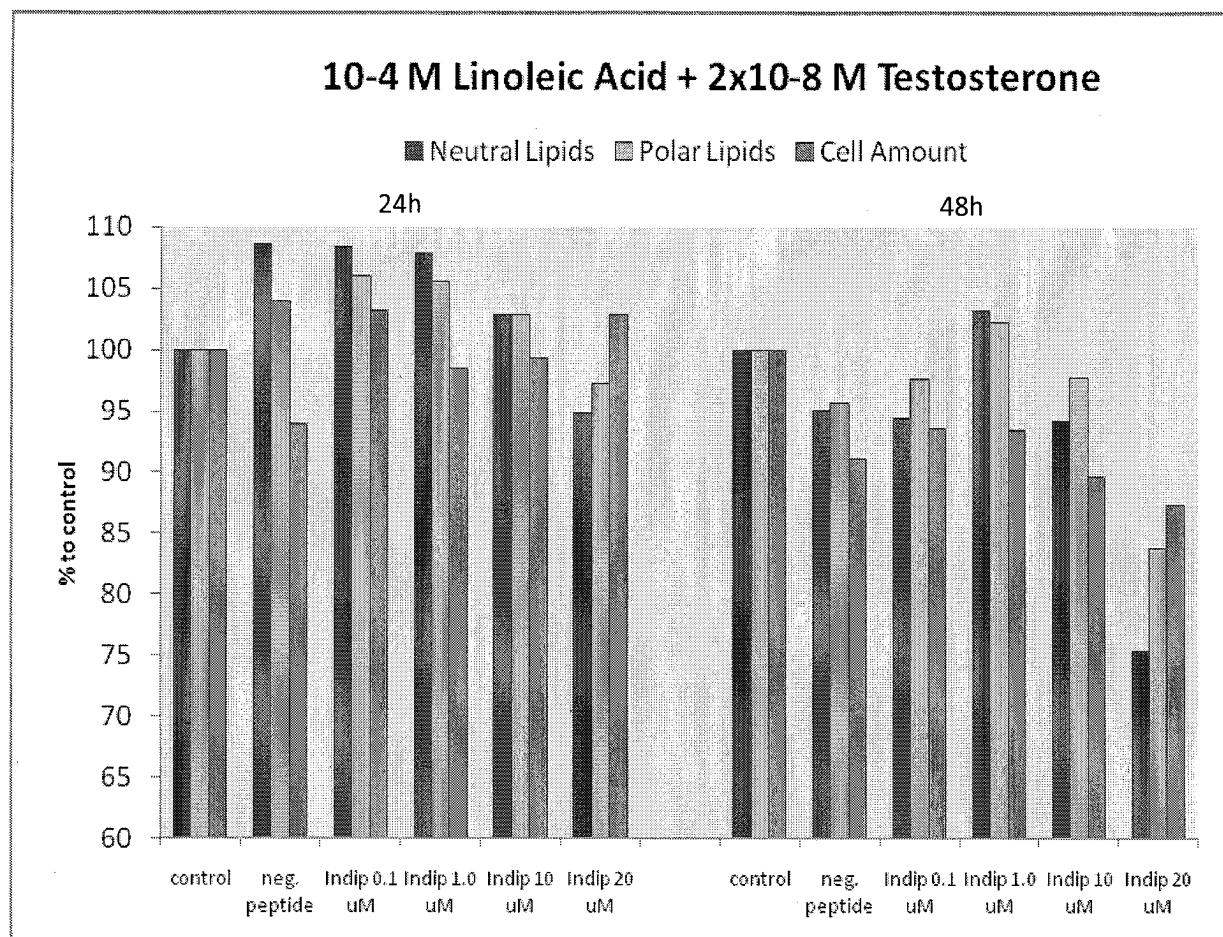
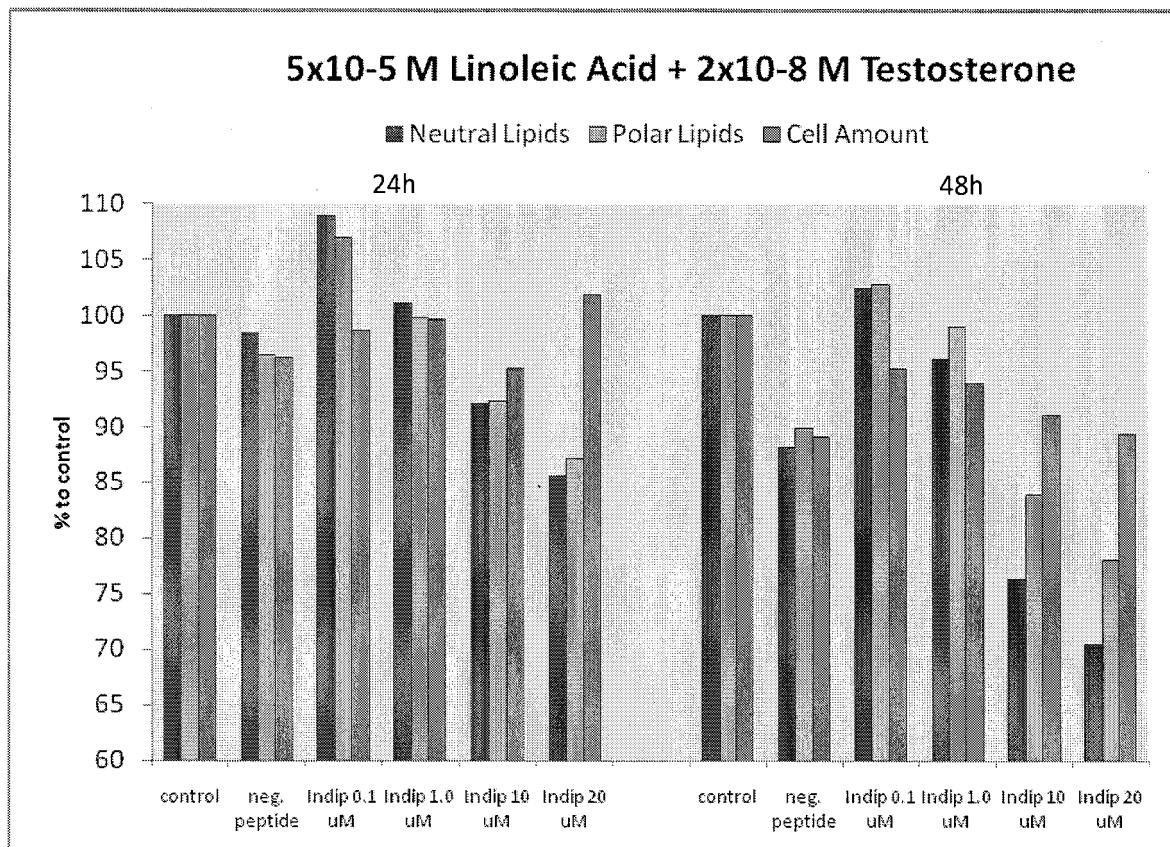


FIGURE 1C

REFERENCES CITED IN THE DESCRIPTION

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