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(54) COMPOSITION FOR AMELIORATING HAIR LOSS COMPRISING BOTULINUM-DERIVED PEPTIDE

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(57) ABSTRACT

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§ 371 (c)(1),
(2) Date: Apr. 22, 2024

(30) Foreign Application Priority Data

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Jun. 28, 2022 (KR) 10-2022-0079197

The present invention relates to a botulinum-derived peptide (botulinum toxin recombinant protein). Since the botulinum toxin recombinant protein according to the present invention can be easily delivered transdermally through fusion with a cell-penetrating peptide and promote the proliferation of dermal papilla cells and enhance prostaglandin F_{2α} expression to promote hair growth in hair loss areas, thereby ameliorating alopecia, it can be effectively used for preventing, ameliorating or treating alopecia in fields such as cosmetics and pharmaceuticals.

Specification includes a Sequence Listing.

Publication Classification

(51) Int. Cl.

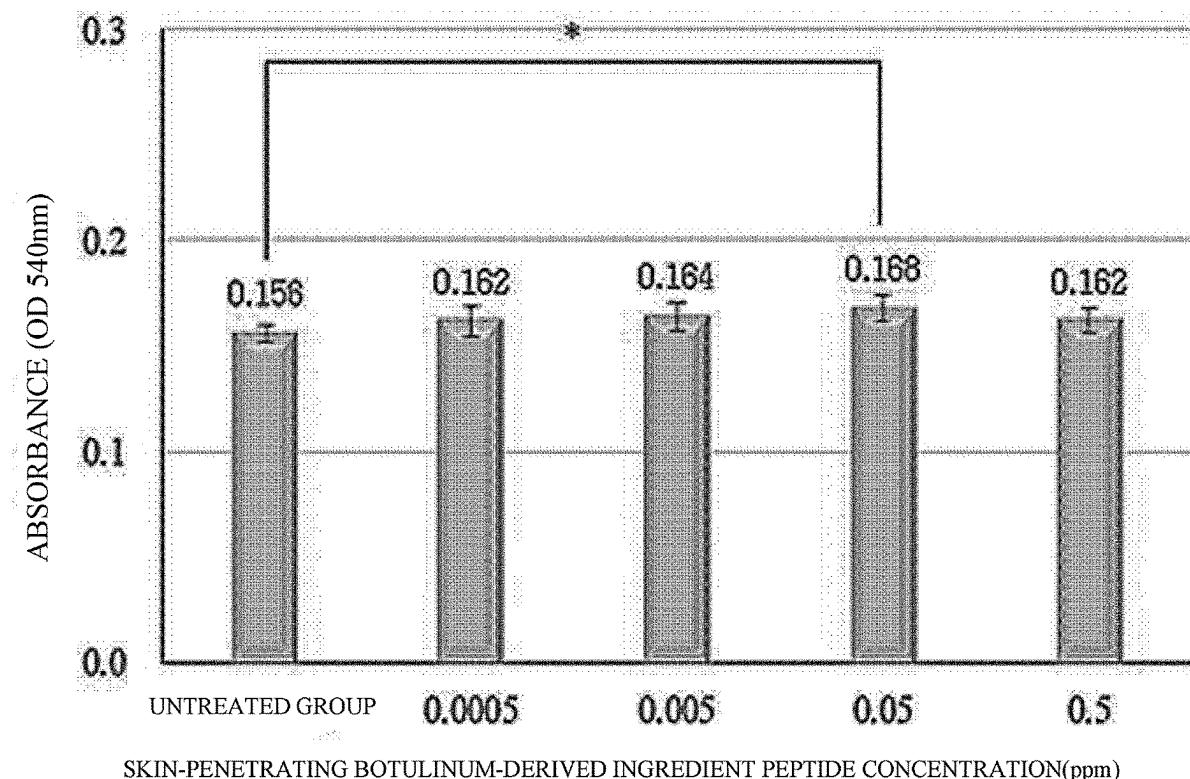
A61K 38/48 (2006.01)
A61K 8/66 (2006.01)

FIG. 1

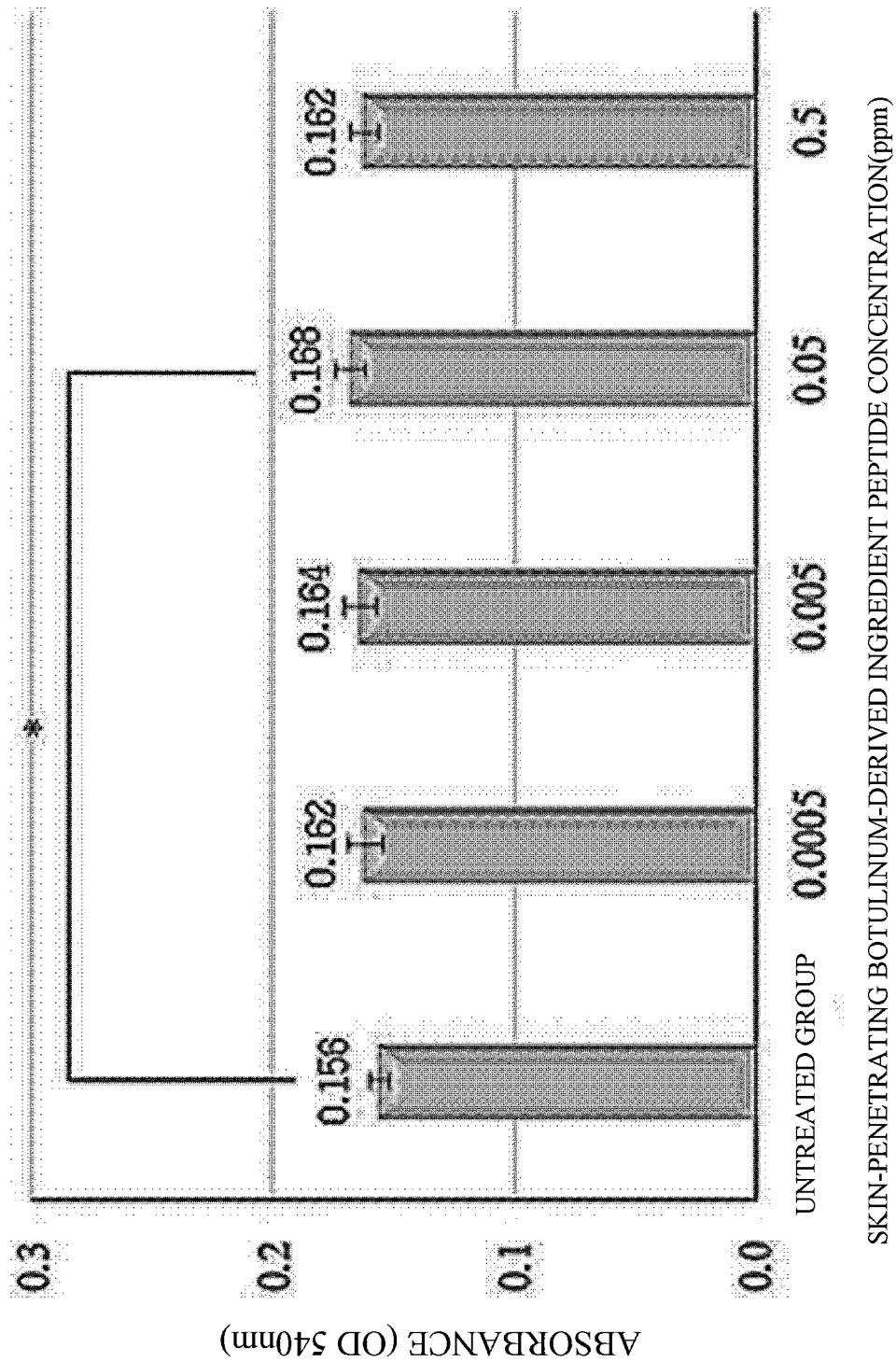


FIG. 2

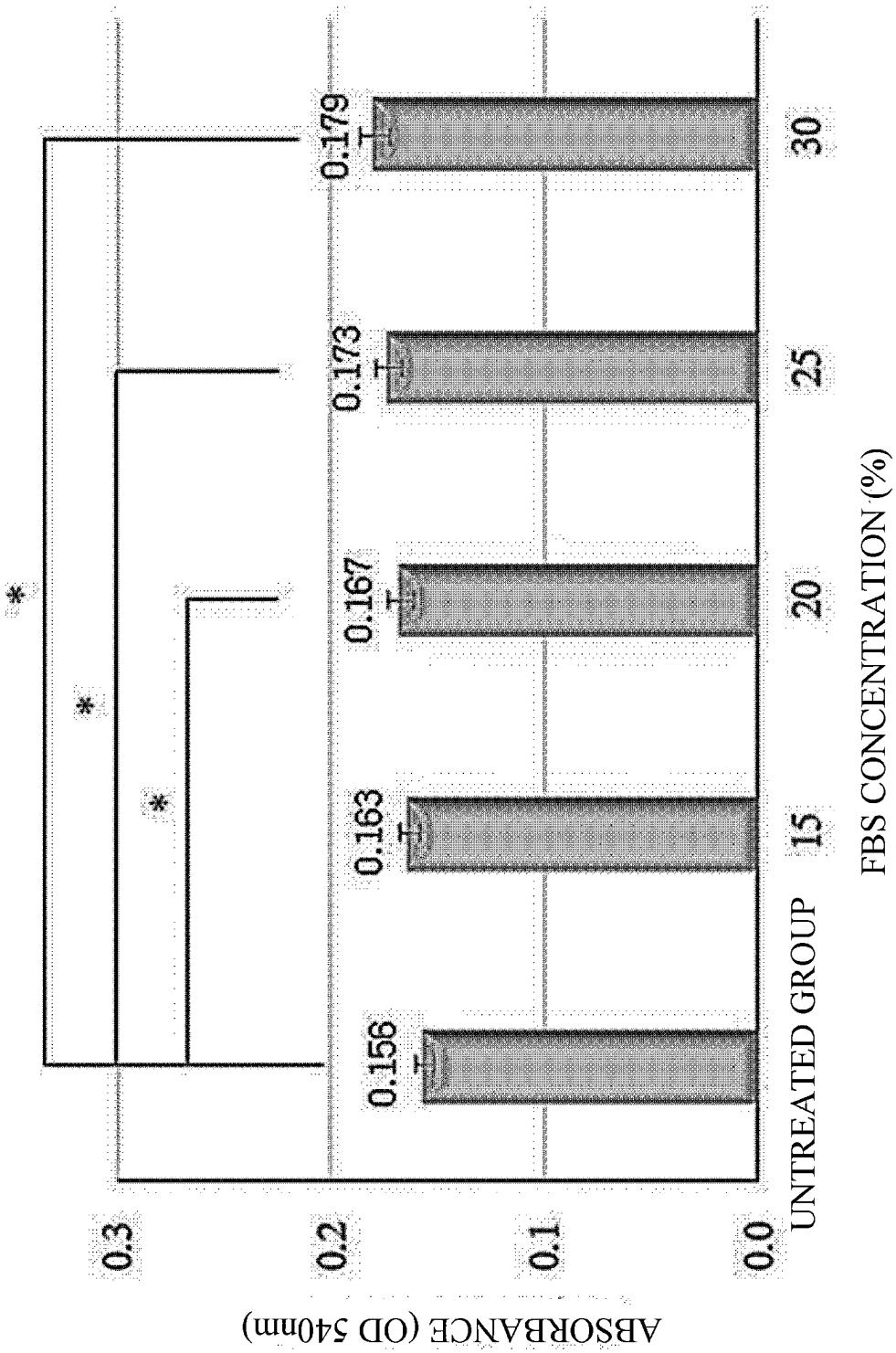


FIG. 3

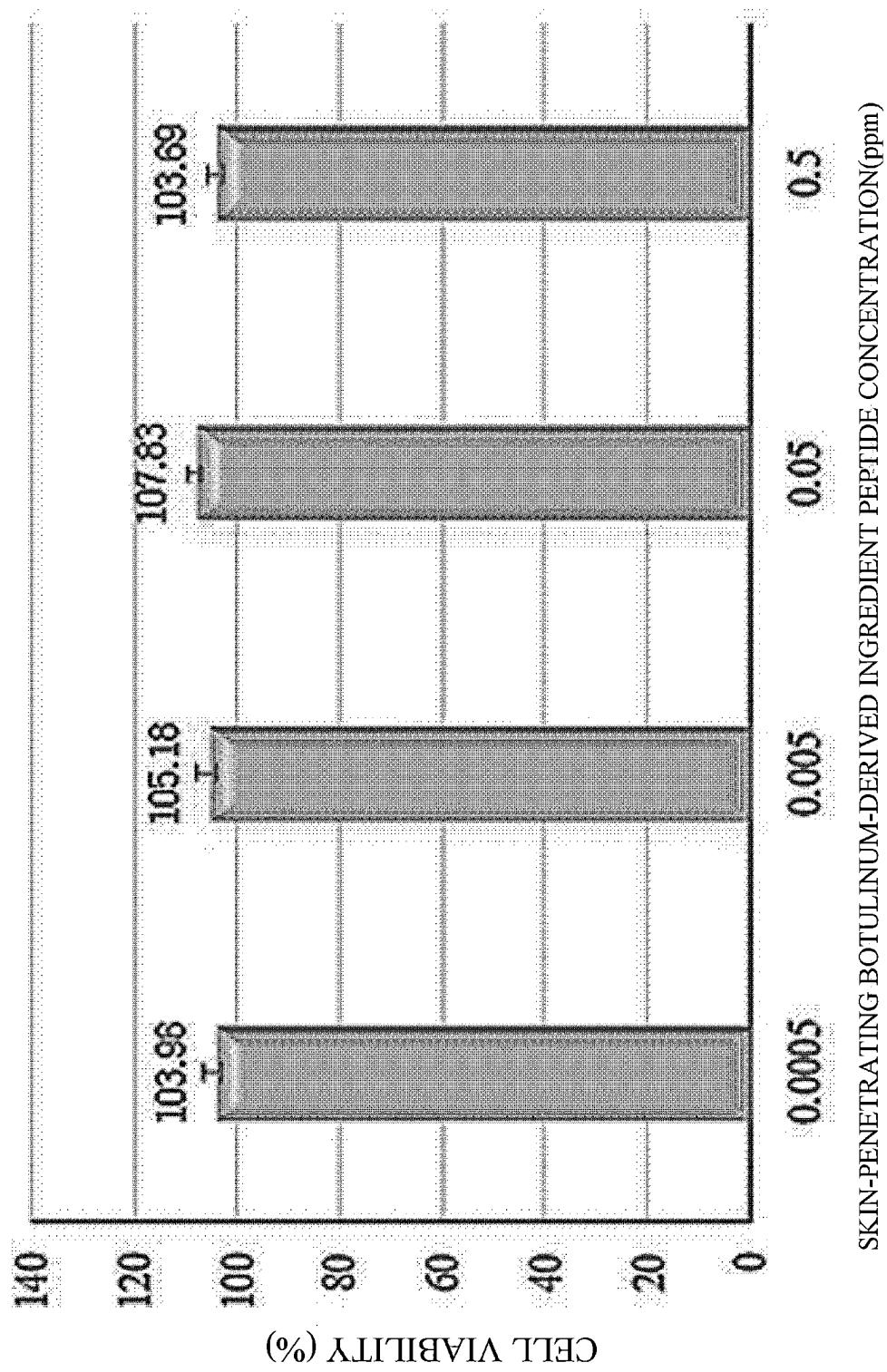


FIG. 4

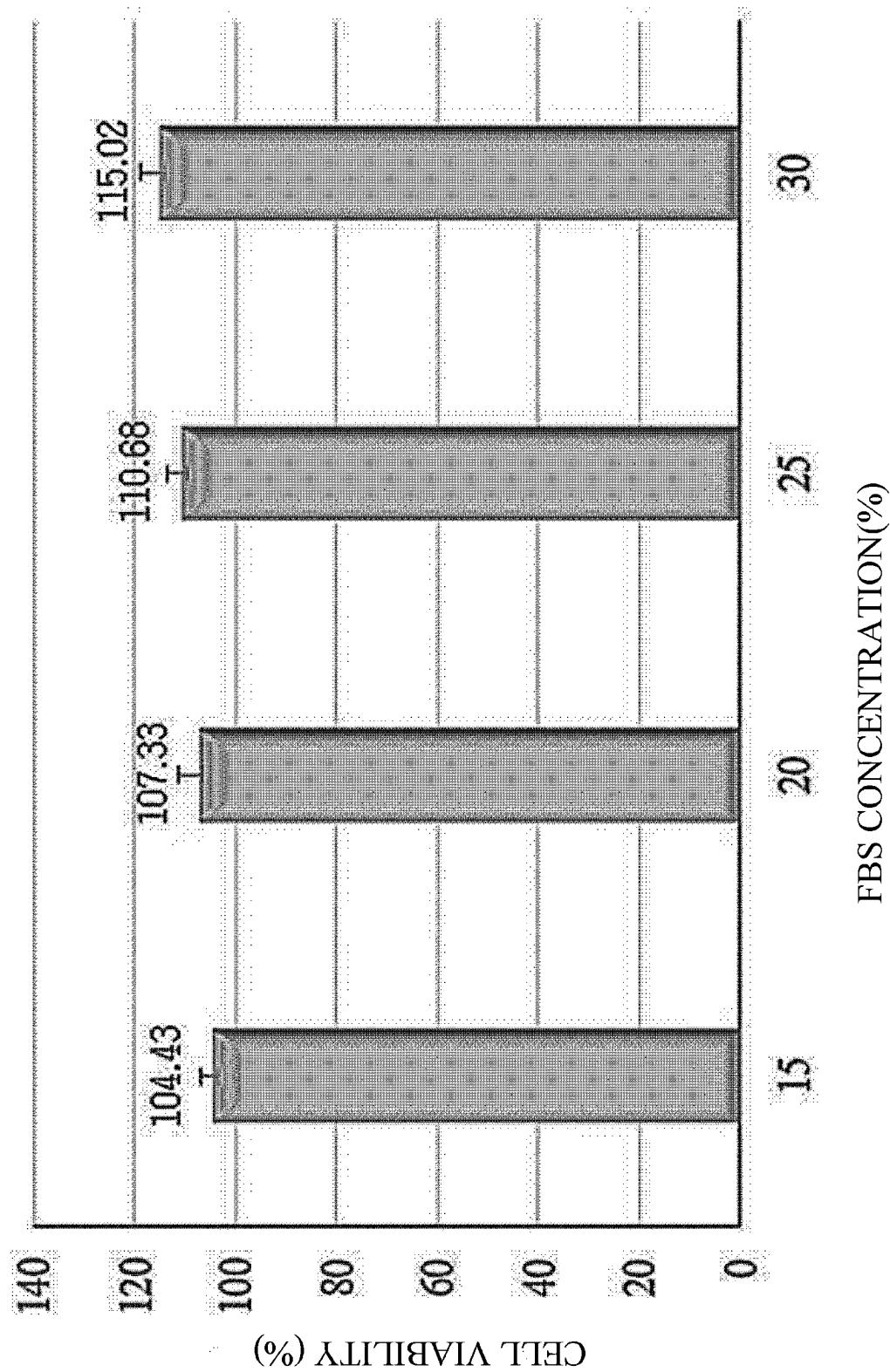


FIG. 5

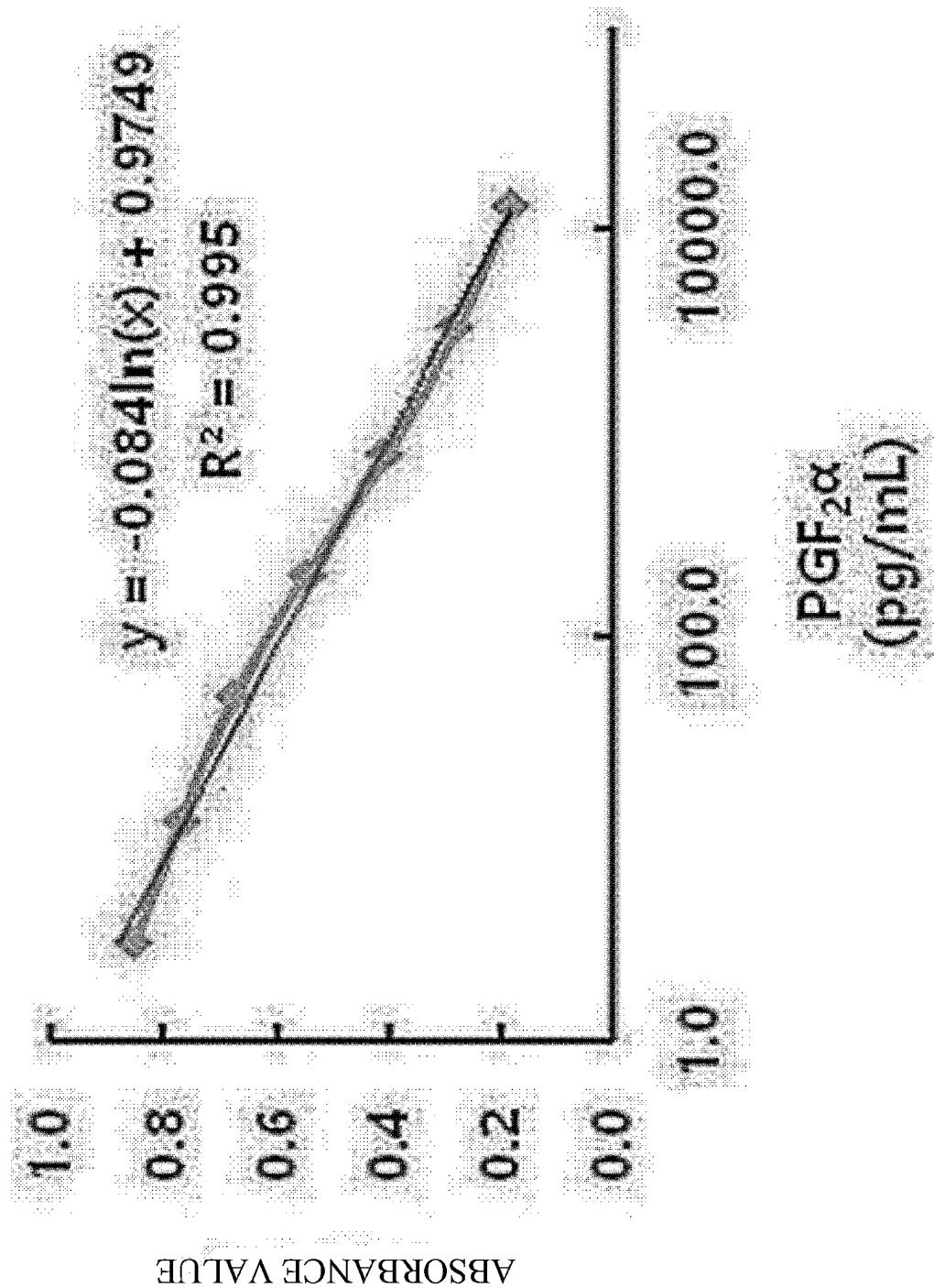


FIG. 6

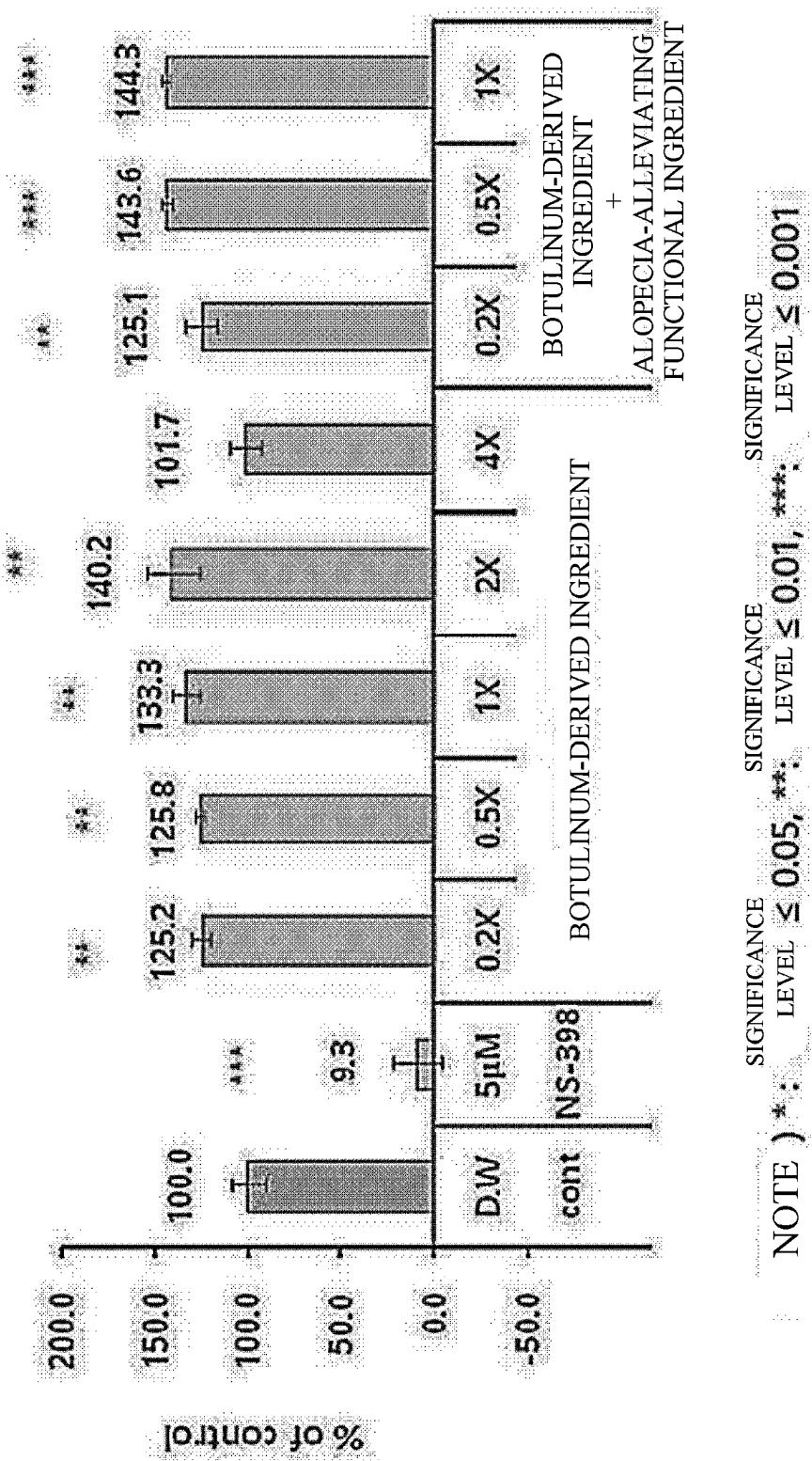


FIG. 7

SUBJECTS' SATISFACTION

PHOTO EVALUATION
BY EVALUATORS

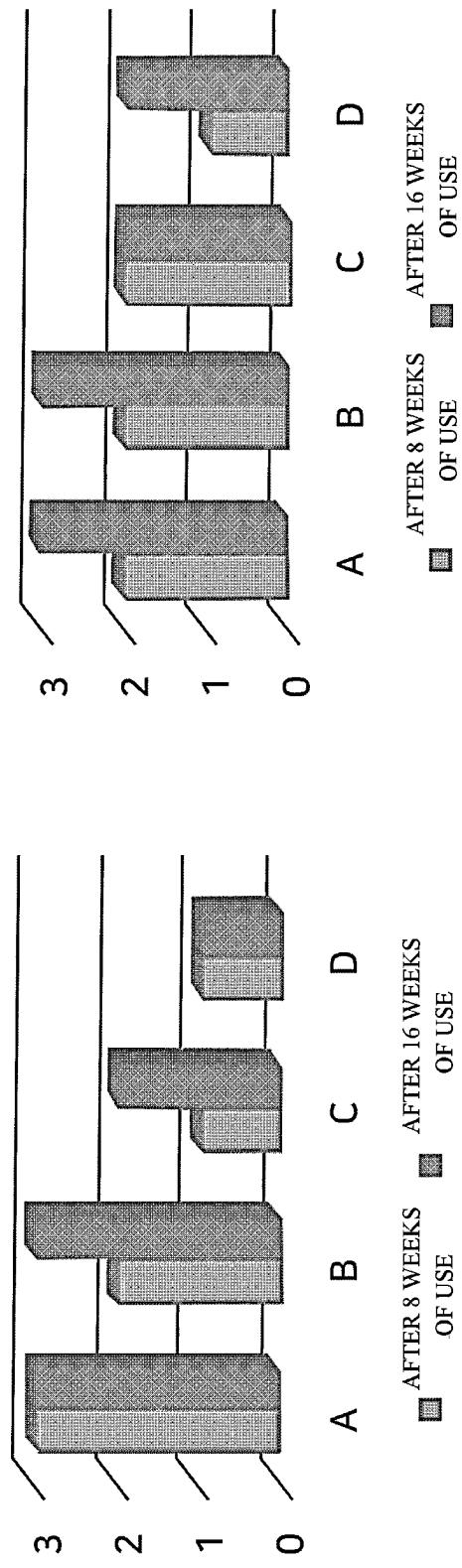
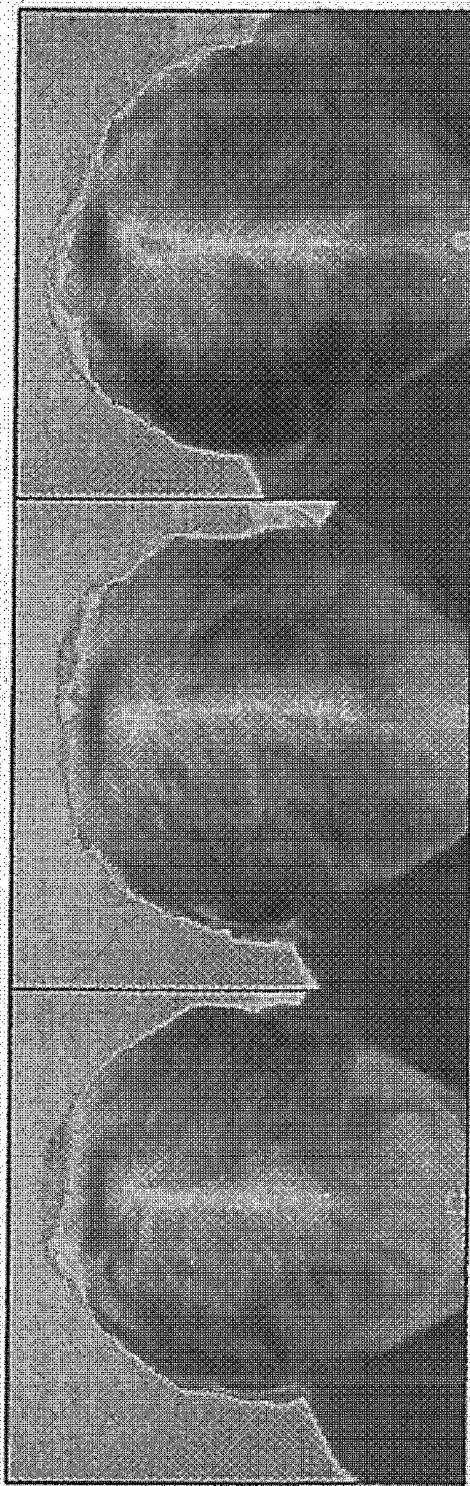


FIG. 8

SUBJECT A (52-YEAR OLD MAN)



BEFORE USE AFTER 8 WEEKS OF USE AFTER 16 WEEKS OF USE

FIG. 9

SUBJECT B (48-YEAR OLD MAN)

9/11

BEFORE USE AFTER 8 WEEKS OF USE AFTER 16 WEEKS OF USE

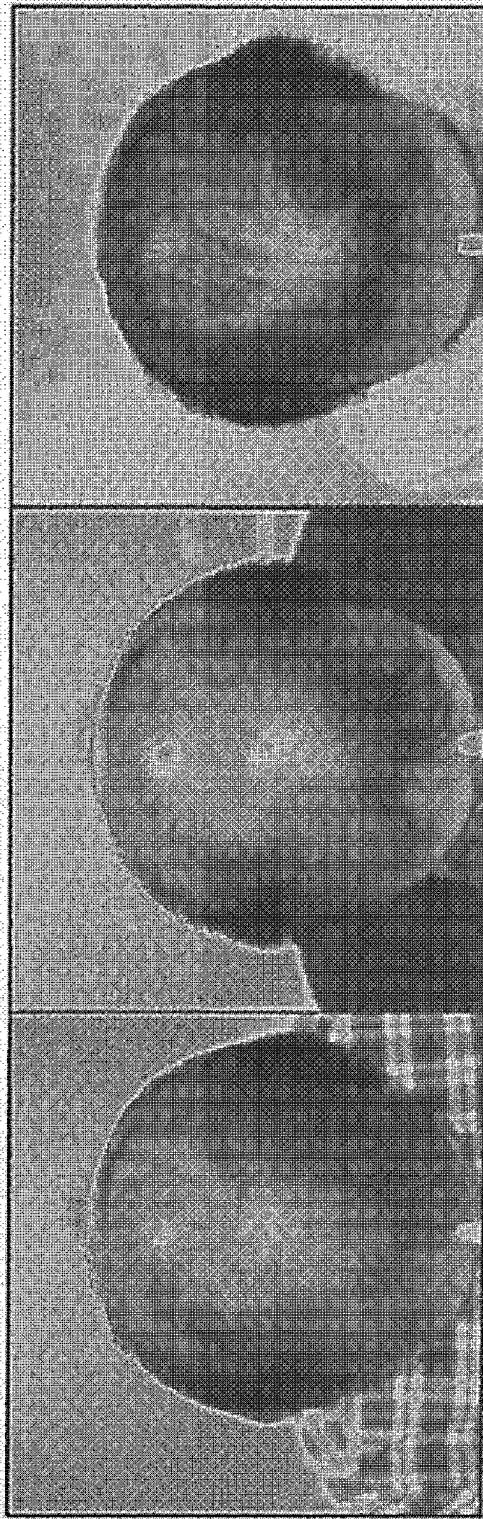


FIG. 10

SUBJECT C (50-YEAR OLD MAN)

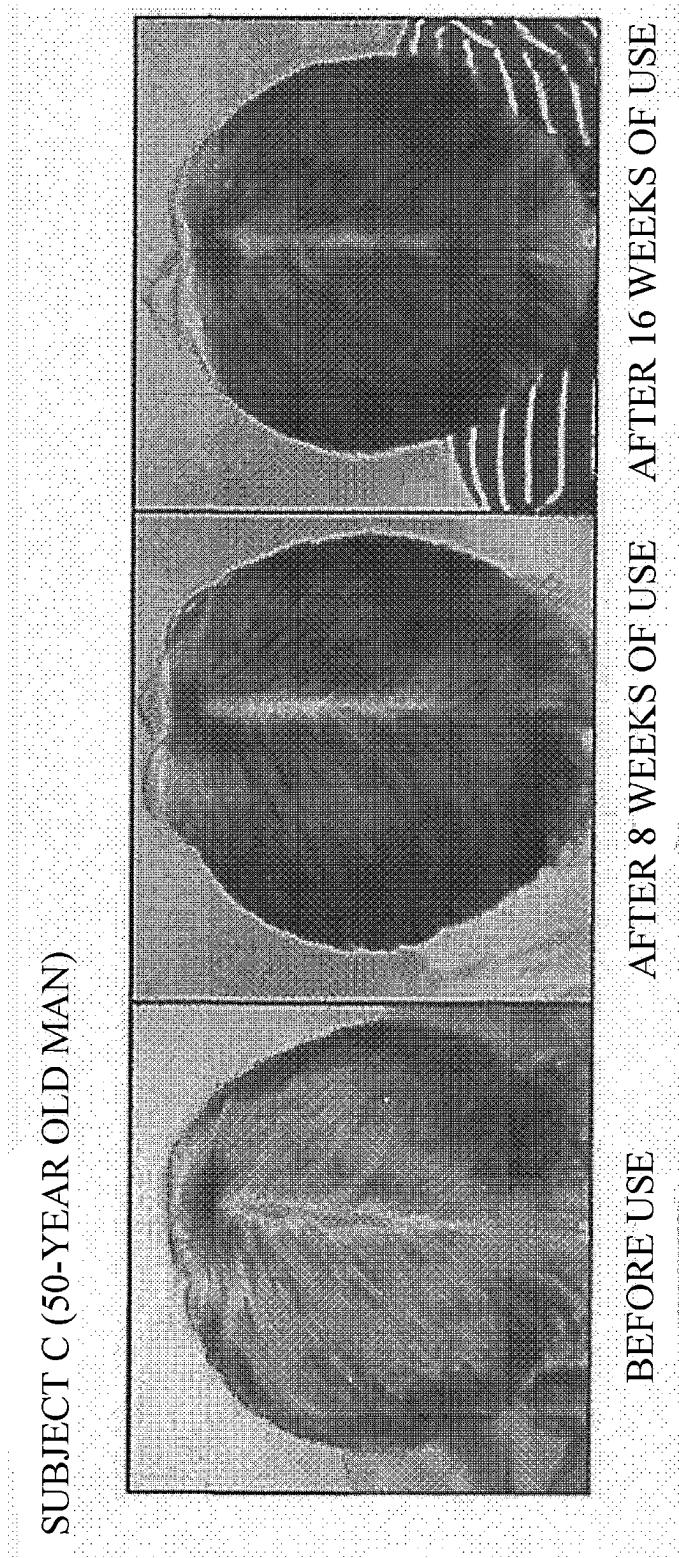
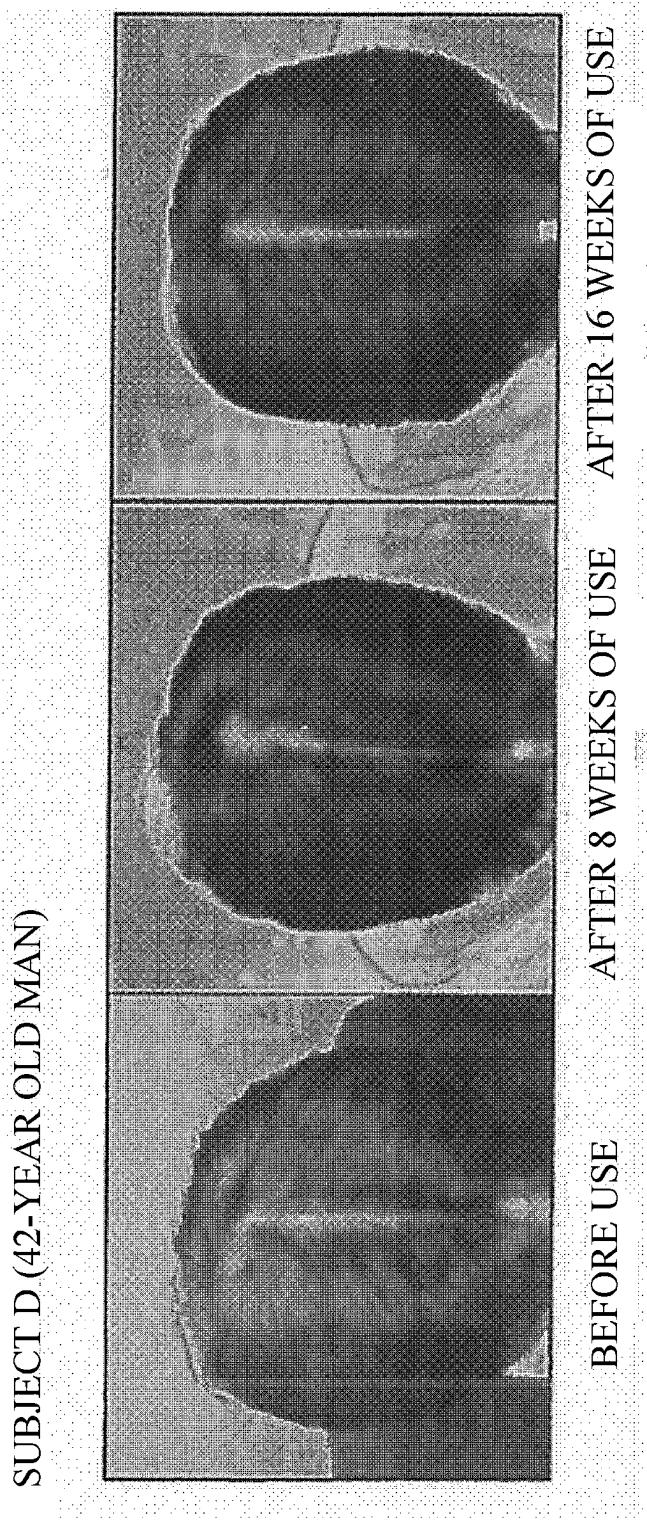


FIG. 11

SUBJECT D (42-YEAR OLD MAN)



COMPOSITION FOR AMELIORATING HAIR LOSS COMPRISING BOTULINUM-DERIVED PEPTIDE

TECHNICAL FIELD

[0001] The present invention relates to a composition for ameliorating alopecia comprising a botulinum-derived peptide (botulinum toxin recombinant protein).

[0002] The present invention claims priority based on Korea Patent Application No. 10-2021-0141684 filed on Oct. 22, 2021 and Korea Patent Application No. 10-2022-0079197 filed on Jun. 28, 2022, and all contents disclosed in the specifications and drawings of the applications are incorporated into the present application.

BACKGROUND ART

[0003] Human hair is very important in our lives not only because it protects our skin and scalp, but also for social and sexual communication. Hair is composed of keratin protein and grows from follicles in the dermis. Hair growth exhibits a certain cycle, which is divided into anagen (growth phase), catagen (regression or transition phase), and telogen (resting phase). Scalp follicles are composed of dermal papilla cells, keratinocytes, inner and outer root sheath cells, and melanocytes. Human hair follicle dermal papilla cells (HFDPCs) are one of special fibroblast cells and participate in the morphogenesis of follicles. Since HFDPCs are related to hair growth, changes in HFDPC transcription factors and cytokines are important. Keratin protein is composed from human keratinocytes and is the main tissue of hair. Recently, factors involved in cell growth (proliferation), degradation, and apoptosis in scalp follicles during the anagen phase have been revealed by various molecular analysis systems. It is known that extracellular signal-regulated kinase (ERK) and serine/threonine protein kinase (AKT) pathways are involved in cell proliferation of scalp dermal papilla. It is well known that the ERK signaling pathway plays a certain role in mitogenesis or cell growth, and it has been reported that AKT plays an important role in mediating survival signals.

[0004] Normal people have a lot of hair in the growth phase, whereas people with alopecia have a lot of hair in the resting phase, resulting in visible hair loss. As alopecia progresses, the growth phase becomes shorter, and as a result, hair becomes increasingly smaller. Therefore, to treat alopecia, it is important to allow follicles in the resting phase to quickly move to the growth phase and to lengthen the shortened growth phase.

[0005] Currently, there are two types of hair growth promoters approved by the FDA: minoxidil (transdermally applied drug) and finasteride (orally administered drug). Minoxidil was used as an oral antihypertension medication, but it was observed that hirsutism appeared in patients taking this medication, so it is currently being used for scalp application to treat androgenetic alopecia. Minoxidil is a pyrimidine derivative that dilates blood vessels in the scalp to locally increase blood flow and activates hair matrix cells to slow down alopecia and promote the growth of downy hair. Therefore, it is currently widely used as an alopecia therapeutic agent. Finasteride, which is the first orally administered therapeutic agent for treating androgenetic alopecia, prevents alopecia and promotes hair growth by

inhibiting type II α -reductase. Since it was approved by the FDA in 1997, finasteride is currently used by about 2.6 million people worldwide.

[0006] However, minoxidil has been reported to have side effects such as weight gain, edema, increased heart rate, angina, dermatitis, and itching, and in the case of finasteride, side effects such as male sexual dysfunction have been reported in clinical cases. Therefore, the use of these drugs is limited or patients themselves show aversion to these drugs. Accordingly, there is increasing consumer interest in safe alopecia prevention and hair growth-promoting substances, and research on this is also being actively conducted.

[0007] Meanwhile, botulinum toxin is a neurotoxin protein produced by *Clostridium botulinum* and is reported to inhibit the secretion of acetylcholine and catecholamine, which are neurotransmitters in neurons. There are eight types of botulinum toxin: types A, B, C, D, E, F, G, and H, and types A and B are commercially used.

[0008] Botulinum toxin is a neurotoxin protein, and the median lethal dose for humans is 1.3 to 2.1 ng/kg when injected intravenously or intramuscularly and 10 to 13 ng/kg when inhaled, indicating that it is a highly toxic substance. However, when adjusted to an appropriate amount, it can be used as a drug for treating neurological disorders, muscle diseases, hyperhidrosis, square jaw or the like, and it is most often used for cosmetic purposes such as reducing wrinkles and calf muscles.

[0009] Since botulinum toxin is a very large molecule having a molecular weight of 150 kDa with combined light and heavy chains, it is difficult to penetrate the skin and is therefore only used through injections. The toxin lasts for 3 to 6 months, and thus the toxin requires regular treatments. Therefore, many studies are being conducted to find another effective delivery means capable of providing user convenience, but the results are still insufficient.

DISCLOSURE

Technical Problem

[0010] The present inventors confirmed that a botulinum toxin recombinant protein (skin-penetrating botulinum-derived ingredient peptide) according to the present invention promotes the proliferation of dermal papilla cells and expression of prostaglandin F_{2 α} and that alopecia was ameliorated when it was applied to hair loss areas, and thereby completed the present invention.

[0011] Therefore, an object of the present invention is to provide a pharmaceutical composition for ameliorating alopecia, comprising a botulinum toxin recombinant protein as an active ingredient, wherein in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain.

[0012] Another object of the present invention is to provide a quasi-drug composition for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0013] Still another object of the present invention is to provide a composition for external skin application for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0014] Yet another object of the present invention is to provide a cosmetic composition for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0015] However, the technical problems to be solved by the present invention are not limited to the problems mentioned above, and other problems not mentioned may be clearly understood from the description below by those skilled in the art to which the present invention pertains.

Technical Solution

[0016] One aspect of the present invention provides a pharmaceutical composition for ameliorating alopecia, comprising a botulinum toxin recombinant protein as an active ingredient, wherein in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain.

[0017] Another aspect of the present invention provides a quasi-drug composition for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0018] Still another aspect of the present invention provides a composition for external skin application for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0019] Yet another aspect of the present invention provides a cosmetic composition for ameliorating alopecia, comprising the botulinum toxin recombinant protein as an active ingredient.

[0020] In one embodiment of the present invention, the botulinum toxin recombinant protein may consist of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 31 to SEQ ID NO: 58, but is not limited thereto.

[0021] In another embodiment of the present invention, the botulinum toxin light chain may consist of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 3 to SEQ ID NO: 9, but is not limited thereto.

[0022] In still another embodiment of the present invention, the botulinum toxin light chain may further include a hexahistidine tag at one end, but is not limited thereto.

[0023] In yet another embodiment of the present invention, the botulinum toxin light chain may be selected from the group consisting of botulinum toxin serotypes A, B, C, D, E, F, and G, but is not limited thereto.

[0024] In yet another embodiment of the present invention, the cell-penetrating peptide may be fused to a carboxyl terminus, an amino terminus, or both of the botulinum toxin light chain, but is not limited thereto.

[0025] In yet another embodiment of the present invention, the fusion may be achieved by a peptide bond or a covalent bond.

[0026] In yet another embodiment of the present invention, the composition may promote the proliferation of dermal papilla cells, but is not limited thereto.

[0027] In yet another embodiment of the present invention, the composition may promote prostaglandin F_{2α} expression, but is not limited thereto.

[0028] In yet another embodiment of the present invention, the composition may promote hair growth and reduce alopecia, but is not limited thereto.

[0029] In yet another embodiment of the present invention, the composition may satisfy one or more of the following characteristics, but is not limited thereto:

[0030] (a) increased hair thickness; (b) increased hair density (reduction in number of lost hairs); (c) inhibition of sebum secretion in the scalp; (d) improved scalp hygiene; and (e) reduced hair sinking.

[0031] In yet another embodiment of the present invention, the composition for ameliorating alopecia may be for transdermal administration, but is not limited thereto.

[0032] In addition, the present invention provides an alopecia prevention or treatment method, comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0033] In addition, the present invention provides a use of a composition comprising the botulinum toxin recombinant protein as an active ingredient for preventing or treating alopecia.

[0034] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for treating alopecia.

[0035] In addition, the present invention provides a method of ameliorating alopecia, comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0036] In addition, the present invention provides a use of a composition comprising the botulinum toxin recombinant protein as an active ingredient for ameliorating alopecia.

[0037] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for ameliorating alopecia.

[0038] In addition, the present invention provides a pharmaceutical composition for promoting hair growth comprising the botulinum toxin recombinant protein as an active ingredient.

[0039] In addition, the present invention provides a method for promoting hair growth comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0040] In addition, the present invention provides a use of a composition comprising the botulinum toxin recombinant protein as an active ingredient for promoting hair growth.

[0041] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for promoting hair growth.

Advantageous Effects

[0042] Since a botulinum toxin recombinant protein according to the present invention can be easily delivered transdermally through fusion with a cell-penetrating peptide and promote the proliferation of dermal papilla cells and enhance prostaglandin F_{2α} expression to reduce hair loss and promote hair growth, thereby ameliorating alopecia, it can be effectively used for preventing, ameliorating or treating alopecia in fields such as cosmetics and pharmaceuticals.

DESCRIPTION OF DRAWINGS

[0043] FIG. 1 is a diagram showing the results of measuring absorbance after treating human papilla cells with a botulinum toxin recombinant protein.

[0044] FIG. 2 is a diagram showing the results of measuring absorbance after treating human papilla cells with

fetal bovine serum (FBS) as a positive control for a botulinum toxin recombinant protein.

[0045] FIG. 3 is a diagram showing the results of measuring cell viability after treating human papilla cells with a botulinum toxin recombinant protein.

[0046] FIG. 4 is a diagram showing the results of measuring cell viability after treating human papilla cells with FBS as a positive control for a botulinum toxin recombinant protein.

[0047] FIG. 5 is a diagram showing a standard curve obtained by applying standard prostaglandin F_{2α} according to the amount to analyze the expression level of prostaglandin F_{2α} in keratinocytes.

[0048] FIG. 6 is a diagram showing the results of analyzing the absorbance value of prostaglandin F_{2α} expression measured in keratinocytes.

[0049] FIG. 7 is a diagram showing the results of evaluation of an alopecia ameliorating effect evaluated by subjects and evaluators over time after administering a composition according to the present invention to various alopecia patients.

[0050] FIGS. 8 to 11 are diagrams showing the results of confirming an alopecia ameliorating effect over time after administering a composition according to the present invention to various alopecia patients.

BEST MODE

[0051] The present inventors confirmed that a botulinum toxin recombinant protein (skin-penetrating botulinum-derived ingredient peptide) obtained by fusing a botulinum toxin light chain to a cell-penetrating peptide promotes the proliferation of dermal papilla cells and enhances the expression of prostaglandin F_{2α} to ameliorate alopecia, resulting in reduced hair loss and promotion of hair growth, and thereby completed the present invention.

[0052] Since a botulinum toxin recombinant protein according to the present invention can be easily delivered transdermally through fusion with a cell-penetrating peptide and promote the proliferation of dermal papilla cells and enhance prostaglandin F_{2α} expression to reduce hair loss and promote hair growth, thereby ameliorating alopecia, it can be effectively used for preventing, ameliorating or treating alopecia in fields such as cosmetics and pharmaceuticals.

[0053] Hereinafter, the present invention will be described in detail.

[0054] Botulinum toxin is expressed as a single polypeptide, but after expression, through a reconstitution process, it is divided into a heavy chain (H chain) of about 100 kDa and a light chain (L chain) of about 50 kDa, and the H chain and the L chain are connected by a disulfide bond. The H chain binds to a receptor on a neuron and allows botulinum toxin to enter the inside through endocytosis. After the L chain of botulinum toxin enters a cell, it exits the endosome, enters the cytoplasm, and cleaves a soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein in the cytoplasm, inhibiting acetylcholine secretion and thereby exhibiting a muscle-paralyzing effect. Therefore, inhibition of acetylcholine secretion from neurons is possible with the L chain alone, and the H chain and L chain may function independently.

[0055] However, a separated botulinum toxin light chain with a molecular weight of 50 kDa is unable to penetrate the cell membrane, and so it cannot function on its own. In general, in order for a botulinum toxin light chain to be

delivered to the cytoplasm of a neuron to exhibit botulinum toxin-specific activity, the help of a botulinum toxin heavy chain of about 100 kDa is essential.

[0056] Therefore, the present invention provides a pharmaceutical composition for ameliorating alopecia, including a botulinum toxin recombinant protein as an active ingredient that allows a botulinum toxin light chain, which is not easily introduced into cells, to be delivered into cells with high efficiency by imparting cell-penetrating properties by fusing a cell-penetrating peptide to the botulinum toxin light chain, and in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain.

[0057] In the present specification, "alopecia" refers to a phenomenon in which hair falls out from the scalp or a state in which hair becomes sparse or thin and may include all types of alopecia classified as alopecia in the art, except for cicatricial (scarring) alopecia. For example, the alopecia may be one or more selected from the group consisting of alopecia areata, androgenetic alopecia, tinea capitis, hypotrichosis, hereditary hypotrichosis simplex, circumscribed alopecia, congenital alopecia, alopecia pubis, alopecia seborrheica, alopecia *senilis*, alopecia totalis, alopecia universalis, and telogen effluvium, but is not limited thereto.

[0058] The term "hair growth" refers to growing hair. An effect of a composition according to the present invention may include an effect of promoting hair growth.

[0059] According to one embodiment of the present invention, it was confirmed that a botulinum toxin recombinant protein according to the present invention may promote the proliferation of dermal papilla cells, promote prostaglandin F_{2α} expression in keratinocytes, promote hair growth, and reduce alopecia (Examples 1 to 3).

[0060] In addition, according to one embodiment of the present invention, it was confirmed that a composition including a botulinum toxin recombinant protein according to the present invention satisfies one or more of the following characteristics, thereby ameliorating pre-symptoms of alopecia and preventing, ameliorating, or treating alopecia (see Example 3):

- [0061] (a) increased hair thickness;
- [0062] (b) increased hair density (reduction in number of lost hairs);
- [0063] (c) inhibition of sebum secretion in the scalp;
- [0064] (d) improved scalp hygiene; and
- [0065] (e) reduced hair sinking.

[0066] The composition of the botulinum toxin recombinant protein (skin-penetrating botulinum-derived ingredient peptide) in the present invention are the same as Korea Patent No. 10-1882461, and all contents disclosed in the above document are incorporated by reference in the present application.

[0067] In the present invention, "botulinum toxin recombinant protein" includes a cell-penetrating peptide and a botulinum toxin light chain and refers to a complex formed by a chemical bond such as peptide bond or covalent bond. Specifically, the botulinum toxin recombinant protein according to the present invention is capable of delivering the botulinum toxin light chain into cells with high efficiency by imparting cell-penetrating properties by fusing a cell-penetrating peptide to the botulinum toxin light chain, which is a macromolecule that is not easily introduced into cells,

and at this time, the cell-penetrating peptide may be fused to a carboxyl terminus, an amino terminus, or both of the botulinum toxin light chain.

[0068] The botulinum toxin recombinant protein according to the present invention may be delivered into cells with high efficiency through the fusion of the botulinum toxin light chain and a cell-penetrating peptide, and the activity and stability of the botulinum toxin light chain are improved to maximize the inherent efficacy of the botulinum toxin *in vivo*.

[0069] In the present invention, “botulinum toxin” refers to any known type of botulinum toxin, whether subsequently discovered or not, including a variant or a fusion protein produced by bacteria or engineered by a recombinant technique.

[0070] In the present invention, the botulinum toxin light chain may be selected from the group consisting of botulinum toxin serotypes A, B, C, D, E, F, and G, and at this time, the botulinum toxin light chain may consist of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 3 to SEQ ID NO: 9. In addition, the botulinum toxin light chain may consist of one amino acid sequence selected from the group consisting of SEQ ID NO: 3 to SEQ ID NO: 9. At this time, the botulinum toxin light chain may be encoded by a polynucleotide consisting of a base sequence selected from the group consisting of SEQ ID NOS: 10 to 16, but is not limited thereto.

[0071] In addition, the botulinum toxin light chain may further include a hexahistidine tag at one end. In the present invention, the form further including a hexahistidine tag at one end of the botulinum toxin light chain may consist of an amino acid sequence selected from the group consisting of SEQ ID NO: 17 to SEQ ID NO: 23, and it may be encoded by a base sequence selected from the group consisting of SEQ ID NO: 24 to SEQ ID NO: 30, but is not limited thereto.

[0072] In the present invention, the botulinum toxin light chain may alternatively be a botulinum toxin derivative, that is, a compound having botulinum toxin activity but optionally having one or more modifications in a part or sequence. For example, compared to the seven serotypes of the botulinum toxin light chain protein, it may be a form modified in a way that maintains the endopeptidase activity of the light chain while simultaneously enhancing properties or reducing side effects thereof by performing methods such as deletion, modification, replacement, and chimeric fusion on an amino acid sequence. Alternatively, a botulinum toxin light chain or a part of a botulinum toxin light chain produced by recombinant or chemical synthesis may be used.

[0073] In the present invention, the botulinum toxin recombinant protein may consist of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 31 to SEQ ID NO: 58, and a polynucleotide encoding the amino acid sequences may be selected from the group consisting of SEQ ID NO: 59 to SEQ ID NO: 86, but is not limited thereto.

[0074] In addition, in the present invention, the botulinum toxin recombinant protein may consist of one amino acid sequence selected from the group consisting of SEQ ID NO: 31 to SEQ ID NO: 58.

[0075] According to one embodiment of the present invention, the botulinum toxin recombinant protein may preferably consist of an amino acid sequence represented by SEQ

ID NO: 45, and a polynucleotide encoding the amino acid sequence may be a nucleotide sequence represented by SEQ ID NO: 73, but is not limited thereto.

SEQ ID NO: 45:
MKAMININKFLNQCPFVNQKQPNYKDPVNGVDIAYIKIPNAGQMQPVKAF
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INVIQPDGSYRSEELNLVIIGPSADIQFECKSFGHEVLNLTRNGYGST
QYIRFSPDFTFGFEESLEVDTNPLLGAGKFATDPAVTLAHELIHAGHRL
YGINAINPNRVFKVNTNAYYEMSGLEVSFEELRTFGGGDAKFIDSLQENE
FRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVPKEKYLLSEDTSKG
FSVDKLKFDFKLYKMLTEIYTEDNFVFKFFVKVLRKTYLNFDKAVFKINIV
PKVNYTIYDGFNLRNTNLAANFNGQNTIEINNMNFTKLKNFTGLFEFYKL
LCVRGIITSKTKSLDKGYNKLEHHHHHH

SEQ ID NO: 73:
atgaaggccatgatcaatacataacaagttcttaatcaatgtcccttgc
tcaacaaacagttcaactacaaggaccagttaatggagtagacatcg
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cctaaagtgaactacaccatctacgacgggttacccgttcaagatcaacatcg

-continued

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ttcacgaagtgaagaactcaccggactttgagtttacaatttg
ctgtgtgtgcgcggatcatcaacttagaagaccaagagccttgacaaagg
gctacaacaagtgactcgagcaccaccaccaccactga
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[0076] In the present invention, the cell-penetrating peptide (Macromolecule Transduction Domain; MTD) consisting of an amino acid sequence of SEQ ID NO: 1 may be a peptide that may mediate intracellular transport of a biologically active molecule and may have permeability with respect to both human skin keratinocytes and neurons, but is not limited thereto.

[0077] The cell-penetrating peptide preferably has no defined enzymatic or therapeutic biological activity, but serves as a carrier allowing intracellular transport across the cell membrane. It may be attached to an N-terminus or C-terminus and both termini of the cargo to be transferred into the cell, and it may be attached in a forward direction or a reverse direction at each terminus. In addition, the peptide according to the present invention is preferably applied as a monomer, but is not limited thereto, and it may also be used in the form of a dimer or polymer. Furthermore, the peptide according to the present invention may be a peptide including an amino acid sequence of SEQ ID NO: 1 as a minimum unit.

[0078] In the present invention, the cell-penetrating peptide may be encoded by a polynucleotide consisting of a base sequence of SEQ ID NO: 2, but is not limited thereto.

SEQ ID NO: 1:
KAMININKFLNQC

SEQ ID NO: 2:
aaggcgatga taaaacataaa caagttcccg aaccagtgc

[0079] In the present specification, "active ingredient" refers to an ingredient that may exhibit desired activity alone or in combination with a carrier that is inactive in itself.

[0080] According to one embodiment of the present invention, the most appropriate administration route for the composition according to the present invention to exhibit an alopecia-ameliorating effect is absorption through the skin, and therefore, the composition according to the present invention may preferably be for transdermal administration and may be administered by methods such as direct application or dispersion to hair or the scalp.

[0081] "Hair" to which the composition of the present invention is applied includes hair roots and follicles of the head, hair on the head, eyelashes, eyebrows, beards, armpit hair, pubic hair, and all parts of the body with hair roots and follicles.

[0082] In the present invention, the composition according to the present invention may further include a transdermal absorption enhancer, but is not limited thereto.

[0083] The "transdermal absorption enhancer" is an ingredient among emulsifiers that affects skin penetration and is commonly used in transdermal patches. In the present invention, it enhances skin penetration and cellular penetration of the botulinum toxin recombinant protein and may be lecithin, lauryl pyrrolidone, glycerol monooleate, glycerol monolaurate, propylene glycol monolaurate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monolaurate, sorbitan

monooleate, sorbitan monostearate, or sorbitan monolaurate, but is not limited thereto.

[0084] An amino acid sequence represented by a specific sequence number described in the present specification is not limited to a protein (peptide) represented by the specific sequence number, and variants of the amino acid sequence are included in the scope of the present invention as long as functional equivalence is maintained. Specifically, an amino acid sequence having a sequence identity of 80% or more, more preferably 90% or more, and even more preferably 95% or more with an amino acid sequence represented by a specific sequence number may be included. For example, it may include a protein (peptide) having a sequence identity of 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. The "percent sequence identity" of an amino acid is confirmed by comparing a comparison region with an optimally aligned sequence, and in the comparison region, a part of the amino acid sequence may include an addition or deletion (i.e. gap) compared to a reference sequence (including no addition or deletion) for the optimal alignment of two sequences.

[0085] A polynucleotide consisting of a base sequence represented by a specific sequence number described in the present specification is not limited to the corresponding base sequence, and variants of the base sequence are included within the scope of the present invention. A nucleic acid molecule of a base sequence of the present invention is a concept including a functional equivalent of the nucleic acid molecule constituting it, for example, variants formed from a nucleic acid molecule in which some base sequences are modified by deletion, substitution, or insertion but are still capable of performing the same function as the nucleic acid. Specifically, a polynucleotide disclosed in the present invention may include a base sequence having a sequence identity of 70% or more, more preferably 80% or more, even more preferably 90% or more, and most preferably 95% or more with a base sequence represented by a specific sequence number. For example, it includes a polynucleotide having a sequence identity of 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%. The "percent sequence identity" of a polynucleotide is confirmed by comparing a comparison region between two optimally aligned sequences, and a part of a polynucleotide sequence in the comparison region may include an addition or deletion (i.e. gap) compared to a reference sequence (including no addition or deletion) for the optimal alignment of two sequences.

[0086] In the present invention, "pharmaceutical composition" refers to a composition prepared for the purpose of preventing or treating a disease, and it may be formulated and used in various forms according to conventional methods. For example, it may be formulated into oral dosage forms such as powder, granules, tablets, capsules, suspensions, emulsions, and syrup or formulated and used in the form of external preparations, suppositories, and sterile injection solutions.

[0087] The pharmaceutical composition according to the present invention may further include appropriate carriers, excipients, and diluents that are commonly used in preparation of pharmaceutical compositions. The excipient may be, for example, one or more selected from the group

consisting of diluents, binders, disintegrants, lubricants, adsorbents, humectants, film-coating materials, and controlled-release additives.

[0088] The pharmaceutical composition according to the present invention may be formulated and used by conventional methods in the form of powder, granules, sustained-release granules, enteric-coated granules, solutions, eye drops, elixirs, emulsions, suspensions, spirits, troches, perfumes, limonade, tablets, sustained-release tablets, enteric-coated tablets, sublingual tablets, hard capsules, soft capsules, sustained-release capsules, enteric-coated capsules, pills, tinctures, soft extracts, dry extracts, liquid extracts, injections, capsules, perfusates, plasters, lotions, pastes, sprays, inhalants, patches, sterilized injection solutions, or external preparations such as aerosols, and the external preparations may be formulated as creams, gel, patches, sprays, ointments, plasters, lotions, liniments, pastes, or cataplasmas.

[0089] Carriers, excipients, and diluents that may be included in the pharmaceutical composition according to the present invention include lactose, dextrose, sucrose, oligosaccharides, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, gum acacia, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinyl pyrrolidone, water, methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, and mineral oil.

[0090] In the case of formulation, the composition according to the present invention may be prepared using diluents or excipients such as commonly used fillers, extenders, binders, wetting agents, disintegrants, and surfactants.

[0091] As additives for tablets, powder, granules, capsules, pills, and troches according to the present invention, excipients such as corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, di-mannitol, precipitated calcium carbonate, synthetic aluminum silicate, calcium hydrogen phosphate, calcium sulfate, sodium chloride, sodium bicarbonate, purified lanolin, microcrystalline cellulose, dextrin, sodium alginate, methylcellulose, sodium carboxymethylcellulose, kaolin, urea, colloidal silica gel, hydroxypropyl starch, hydroxypropylmethyl cellulose (HPMC) 1928, HPMC 2208, HPMC 2906, HPMC 2910, propylene glycol, casein, calcium lactate, and Primogel; and binders such as gelatin, gum arabic, ethanol, agar powder, cellulose acetate phthalate, carboxymethyl cellulose, calcium carboxymethyl cellulose, glucose, purified water, sodium caseinate, glycerin, stearic acid, sodium carboxymethyl cellulose, sodium methyl cellulose, methyl cellulose, microcrystalline cellulose, dextrin, hydroxycellulose, hydroxypropyl starch, hydroxymethyl cellulose, refined shellac, starch gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and polyvinylpyrrolidone may be used; and disintegrants such as hydroxypropyl methyl cellulose, corn starch, agar powder, methyl cellulose, bentonite, hydroxypropyl starch, sodium carboxymethyl cellulose, sodium alginate, calcium carboxymethyl cellulose, calcium citrate, sodium lauryl sulfate, silicic acid anhydride, 1-hydroxypropyl cellulose, dextran, ion exchange resins, polyvinyl acetate, formaldehyde-treated casein and gelatin, alginic acid, amylose, guar gum, sodium bicarbonate, polyvinylpyrrolidone, calcium phosphate, gelled starch, gum arabic, amylopectin, pectin, sodium polyphosphate, ethyl cellulose, white sugar, magnesium aluminum silicate, D-sorbitol solution, and light anhy-

drous silicic acid; and lubricants such as calcium stearate, magnesium stearate, stearic acid, hydrogenated vegetable oils, talc, Lycopodium, kaolin, Vaseline, sodium stearate, cacao fat, sodium salicylate, magnesium salicylate, polyethylene glycol (PEG) 4000, PEG 6000, liquid paraffin, hydrogen-added soybean oil (Lubri wax), aluminum stearate, zinc stearate, sodium lauryl sulfate, magnesium oxide, Macrogol, synthetic aluminum silicate, silicic anhydride, higher fatty acids, higher alcohols, silicone oil, paraffin oils, polyethylene glycol fatty acid ether, sodium chloride, sodium acetate, sodium oleate, DL-leucine, and light anhydrous silicic acid may be used.

[0092] As additives for liquid formulations according to the present invention, water, dilute hydrochloric acid, dilute sulfuric acid, sodium citrate, sucrose monostearate, polyoxyethylene sorbitol fatty acid esters (Tween esters), polyoxyethylene monoalkyl ethers, lanolin ethers, lanolin esters, acetic acid, hydrochloric acid, ammonia water, ammonium carbonate, potassium hydroxide, sodium hydroxide, prolamin, polyvinylpyrrolidone, ethyl cellulose, sodium carboxymethyl cellulose or the like may be used.

[0093] A solution of white sugar, other sugars, or sweeteners or the like may be used in the syrup according to the present invention, and flavoring agents, colorants, preservatives, stabilizers, suspending agents, emulsifiers, thickening agents or the like may be used as needed.

[0094] Purified water may be used in the emulsions according to the present invention, and emulsifiers, preservatives, stabilizers, flavoring agents or the like may be used as needed.

[0095] Suspending agents such as acacia, tragacanth, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose, sodium alginate, HPMC, HPMC 1828, HPMC 2906, HPMC 2910 or the like may be used in the suspensions according to the present invention, and surfactants, preservatives, stabilizers, colorants, and flavoring agents may be used as needed.

[0096] The injections according to the present invention may include solvents such as distilled water for injection, 0.9% sodium chloride for injection, Ringer's solution, dextrose for injection, dextrose+sodium chloride for injection, PEG, lactated Ringer's solution, ethanol, propylene glycol, non-volatile oil-sesame oil, cottonseed oil, peanut oil, soybean oil, corn oil, ethyl oleate, isopropyl myristic acid, benzyl benzoate; solubilizing agents such as sodium benzoate, sodium salicylate, sodium acetate, urea, urethane, monoethyl acetamide, butazolidine, propylene glycol, Tweens, nicotinic acid amide, hexamine, and dimethylacetamide; buffers such as weak acids and salts thereof (acetic acid and sodium acetate), weak bases and salts thereof (ammonia and ammonium acetate), organic compounds, proteins, albumin, peptone, and gums; isotonic agents such as sodium chloride; stabilizers such as sodium bisulfite (NaHSO_3) carbon dioxide gas, sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$), sodium sulfite (Na_2SO_3), nitrogen gas (N_2), and ethylenediaminetetraacetic acid; antioxidants agents such as sodium bisulfide 0.1%, sodium formaldehyde sulfoxylate, thiourea, disodium ethylenediaminetetraacetate, and acetone sodium bisulfite; analgesics such as benzyl alcohol, chlorobutanol, procaine hydrochloride, glucose, and calcium gluconate; and suspending agents such as carboxymethyl (CM) sodium, sodium alginate, Tween 80, and aluminum monostearate.

[0097] In the suppositories according to the present invention, bases such as cacao oil, lanolin, Witepsol, polyethylene glycol, glycerogelatin, methylcellulose, carboxymethylcellulose, a mixture of stearic acid and oleic acid, Subanal, cottonseed oil, peanut oil, palm oil, cacao butter+cholesterol, lecithin, Lanette wax, glycerol monostearate, Tween or Span, Imhausen, monolene (propylene glycol monostearate), glycerin, Adeps solidus, Buytvrum Tego-G), Cebes Pharma 16, Hexalide Base 95, Cotomar, Hydrocote SP, S-70-XXA, S-70-XX75 (S-70-XX95), Hydrokote 25, Hydrokote 711, Idropostal, Massa estrarium (A, AS, B, C, D, E, I, T), Massa-MF, Massaupol, Masupol-15, Neosupostal-N, Paramount-B, Suposiro (OSI, OSIX, A, B, C, D, H, L), suppositories base type IV (AB, B, A, BC, BBG, E, BGE, C, D, 299), Supostal (N, Es), Wecobi (W, R, S, M, Fs), Tegestor triglyceride base (TG-95, MA, 57) may be used.

[0098] Solid preparations for oral administration include tablets, pills, powder, granules, and capsules. These solid preparations are prepared by mixing the extract with at least one excipient, for example, starch, calcium carbonate, sucrose, lactose, gelatin, etc. In addition to simple excipients, lubricants such as magnesium stearate and talc are also used.

[0099] Suspensions, oral solutions, emulsions, syrup, and the like correspond to liquid preparations for oral administration, and in addition to the commonly used simple diluents such as water and liquid paraffin, various excipients, for example, wetting agents, sweeteners, flavoring agents, and preservatives may be included. Preparations for parenteral administration include sterilized aqueous solutions, non-aqueous solutions, suspensions, emulsions, freeze-dried preparations, and suppositories. As non-aqueous solvents and suspensions, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and an injectable ester such as ethyl oleate may be used.

[0100] The pharmaceutical composition according to the present invention is administered in a pharmaceutically effective amount. In the present invention, “pharmaceutically effective amount” refers to an amount that is sufficient to treat a disease with a reasonable benefit/risk ratio applicable to medical treatment, and an effective dose level may be determined based on factors including the type and severity of a patient’s disease, drug activity, sensitivity to drug, administration time, administration route and excretion rate, treatment duration, and drugs used simultaneously, and other factors well known in the medical field.

[0101] The pharmaceutical composition according to the present invention may be administered as an individual therapeutic agent or concomitantly with another therapeutic agent, and it may be administered sequentially or simultaneously with conventional therapeutic agents, and it may be administered once or multiple times. It is important to administer an amount that may achieve the maximum effect with the minimum amount without side effects by considering all of the above factors, and this may be easily determined by those skilled in the art to which the present invention pertains.

[0102] The pharmaceutical composition of the present invention may be administered to a subject through various routes. All modes of administration are considered, and it may be administered by, for example, oral administration, subcutaneous injection, intraperitoneal administration, intravenous injection, intramuscular injection, paraspinal space (intrathecal) injection, sublingual administration, buccal

administration, intrarectal injection, vaginal injection, ocular administration, auricular administration, nasal administration, inhalation, spraying through the mouth or nose, dermal administration, transdermal administration or the like.

[0103] The pharmaceutical composition of the present invention is determined according to the type of drug that is an active ingredient along with various relevant factors such as the disease to be treated, administration route, the patient’s age, gender, and weight, and the severity of the disease.

[0104] In addition, the present invention provides an alopecia prevention or treatment method, comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0105] In addition, the present invention provides a use of a composition comprising the botulinum toxin recombinant protein as an active ingredient for preventing or treating alopecia.

[0106] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for treating alopecia.

[0107] In addition, the present invention provides a method of ameliorating alopecia, comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0108] In addition, the present invention provides a use of a composition comprising the botulinum toxin recombinant protein as an active ingredient for ameliorating alopecia.

[0109] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for ameliorating alopecia.

[0110] In addition, the present invention provides a method for promoting hair growth comprising administering a composition comprising the botulinum toxin recombinant protein as an active ingredient to a subject in need thereof.

[0111] In addition, the present invention provides a use for promoting hair growth of a composition comprising the botulinum toxin recombinant protein as an active ingredient.

[0112] In addition, the present invention provides a use of the botulinum toxin recombinant protein for preparing a drug for promoting hair growth.

[0113] In the present invention, “subject” refers to a subject that requires treatment of a disease, and more specifically, human or non-human primates, and mammals such as mice, rats, dogs, cats, horses, and cows.

[0114] In the present invention, “administration” refers to providing a predetermined amount of the composition of the present invention to a subject by any appropriate method.

[0115] In the present invention, “ameliorating” may refer to any action by which alopecia symptoms are changed for the better or beneficially changed by administration of the composition according to the present invention, and may also include preventive or therapeutic actions.

[0116] In the present invention, “prevention” refers to all actions that suppress or delay the onset of a target disease, and “treatment” refers to all actions that change for the better or beneficially change a target disease and associated metabolic abnormalities thereof by administration of the pharmaceutical composition according to the present invention.

[0117] In the present invention, “treating” may include without limitation any act of administering the botulinum

toxin recombinant protein to a subject and allowing a subject to be in contact with the same.

[0118] In addition, as another aspect of the present invention, the present invention provides a quasi-drug composition for ameliorating alopecia, comprising a botulinum toxin recombinant protein as an active ingredient, and in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain. The specific details of the botulinum toxin recombinant protein are as described above.

[0119] The term "quasi-drug" of the present invention refers to articles with a milder effect than that of pharmaceuticals among articles used for the purpose of diagnosing, treating, ameliorating, alleviating, treating, or preventing diseases in humans or animals. For example, according to the Pharmaceutical Affairs Act, a quasi-drug excludes articles used for pharmaceutical uses and includes products used for treatment or prevention of diseases in humans/animals and products that have a mild or no direct effect on the human body.

[0120] When the botulinum toxin recombinant protein according to the present invention is used as a quasi-drug additive, the composition may be added as is or used together with another quasi-drug or quasi-drug component, and may be used appropriately according to conventional methods. The mixing amount of an active ingredient may be appropriately determined according to the purpose of use.

[0121] A quasi-drug composition for ameliorating hair loss of the present invention is not particularly limited in dosage forms thereof, and may be formulated in various forms as quasi-drugs known in the art to exhibit an effect of ameliorating alopecia. The above formulated quasi-drugs include hair tonics, hair lotions, hair creams, hair sprays, hair mousse, hair gels, hair conditioners, hair shampoos, hair rinses, hair packs, hair treatments, eyebrow growth agents, eyelash growth agents, eyelash nutritional agents, pet shampoos, pet rinses, hand sanitizers, detergent soaps, soaps, disinfectants, wet wipes, masks, ointments, patches or filter fillers, and include all quasi-drugs in the conventional sense.

[0122] In addition, in each formulation, other ingredients may optionally be selected and mixed with a quasi-drug composition for ameliorating alopecia depending on the formulation or purpose of use of other quasi-drugs. The mixing amount of an active ingredient may be appropriately determined depending on the purpose of use and may include, for example, conventional adjuvants such as thickeners, stabilizers, solubilizing agents, vitamins, pigments, and fragrances, and carriers. A quasi-drug composition including the botulinum toxin recombinant protein of the present invention as an active ingredient has almost no toxicity or side effects on cells and thus may be effectively used as a quasi-drug material.

[0123] In addition, as still another aspect of the present invention, the present invention provides a composition for external skin application for ameliorating alopecia, comprising a botulinum toxin recombinant protein as an active ingredient, and in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain. The specific details of the botulinum toxin recombinant protein are as described above.

[0124] The composition for external skin application of the present invention includes a botulinum toxin recombi-

nant protein as an active ingredient and may include a pharmaceutically acceptable carrier. In addition, the composition for external skin application of the present invention may further include adjuvants commonly used in the field of dermatology such as fatty substances, organic solvents, solubilizing agents, thickening and gelling agents, softeners, antioxidants, suspending agents, stabilizers, foaming agents, flavoring agents, surfactants, water, ionic or non-ionic emulsifiers, fillers, sequestering agents and chelating agents, preservatives, vitamins, blocking agents, wetting agents, essential oils, dyes, pigments, hydrophilic or lipophilic active agents, lipid vesicles or any other ingredients commonly used in external skin preparations. In addition, the ingredients may be introduced in amounts commonly used in the field of dermatology.

[0125] Pharmaceutically acceptable carriers in the composition for external skin application of the present invention vary depending on the formulation form, but they may include hydrocarbons such as Vaseline, liquid paraffin, and gelled hydrocarbons (Plastibase); animal and vegetable oils such as medium chain fatty acid triglycerides, pork fat, hard fat, and cocoa fat; higher fatty alcohols and fatty acids, and esters thereof such as cetanol, stearyl alcohol, stearic acid, and isopropyl palmitate; water-soluble bases such as polyethylene glycol, 1,3-butylene glycol, glycerol, gelatin, white sugars, and sugar alcohols; emulsifiers such as glycerin fatty acid ester, polyoxyl stearate, and polyoxyethylene hydrogenated castor oil; adhesives such as acrylic acid ester and sodium alginate; propellants such as liquefied petroleum gas and carbon dioxide; and preservatives such as paraoxybenzoic acid esters. Furthermore, in addition to these, stabilizers, fragrances, colorants, pH adjusters, diluents, surfactants, preservatives, antioxidants, and the like may be added as needed. When the composition for external skin application according to the present invention is used, it is preferable to apply it by a conventional method to the skin of a hair loss area.

[0126] The composition for external skin application according to the present invention may be formulated to include a cosmetically or dermatologically acceptable medium or base. This is a formulation suitable for transdermal administration, and the composition for external skin application may be provided in the form of solutions, gels, solids, pasty anhydrous products, emulsions obtained by dispersing an oil phase in an aqueous phase, suspensions, microemulsions, microcapsules, microgranules or ionic (liposome) and non-ionic vesicular dispersant, or in the form of creams, toners, lotions, powder, ointments, sprays, packs, conceal sticks, hair tonic, hair nourishing lotions, hair treatments, hair rinses, hair shampoos, hair lotions or the like. The composition for external skin application may also be used in the form of foam or in the form of an aerosol composition further containing a compressed propellant. These compositions may be prepared according to conventional methods in the art.

[0127] The dosage of the composition for external skin application may vary depending on the weight, age, gender, and health conditions of a subject to be administered, administration period, clearance rate, severity of disease and the like.

[0128] In addition, as yet another aspect of the present invention, the present invention provides a cosmetic composition for ameliorating alopecia, comprising a botulinum toxin recombinant protein as an active ingredient, and in the

botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain. The specific details of the botulinum toxin recombinant protein are as described above.

[0129] Meanwhile, ingredients included in the cosmetic composition of the present invention may include ingredients commonly used in cosmetic compositions in addition to the botulinum toxin recombinant protein of the present invention as an active ingredient, for example, they may include conventional adjuvants such as antioxidants, stabilizers, solubilizing agents, vitamins, pigments, and fragrances, and carriers.

[0130] The cosmetic composition of the present invention may be prepared in any formulations commonly prepared in the art, for example, solutions, suspensions, emulsions, pastes, hair gels, hair creams, hair lotions, hair powder, soaps, surfactant-containing shampoos, surfactant-free shampoos, hair oils, hair packs, hair essence, sprays, but is not limited thereto.

[0131] When the formulation of a cosmetic composition of the present invention is a paste, cream or gel, animal oil, vegetable oils, wax, paraffin, starch, tragacanth, cellulose derivatives, polyethylene glycol, silicone, bentonite, silica, talc or zinc oxide or the like may be used as a carrier ingredient.

[0132] When the formulation of the cosmetic composition of the present invention is a solution or emulsion, a solvent, solubilizing agent, or emulsifying agent is used as a carrier ingredient, and it may include, for example, water, ethanol, isopropanol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylglycol oil, glycerol aliphatic esters, polyethylene glycol or fatty acid esters of sorbitan.

[0133] When the formulation of the cosmetic composition of the present invention is a suspension, a liquid diluent such as water, ethanol, and propylene glycol, a suspending agent such as ethoxylated isostearyl alcohol, polyoxyethylene sorbitol ester, and polyoxyethylene sorbitan ester, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar, or tragacanth may be used as a carrier ingredient.

[0134] When the formulation of the cosmetic composition of the present invention is powder or a spray, lactose, talc, silica, aluminum hydroxide, calcium silicate, or polyamide powder may be used as a carrier ingredient, and in particular, when the formulation is a spray, it may further include a propellant such as chlorofluorohydrocarbon, propane/butane, and dimethyl ether.

[0135] When the formulation of the cosmetic composition of the present invention is a surfactant-containing shampoo, aliphatic alcohol sulfate, aliphatic alcohol ether sulfate, sulfosuccinic acid monoester, isethionate, imidazolinium derivatives, methyl taurate, sarcosinate, fatty acid amide ether sulfate, alkylamido betaine, aliphatic alcohols, fatty acid glyceride, fatty acid diethanolamide, vegetable oils, lanolin derivatives, or ethoxylated glycerol fatty acid ester may be used as a carrier ingredient.

[0136] When the cosmetic composition of the present invention is in the form of a soap, surfactant-containing shampoo, or surfactant-free shampoo formulation, it can be applied to the skin and then wiped off, removed, or washed with water. As a specific example, the soap includes liquid soaps, powdered soaps, solid soaps, and oil soaps, but is not limited thereto.

Modes of the Invention

[0137] Hereinafter, preferred examples are presented to aid understanding of the present invention. However, the following examples are provided only for easier understanding of the present invention, and the content of the present invention is not limited by the following examples.

EXAMPLES

Example 1. Evaluation of Cytotoxicity in Human Follicle Dermal Papilla Cells (HFDPCs)

1-1. Cell Line Selection and Cell Culture

[0138] To evaluate the cell viability of a skin-penetrating botulinum-derived ingredient peptide (botulinum toxin recombinant protein) prepared according to Korea Patent No. 10-1882461, HFDPCs (PromoCell, Germany) were purchased and used. The HFDPCs were inoculated into each 100 mm² culture dish at 1×10⁶ cells/dish and cultured at 37° C. in an incubator (Sanyo, Japan) containing 5% carbon dioxide after adding a human dermal papilla growth medium containing penicillin (100 IU/ml), streptomycin (100 g/mL), and supplements.

1-2. Cell Viability Evaluation Method

[0139] The thiazolyl blue tetrazolium bromide (MTT) analysis method is a test method for measuring the ability of mitochondria to reduce MTT tetrazolium, which is a yellow water-soluble substrate, to red-purple formazan (3-(4,5-dimethylthizol-2-yl)-2,5-diphenyl tetrazolium) by the action of cellular dehydrogenase. Since MTT reduction occurs in metabolically active cells, it is widely used to evaluate cytotoxicity and cell viability in cultured cells.

[0140] The HFDPC cells subcultured in Example 1-1 were dispensed into a 96-well plate at 1×10⁴ cells/well and cultured for 24 hours in an incubator containing 5% carbon dioxide at 37° C. Next, the HFDPC cells were treated with a skin-penetrating botulinum-derived ingredient peptide at final concentrations of 0.0005, 0.005, 0.05, and 0.5 ppm, and in the positive control group (FBS), cells were treated with fetal bovine serum (FBS) diluted to final concentrations of 15%, 20%, 25%, and 30% and cultured under cell culture conditions for 24 hours.

[0141] After culture, the MTT solution was added to each well and allowed to react for two hours under light blocking conditions. Then, the supernatant was removed, the resulting formazan was completely dissolved with dimethyl sulfoxide (DMSO), and the absorbance was measured at 540 nm with a microplate reader (Bioteck Synergy-HT, USA).

[0142] The cell viability test was repeated three times, and the result values were calculated using Equation 1 and expressed as cell viability compared to the untreated group, and expressed as the average±standard deviation of the three experiments.

Cell viability =

[Equation 1]

$$\frac{\text{Absorbance of the group treated with the sample}}{\text{Absorbance of the group untreated with the sample}} \times 100$$

[0143] The experimental results were analyzed as follows:

[0144] (1) The test was repeated three times, and the results were expressed as mean±standard deviation.

[0145] (2) The values measured as a result of the cytotoxicity test were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney U test, and then Bonferroni correction was performed ($p<0.0125$).

[0146] (3) The significance of the values measured in the test was confirmed using IBM SPSS statistics version 21.0 with a hypothesized mean difference of 5% ($p<0.05$).

1-3. Results

[0147] The HFDPC cells were treated with 0.0005, 0.005, 0.05, and 0.5 ppm of the skin-penetrating botulinum-derived ingredient peptide and 15%, 20%, 25%, and 30% of FBS as a positive control, respectively, and the absorbance and cell viability were measured as shown in Tables 1 and 2 and FIGS. 1 to 4.

[0148] As a result of the test, the group treated with the skin-penetrating botulinum-derived ingredient peptide showed a cell viability of 103.96% at the 0.0005 ppm concentration, 105.18% at the 0.005 ppm concentration, 107.83% at the 0.05 ppm concentration, and 103.69% at the 0.5 ppm concentration, compared to the untreated group. In the FBS-treated group used as a positive control, the cell viability was 104.43% at the 15% concentration, 107.38% at the 20% concentration, 110.68% at the 25% concentration, and 115.02% at the 30% concentration compared to the untreated group.

[0149] In other words, the skin-penetrating botulinum-derived ingredient peptide did not affect cytotoxicity at all concentrations, and at a 0.05 ppm concentration of the skin-penetrating botulinum-derived ingredient peptide, the cell viability significantly increased compared to the untreated group, indicating that the viability of the HFDPCs increased.

TABLE 1

Untreated	Concentration of skin-penetrating botulinum-derived ingredient peptide (ppm)				
	group ^a	0.0005	0.005	0.05	0.5
Absorbance (OD 540)	0.156 ± 0.004	0.162 ± 0.007	0.164 ± 0.007	0.168 ± 0.006	0.162 ± 0.006
p-value ^b	—	0.050	0.019	<0.001*	0.050
cell viability (%)	100 ± 0.00	103.96 ± 2.51	105.18 ± 2.80	107.83 ± 1.79	103.69 ± 2.16

^aUntreated group: Group treated with only the culture solution.

^bProbability p (Mann-Whitney U test with Bonferroni correction, Significant; * $p < 0.0125$).

Example 2. Evaluation of Prostaglandin F_{2α} Expression

[0150] About 30 subtypes of prostaglandins are known to date. In particular, it is known that prostaglandin E₂ and prostaglandin F_{2α} are mainly distributed in the skin. Prostaglandin F_{2α} received attention when studies were conducted on the side effects of lengthened eyelashes, increased number of eyelash hairs, and excessive pigmentation in the peripheral regions when a latanoprost eye drop containing a derivative thereof as a main ingredient was used as a therapeutic agent for glaucoma. Afterward, through many studies, Prostaglandin F_{2α} became known as a factor inducing hair growth, and by checking whether the expression of prostaglandin F_{2α} increases or decreases according to the treatment of samples, it is used as data to determine the possibility of controlling hair growth and controlling pigmentation.

[0151] Accordingly, to evaluate and investigate whether a skin-penetrating botulinum-derived ingredient peptide may induce quantitative changes in prostaglandin F_{2α}, changes in the expression level of prostaglandin F_{2α} secreted from keratinocytes were analyzed according to treatment of samples.

[0152] 2-1. Preparation of samples A skin-penetrating botulinum-derived ingredient peptide at a concentration 2000-fold that of the finished product (0.005 ppm) and/or an alopecia-alleviating functional ingredients (niacinamide+dexapanthenol) at a concentration 200-fold that of the finished product (niacinamide (0.1%) and dexapanthenol (0.2%)) were diluted in purified water and treated in the final cell culture medium at a concentration of 0.2, 0.5, 1, and 2 times the concentration of the finished product, and the control group was treated with purified water in the same amount as the sample treatment amount.

TABLE 2

Untreated	Control group (FBS treated group) concentration (%)				
	group ^a	15	20	25	30
Absorbance (OD 540)	0.156 ± 0.004	0.163 ± 0.005	0.167 ± 0.006	0.173 ± 0.006	0.179 ± 0.007
p-value ^b	—	0.014	<0.001*	<0.001*	<0.001*
cell viability (%)	100 ± 0.00	104.43 ± 2.07	107.33 ± 2.35	110.68 ± 2.32	115.02 ± 2.62

^aUntreated group: Group treated with only the culture solution.

^bProbability p (Mann-Whitney U test with Bonferroni correction, Significant; * $p < 0.0125$).

2-2. Experimental Method

- [0153] 1) Keratinocytes were inoculated at $3 \times 10^5/6$ wells and cultured for two days.
- [0154] 2) The cells were cultured for one day in a starvation state.
- [0155] 3) The cells were treated with the samples and cultured for one day.
- [0156] Treated samples:
- [0157] a) Skin-penetrating botulinum-derived ingredient peptide
 - [0158] b) Skin-penetrating botulinum-derived ingredient peptide+alopecia-alleviating functional ingredient
 - [0159] c) Negative control (COX-2 inhibitor, NS-398)
- [0160] 4) After centrifuging the cell culture medium, the expression level of prostaglandin $F_{2\alpha}$ was measured using a prostaglandin $F_{2\alpha}$ assay kit. Specifically, the prostaglandin $F_{2\alpha}$ test method is a colorimetric method in which absorbance is measured using a spectrophotometer and the results are analyzed. Since the expression of prostaglandin F_2 is highly sensitive to cell conditions and treatment methods, appropriate cell culture and sample treatment methods are important, and standard prostaglandin $F_{2\alpha}$ should be measured and comparatively analyzed by concentration in each test.
- [0161] 5) The cell activity is measured using the MTT method, and the prostaglandin $F_{2\alpha}$ values are corrected and analyzed.

2-3. Cytotoxicity Test Results

[0162] In the cytotoxicity test, measurement was performed by the MTT method. Determination of cytotoxicity is based on the time when cell activity decreases by more than 20% compared to the control group.

[0163] Each sample was treated with a cell culture medium at final concentrations of $0.2\times$, $0.5\times$, $1\times$, $2\times$, and $4\times$. In the group treated with the skin-penetrating botulinum-derived ingredient peptide alone, no toxicity was observed up to $4\times$, and in the group treated with the skin-penetrating botulinum-derived ingredient peptide+alopecia-alleviating functional ingredient, strong toxicity was observed starting from the $2\times$ concentration, so the group was excluded from the test groups. The cytotoxicity test results are shown in Table 3.

TABLE 3

Sample conditions	Treatment concentration	1	2	3	4	Mean	% of control
cont	D.W	0.8770	0.8520	0.8420	0.8480	0.8548	100
NS-398	5 μ M	0.8690	0.8540	0.8790	0.8860	0.8720	102.0
BDI	0.2X	0.8510	0.8610	0.8800	0.8860	0.8695	101.7
	0.5X	0.8540	0.8650	0.8870	0.8840	0.8725	102.1
	1X	0.8540	0.8540	0.8800	0.8820	0.8675	101.5
	2X	0.8580	0.8550	0.8720	0.8720	0.8643	101.1
	4X	0.8780	0.8590	0.8640	0.8710	0.8680	101.6
BDI + AFI	0.2X	0.8790	0.8730	0.8880	0.8890	0.8823	103.2
	0.5X	0.8600	0.8620	0.8680	0.8750	0.8663	101.3
	1X	0.8710	0.8790	0.8540	0.8530	0.8643	101.1

BDI: Botulinum-derived ingredient; AFI: alopecia-alleviating functional ingredient.

2-4. Results of Prostaglandin $F_{2\alpha}$ Analysis Using Spectrophotometer

[0164] The prostaglandin F_2 analysis using a spectrophotometer is a test method that has the characteristic that the higher the expression level of prostaglandin $F_{2\alpha}$, the lower the absorbance value, as shown in the absorbance measured at each concentration of standard prostaglandin $F_{2\alpha}$. Specifically, as shown in Table 4 and FIG. 5, a standard curve was obtained by applying standard prostaglandin $F_{2\alpha}$ according to the amount, and the amount of prostaglandin F_2 % was analyzed using this standard curve. This absorbance value was recalibrated to the cell activity value for a final analysis, and the results are shown in Tables 5 and 6 and FIG. 6.

TABLE 4

PGF $_{2\alpha}$ (pg/mL)	Absorbance value (405 nm)
0	0.9360
3.1	0.8570
12.2	0.7710
48.8	0.6750
195.3	0.5470
781.3	0.4060
3125	0.2830
12500	0.1860

[0165] As a result of the analysis, considering the expression level of prostaglandin $F_{2\alpha}$ in the control group as 100%, in the group treated with the skin-penetrating botulinum-derived ingredient peptide alone, an increase in expression of 25.2% at the treatment concentration of $0.2\times$, 25.8% at $0.5\times$, 33.3% at $1\times$, and 40.2% at $2\times$ was confirmed. However, at $4\times$, a decrease in the expression level to the level of the control group was observed. In the combined treatment of the skin-penetrating botulinum-derived ingredient peptide and alopecia-alleviating functional ingredient, an increase in expression of 25.1% at the treatment concentration of $0.2\times$, 43.4% at $0.5\times$, and 44.3% at $1\times$ was confirmed.

[0166] At this time, n=4 in the test, and as a result of an analysis using the Student's t-test as a statistical technique, it was confirmed that significance was found in all sections where the expression level of prostaglandin $F_{2\alpha}$ increased.

TABLE 5

SC	[T]	Absorbance value (405 nm)					PGF ₂ alpha (pg/mL)					PGF ₂ alpha (pg/mL)/MTT		M	SD	
		D.W	0.4220	0.4150	0.4160	0.4060	722.1	784.8	775.5	873.6	823.4	921.2	921.1	1030.2	923.9	84.5
cont.		5µM	0.6170	0.6000	0.6110	0.6220	70.9	86.8	76.1	66.8	81.5	101.6	86.6	75.4	86.3	11.2
NS-398		0.2X	0.4010	0.3970	0.3880	0.3910	927.2	972.4	1082.4	1044.4	1089.5	1129.4	1230.0	1178.8	1156.9	60.9
		0.5X	0.3930	0.3970	0.3920	0.3920	1019.8	972.4	1032.0	1032.0	1194.2	1124.2	1163.5	1167.5	1162.3	28.9
		1X	0.3920	0.3970	0.3800	0.3880	1032.0	972.4	1190.5	1082.4	1208.5	1138.6	1352.9	1227.2	1231.8	89.3
		2X	0.3890	0.3700	0.3940	0.3900	1069.6	1341.0	1007.8	1056.9	1246.6	1568.5	1155.7	1212.0	1295.7	185.7
		4X	0.4190	0.4160	0.4090	0.4040	748.3	775.5	842.9	894.6	852.3	902.8	975.6	1027.1	939.5	77.3
BDI +		0.2X	0.3950	0.4040	0.3870	0.3870	995.8	894.6	1095.3	1095.3	1132.9	1024.8	1233.5	1232.1	1155.8	99.2
AFI		0.5X	0.3860	0.3850	0.3790	0.3820	1108.4	1121.7	1204.8	1162.5	1288.9	1301.3	1388.0	1328.6	1326.7	44.1
		1X	0.3820	0.3840	0.3820	0.3830	1162.5	1135.2	1162.5	1148.7	1334.7	1291.4	1361.2	1346.7	1333.5	30.1

SC: Sample Conditions; [T]: Treatment Concentration; M: Mean; SD: Standard Deviation; BDI: Botulinum-derived ingredient; AFI: alopecia-alleviating functional ingredient.

TABLE 6

Sample conditions	Treatment concentration	% of control
cont.	D.W	100.0
NS-398	5 µM	9.3
BDI	0.2X	125.2
	0.5X	125.8
	1X	133.3
	2X	140.2
	4X	101.7
BDI + AFI	0.2X	125.1
	0.5X	143.6
	1X	144.3

BDI: Botulinum-derived ingredient; AFI: alopecia-alleviating functional ingredient.

[0167] From the above results, it could be confirmed that in both the group treated with the skin-penetrating botulinum-derived ingredient peptide alone and the group treated in combination with the alopecia-alleviating functional ingredient, the expression and secretion of prostaglandin F_{2α} were induced in keratinocytes.

[0168] Since the increase in prostaglandin F_{2α} expression is related to hair growth, it was determined that applying a skin-penetrating botulinum-derived ingredient peptide to the skin could induce hair growth.

Example 3. Evaluation of Alopecia-Ameliorating Effect

3-1. Experimental Materials and Methods

[0169] A total of 4 men (42 to 52 years old) with alopecia symptoms were asked to apply 2.5 cc of a solution contain-

ing the skin-penetrating botulinum-derived ingredient peptide (botulinum toxin recombinant protein) directly to the alopecia area every morning, and the conditions of the subjects' scalp was confirmed by taking photos before use, after 8 weeks of use, and after 16 weeks of use. The subjects were asked to evaluate the amelioration of alopecia symptoms as no effect (0)/good (1)/satisfied (2)/very satisfied (3).

[0170] In addition, to objectify the experimental results, two evaluators were asked to evaluate the amelioration of alopecia symptoms as no amelioration (0)/slight amelioration (1)/amelioration (2)/excellent amelioration (3).

[0171] Furthermore, after 16 weeks of use, a survey was conducted with the subjects about changes in hair thickness, number of hairs lost, reduction in scalp oiliness, cleanliness around hair roots (reduction in sebum, etc.), and hair sinking in the afternoon.

3-2. Results

[0172] As a result of evaluating the alopecia-ameliorating effect of the skin-penetrating botulinum-derived ingredient peptide by the subjects and evaluators, as shown in Table 7 and FIG. 7, the satisfaction of the subjects increased as the period of use increased, and both evaluators evaluated that the subjects' alopecia symptoms were significantly improved. No particular side effects were found in any of the subjects during the 16-week experiment period. FIGS. 8 to 11 show changes in the subjects' scalp.

TABLE 7

	Subjects' satisfaction		Photo evaluation by evaluators	
	After 8 weeks of use	After 16 weeks of use	After 8 weeks of use	After 16 weeks of use
Subject A	3	3	2	3
Subject B	2	3	2	3
Subject C	1	2	2	2
Subject D	1	1	1	2

*Subjects' satisfaction: 0 (no effect)/1 (good)/2 (satisfied)/3 (very satisfied).

**Photo evaluation by evaluators: 0 (no amelioration)/1 (slight amelioration)/2 (amelioration)/3 (excellent amelioration).

[0173] In addition, as shown in Table 8, in the survey administered to the subjects after 16 weeks of use, overall improvement was found in the subjects' hair thickness, number of hairs lost, reduction in oiliness of the scalp, cleanliness around the hair roots (reduction of sebum, etc.), and hair sinking in the afternoon.

TABLE 8

Changes in hair thickness	No change	Slightly thickened	Much thickened	Hairs thickened and strengthened
Number of respondents		2	1	1
Number of hairs lost	No change	Slightly reduced	Much reduced	Almost no hair lost
Number of respondents			3	1
Reduction in oiliness of the scalp	Slightly reduced	Reduced	Much reduced	Scalp and hairs remaining dry in the afternoon
Number of respondents	1	1		2
Cleanliness around the hair roots	Slightly reduced	Reduced	Much reduced	Remain clean all day long
Number of respondents		3	1	
Hair sinking in the afternoon	Slightly improved	Improved	Much improved	No sinking all day long
Number of respondents	2		1	1

[0174] The description of the present invention described above is for illustrative purposes, and those skilled in the art will understand that the present invention can be easily modified into other specific forms without changing the technical idea or essential features of the present invention. Therefore, the examples described above should be understood in all respects as illustrative and not restrictive.

INDUSTRIAL APPLICABILITY

[0175] Since the botulinum toxin recombinant protein according to the present invention can be easily delivered transdermally through fusion with a cell-penetrating peptide and promote proliferation of dermal papilla cells and enhance prostaglandin F_{2α} expression to reduce hair loss and promote hair growth, thereby ameliorating alopecia, it can be effectively used for preventing, ameliorating or treating alopecia in fields such as cosmetics and pharmaceuticals. Therefore, the present invention has industrial applicability.

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ggcattaaag tagatgattt accaattgt a ccaaatgaaa aaaaattttt tatgcaatct 780
acagatgtca tacaggcaga agaactatat acatggtag gacaagatcc cagcatcata 840
actccttcg cggataaaat tagtctatgaa aaggtttgc aaaattttag agggatagt 900
gatagactta acaagggtttt agtttgatata tcgatcttca attttatata taatataat 960
aaaataat ttaaagatata atataatcc gttgaagatt ctgagggaaa atatagtata 1020
gatgttagaa gttttatata attatataaa agcttaatgt ttgtttttatc aagaactata 1080
atagcagaaa attataataaa aaaaacttaga gcttcttatt ttgtgttattt ctaccaccca 1140
gtaaaaataaa aaaatttttatt agataatgaa atcttactata tagaggaagg gttaatata 1200
tctgataaaat atatggaaaa agaatataga ggctcagaata aagctataaa taacaacgt 1260
tatgaagaaa ttagcaaggg a gcattttggct gtatataaga tacaatgtg taaaatgtt 1320
aaa 1323

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SEQ ID NO: 12          moltype = DNA  length = 1347
FEATURE              Location/Qualifiers
source               1..1347
                     mol_type = other DNA
                     organism = synthetic construct
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SEQ ID NO: 13          moltype = DNA  length = 1326
FEATURE              Location/Qualifiers
source               1..1326
                     mol_type = other DNA
                     organism = synthetic construct
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SEQ ID NO: 14 moltype = DNA length = 1266
FEATURE Location/Qualifiers
source 1..1266
mol_type = other DNA

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caaataatata	aaaataaaata	tgattttgtt	gaagatccta	atggaaaata	tagtgttagat	1020
aaggataagt	ttgataaatt	atacaggcc	ttaatgttttgc	cttactga	aactaatcta	1080
gctggtaat	atggaaaaa	aactaggat	tcttatttttgc	gtaatatttgc	ccaccgata	1140
aaaactgaaa	aattgttaga	caatacaatt	tataactcaaata	atgaaggcctt	taacatagct	1200
agtaaaaatc	tcaaaaacgga	atthaatggt	cagaataagg	cggtaaataa	agaggcttat	1260
gaagaaaatca	gcctagaaca	tctcgttata	tatagaatag	caatgtgcaa	gcctgtatgc	1320
tacaaa						1326

SEQ ID NO: 17	moltype = AA	length = 468	
FEATURE	Location/Qualifiers		
source	1..468		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 17			
MGSSHHHHHH SSSLVPRGSH	MPFVNQFN	KDPVNGVDIA YIKIPNAGQM QPVKAFKIHN	60
KIWIPIPERDT	FTNPEEGDLN	PPPEAKQPV SYYDSTYLST DNEKDNYLKG VTKLFERIYS	120
TDLGRMLLTS	IVRGIPFWGG	STIDTELKVI DTNCINVQDG SYRSEELN LVIIGPSADI	180
IQFECKSFGH	EVNLNLTRNGY	GSTQYIRFSP DFTFGFEESL EVDTNPLLGA GKFA TDPAVT	240
LAHELIHAGH	RLYGIAINPN	RVFVKVNTNAY YEMSGLEVFSP EELRTFGGH AKFIDSLQEN	300
EFLYLYYYNKF	KDIASLTNAKA	QYMKNVFKEK YLLSEDTSGK FSVDKLKFDK	360
LYKMLTEIYT	EDNFVKFFKV	LNRKTYLNFD KAVFKINIVP KVNYTIYDGF NLRNTNLAA	420
FNGQNTEINN	MNFTKLKNFT	GLFEFYKLLC VRGIITSKTK SLDFKGYNK	468

SEQ ID NO: 18	moltype = AA	length = 461	
FEATURE	Location/Qualifiers		
source	1..461		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 18			
MGSSHHHHHH SSSLVPRGSH	MPVTINNFNY	NDPIDNNNII MMEPPFARGT GRYYKAFKIT	60
DRIWIPIPERY	TFGYKPEDFN	KSSGIFNRDV CEYYPDYLN TNDKKNIFLQ TMKLFNRIK	120
SKPLGEKLLM	MIINGIPYLG	DRRVPLLEFN TNIASVTNK LISNPGEVER KKGIFPANLII	180
FGPGPVLNEN	ETIDIGIQNH	FASREGFGGI MQMKFCPEVY SVFNNVQENK GASIFNRRGY	240
FSDPALILMH	ELIHVLHGLY	GIKVDDLPV PNEKKFFMQS TDAIQAEELY TFGGQDPSII	300
TPSTDKSIYD	KVLQNFRGIV	DRLNQVLVCI SDPNININII KNKFKDKYKF VEDSEGKYSI	360
DVESFDKLYK	SLMFGPTETN	IAENYKIKTR ASYFSDSLPP VIKINLLDNE IYTIEEGFNI	420
SDKDMEKEYR	GQNKAINKQA	YEEISKEHLA VYKIQMCKSVK	461

SEQ ID NO: 19	moltype = AA	length = 469	
FEATURE	Location/Qualifiers		
source	1..469		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 19			
MGSSHHHHHH SSSLVPRGSH	MPITINNFNY	SDPVDNKNIL YLDTHLNTLA NEPEKAFRIT	60
GNIWVIPDRF	SRNSNPNLNK	PPRVTPSKSG YYDPNLYSTD SDKDPFLKEI IKLFRINSR	120
EIGEELIYRL	STDIPPGNN	NTPINTFDFD VDPNSVDVKT RQGNWVKTG SINPSVIITG	180
PRENIIDPET	STFKLTNTNTF	AAQEGFGALS IIISPRPML TYSNATNDVG EGRPSKSEFC	240
MDPILILMH	LNHAMHNLGY	IAIPNDQTIS SVTSNIFYSQ YNVKLEYAEI YAFGGPTIDL	300
IPKSARKYFE	EKALDYRSI	AKRRLNSITTA NPSSFNKYIG EYKQKLLRKY RFVVESSGEV	360
TVNRRNKFVEL	YNELOQIFTE	FNYAKIYNQ NRKIYLSNVY TPVTANILDD NVYDIQNGFN	420
IPKSNLNVLF	MGQNLRSNPA	LRKVNPNML YLFTKFCHKA IDGRSLYNNK	469

SEQ ID NO: 20	moltype = AA	length = 462	
FEATURE	Location/Qualifiers		
source	1..462		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 20			
MGSSHHHHHH SSSLVPRGSH	MTWPVKDFNY	SDPVNDNDIL YLRIPQNKLI TPPVKAFMIT	60
QNIWVIPERF	SSDTNPSLSK	PPRPTSKYQS YYDPSYSTD EQKDTFLKGII KIPLFRINER	120
DIGKKLINAL	VVGSPFMGDS	STPEDTFDFT RHTTNIAVEK FENGSWKVTN IITPSVLIFG	180
PLPNILDYTA	SLTLOGQQSN	PSFEGFGTLS ILKVAPEPLL TFSDVTSNQS SAVLGKSFIC	240
MDPVIALMHE	LTHSLHQLYG	INIPSDKIR PQVSEGFPSQ DGPNVQFEEL YTFFGLDVEI	300
IPQIERSK	EKALGHYKDI	IPSSWISNINKT KYKKIFSEKY NFDKDNTGNF	360
VVNIDKFNLSL	YSDLTNVMSE	VVYSSQYNVK NRTHYFSRHY LPVFANILDD NIYTIRDGFN	420
LTNKGFIEN	SGQNIERNPA	LQKLSSESVV DLFTKVCLRL TK	462

SEQ ID NO: 21	moltype = AA	length = 442	
FEATURE	Location/Qualifiers		
source	1..442		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 21			
MGSSHHHHHH SSSLVPRGSH	MPTINSFNYN	DPVNNRTILY IKPGGCQQFY KSFNIMKNIW	60
IIIPERNVIGT	IPQDFLPPTS	LNGDSSYYD PNYLQSDQE DKFLKIVTKI FNRINDNLG	120

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RILLEELSKA	NPYLGNDNTP	DGDFIINDAS	AVPIQFSNGS	QSILLLPVII	MGAEPDLFET	180
NNSNISLRRN	YMPSNHGFGS	IAIVTFSPEY	SFRFKDNSMN	EFIQDPALTL	MHELIHSLHG	240
LYGAKGITTK	YTITQKQNPL	ITNIRGTNIE	EFLTFGGTDL	NIITSAQ SND	IYTNNLLADYK	300
KIASKLKVQ	VSNPLLPNPKY	DVFEAKYGLD	KDASGIYSVN	INKFNDIFKK	LYSFTEFDLA	360
TKFQVKCRQT	YIGQYKYFKL	SNLLNDSIYN	ISEGYNINNL	KVNFRGQNN	LNPRIITPIT	420
GRGLVKKIIR	PCKNIVSVKG	IR				442

SEQ ID NO: 22	moltype = AA	length = 456				
FEATURE	Location/Qualifiers					
source	1..456					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 22						
MGSSHHHHHH SSGLVPRGSH	MPVAINSFNY	NDPVNDDTIL	YMQIPYEEKS	KKYYKAF EIM	60	
RNVWIIPERN	TIGTNPSDFD	PPASLKN GSS	AYYDPNLYLT	DAEKDRYLKT	TIKLFKRINS	120
NPAAGKVLLQE	ISYAKPYLGN	DHTPIDEFSP	VTRTTSVNIK	LSTNVES SML	LNLLVLGAGP	180
DIFESCCYPV	RKLIDPDVVY	DPSNYGFGSI	NIVTFSPEYE	YTFNDISGH	NSSTESFIAD	240
PAISLAHELI	HALHGLYGR	GVTYEETIEV	KQAPLMTAEK	PIRLEELTF	GGQDLNIITS	300
AMKEKIYNNL	LANYEKIATR	LSEVNSAPPE	YDINEYKDYF	QWKYGLDKNA	DGSYTVNENK	360
FNBIYKKLYS	FTESDLANKF	KVKCRNTYFI	KYEFLKVPNL	LDDDIYTVSE	GFNIGNLAVN	420
NRGQSIKLN P	KIIDSIPDKG	LVEKIVKFCK	SVIPRK			456

SEQ ID NO: 23	moltype = AA	length = 461				
FEATURE	Location/Qualifiers					
source	1..461					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 23						
MGSSHHHHHH SSGLVPRGSH	MPVNIKFNYN	DPINNDDII M	MEPFNDPGPG	TYYKAFRIID	60	
RIWIVPVERFT	YGFQPDQFNA	STGVFSKDVY	EYDPTYLK T	DAEKDKFLKT	MIKLFNRINS	120
KPSGQRLLDM	ASTDAIPYLG N	A VNVNSINKK	IIQPGAEDQI	KGLMTNLII IF	180	
GPGPVLSDLNF	TDSMIMNGHS	PISEGFGARM	MIRFCPSCLN	VFPNVQENKD	TSIFSRRAYF	240
ADPALTLHM E	LIHVLHGLY G	IKISNLPITP	NTKEFFMQHS	DPVQAELYT	FGGHDPVIS	300
PSTDMDIYLN K	ALQNFQDIAN	R LNIVSSA QG	SGIDISLYKQ	IYKNKYD FVE	DPNGKYSVDK	360
DKFDKLYKAL	MFGFTETNLA	GEYGIKTRY S	YFSEYLPPKI	TEKLLDNTI Y	TQNEGFIAS	420
KNLKTEFNGQ	NKAVNKEAYE	EISLEHLVI Y	RIAMCKPVMY	K		461

SEQ ID NO: 24	moltype = DNA	length = 1437				
FEATURE	Location/Qualifiers					
source	1..1437					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 24						
atgggcagca	gccatcatca	tcatcatca	agcagccgc	ttgtgcgcgc	cggcaggccat	60
atgatgcct	ttgtcaacaa	acagtcaac	tacaaggacc	cagttaatgg	agtagacatc	120
gcatatatca	agattccaa	cgctggccag	atgcaacccg	ttaaggcatt	taaaatccat	180
aacaaaatct	gggttatccc	agagccggat	accttaccca	accccgagg	gggcgatctg	240
aaccccccgc	cggaggcga	gcaggctcca	gtgagact	acatagac	ctacctcagc	300
accgacaa	agaaggacaa	ctacctcaa	ggagtca	agttgttcg	gagaatctac	360
tccacagacc	tcggccgat	gettctaacc	agcattgtgc	gtggcattcc	cttttgggc	420
ggtctacca	tcgacacaga	gctyaagg	atagacacca	actgcatcaa	cgtaatccag	480
cctgacggca	gctaccga	cgaggact	aacctgg	tcatcggcc	ttccggccat	540
atcatccat	tccagtgca	gagtcggc	cacggatc	tgaaccc	ccggaaaccc	600
tatggaa	cccagtacat	aagattcago	cctgactca	ccttcgggtt	tgaggagac	660
ttggaggctc	acacaaaccc	cctgtggaa	gcccggaa	tgcgcaactg	cccagccgt	720
actctggcac	acgagctgt	ccacccgg	caccgcgt	acggcata	tataaacc	780
aacagggtgt	tcaaaatgaa	caacaaatc	tactatgaa	tgagccgc	ggagggtgac	840
ttcgaggagc	tgagaacgtt	cggggacat	gatgctaa	ttatcgac	cctgcaggag	900
aacaggatca	ggctgtacta	ctacaataa	tcaaggata	tagcga	cac tctgaac	960
gccaaggatc	tcgttaggcac	tactgcatc	ctccagta	tgaagaatgt	gttcaaagag	1020
aaataacctgc	tgagcgagga	taccagggt	aagttcag	tggataa	taatgtcgac	1080
aagctgtata	agatgtcac	cgaaaatctac	accgaggata	atttcgtt	aa gttctcaag	1140
gtcttgcac	ggaagaccta	cctgaactc	gacaaggcc	tgttcaagat	caacatcg	1200
cctaaatgt	actacccat	ctacgacgg	ttaaccc	cctggccg	1260	
aacttcaacg	ggcagaacac	agagatca	aacatgaa	tcacga	ttt gaagaatc	1320
acccgactgt	ttgaggctca	caattgtct	tgtgtgcgc	ggatcatc	ac tagcaagacc	1380
aagagccctt	acaaggc	ta caacatgt	ctcgagc	accacc	cca ctactga	1437

SEQ ID NO: 25	moltype = DNA	length = 1413				
FEATURE	Location/Qualifiers					
source	1..1413					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 25						
atgggcagca	gccatcatca	tcatcatca	agcagccgc	ttgtgcgcgc	cggcaggccat	60
atgatgcct	ttacaataaa	taattttaat	tataatgatc	ctattgata	taataatatt	120

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attatgtatgg	agcctccatt	tgcgagaggt	acggggagat	attataaago	ttttaaaatc	180
acagatcgta	tttgataat	accggaaaga	tatactttg	gatataaacc	tgaggatttt	240
aataaaaagt	cgggtattt	taatagagat	gttggtaat	attatgatcc	agattactta	300
aactaatgt	ataaaaaaaag	tatatttttca	caaacaatgt	tcaagtattt	taataatgc	360
aaatcaaaac	cattgggtga	aaagtatttata	gagatgatta	taaatggtat	actttatctt	420
ggagatagac	gtgttccact	cgaagagttt	aacacaaca	ttgctagtgt	aactgttaat	480
aaataatcat	gtaatccagg	aaagaatggag	cgaaaaaaag	gtatttccg	aaattaata	540
atatttggac	ctggggcagt	tttaaatgaa	aatgagacta	tagatattgg	tataaaaaat	600
cattttgcatt	caaggaaagg	cttcgggggtt	ataatgcata	tgaaattttgc	ccccaaataat	660
gtaagcgtat	ttaataatgt	tcaagaaaaac	aaaggcgc当地	gtatatttaa	tagacgtgg	720
tattttcag	atccagccctt	gatattatgt	catgaactta	tacatgtttt	acatggat	780
tatggcatta	aagttagatgt	tttaccaatt	gtaccaatgt	aaaaaaaaat	ttttatgc	840
tctacatcgat	ctataccaggc	agaadacta	tatatacttg	gaggacaaga	ttccagatc	900
ataactccctt	ctacggataa	aagtatctt	gataaagtttt	tgcaaaat	tttagggata	960
gtttagatagac	ttaacaatgg	ttttagtttgc	atatacgatc	ctaactatcaa	tattatataat	1020
tataaaaat	aattttaaaga	taatataaaa	ttcggttgaag	attctgggg	aaaataatgt	1080
atagatgtat	aaagttttga	taaattatata	aaaagcttta	ttgttgggtt	tcacaaaaact	1140
aatatagcag	aaaattataa	aataaaaaact	agagttctt	attttagtga	ttcccttacca	1200
ccagaaaaaa	taaaaaaaat	attagataat	gaaatcttata	ctatagagga	agggttaat	1260
atatctgtata	aagatatgtt	aaaaagatata	agaggctcaga	ataaaagctat	aaataaaaaac	1320
gctttagaag	aaatgtacaa	ggggatttgc	gctgtatata	agatacaat	gtgtaaaaat	1380
gtttaactcg	agcaccacca	ccaccacac	tga			1413

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SEQ ID NO: 26          moltype = DNA  length = 1437
FEATURE                Location/Qualifiers
source                 1..1437
                      mol_type = other DNA
                      organism = synthetic constru
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SEQUENCE: 26

atgggcgcga	gccatcatca	tcatcatcac	agcaggccc	tggtgcgcg	ccgcagccat	60
atgatgcca	taacaattaa	caacttataat	tattcagac	ctgttgataaa	aaaatatttt	120
ttatatttg	atactattt	aaatacatac	gctaatacg	ctgaaaaaagc	ctttcgatt	180
acagaaaaata	tatgggtaat	acctgtataga	ttttcaagaa	atcttatacc	aaatataat	240
aaaccccttc	gagttacaag	ccctaaaagt	ggttattatg	atcctatta	ttttagtact	300
gattctgaca	aagatacatt	tttaaaagaa	attataaagt	tattttaaaag	aatattttt	360
agagaaaaat	gagaagaat	aatataataga	cttgcacag	atataccct	tcctggaaat	420
aaacatactc	caattaatc	ttttgttattt	gatgtatatt	ttaaacatgt	tgatgtttaa	480
actagacaag	gtaacaactg	ggttaaaact	ggtagatcaa	atcctagtgt	tataataact	540
ggccatcttag	aaaacattat	agatccggaa	actcttcacgt	ttttaaaatcc	taaataactat	600
tttgcggcac	aagaaggatt	tggtgctta	tcaataattt	caatatcacc	tagattttatg	660
ctaacatata	gtatgcac	taatgtatgt	ggagagggtt	gattttctaa	gtctgaattt	720
tgcatggatc	caatactaaat	tttaatgcatt	gaacttaatc	atgcaatgc	taattttatat	780
ggaataatgca	taccaatata	tccaaaattt	tcatctgtat	cttagataat	ttttttttat	840
caataatata	tggaaatttga	gtatgcgaa	atatatgcatt	ttggagggtcc	aactatagac	900
tttatttctt	aaagtgcac	gaaatattttt	gaggaaaaagg	cattggattt	ttatagatctt	960
atagctaaa	gacttaatag	tataactact	gcaaaatcc	caaggtttaa	taaatatata	1020
ggggatataa	aacagaaaact	tataggaaag	tataatgttc	tgtagataat	ttccatgtgaa	1080
gttacagttaa	atcgtaat	gtttgtttag	tttatataatg	aacttacaca	aatattttca	1140
gaattttact	acgtctaaaat	ataataatgt	caaaaatagga	aaatataatct	ttcaaatgtt	1200
tatactccgg	ttacggcgaa	tatatttagac	gataatgtt	atgatataca	aatatggattt	1260
aatatactca	aaagttaattt	aaatgtacta	ttttagggtc	aaaattttatc	tgcataatcc	1320
gcatttaagaa	aagtcaatcc	tgaaaatatt	cttttatttt	ttacaaaaat	ttgttcataaa	1380
gcaatataatg	gtatgtatcc	atataataaa	tcgcagccacc	accacccaca	ccactgttt	1437

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SEQ ID NO: 27          moltype = DNA  length = 1416
FEATURE                Location/Qualifiers
source                 1..1416
                      mol_type = other DNA
                      organism = synthetic construct
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SEQUENCE: 27

atgggcgaca	gccatcatca	tcatcatcac	agcagccgccc	tggtgcgcgcg	cggcagccat	60
atgatgacat	ggcccaagtaaa	agattttaat	tatagtgtac	ctgttataatgc	caatgtatata	120
ttatattaa	gaataccaca	aaataaagtgt	attactacac	ctgtaaaaggc	ttttatgtatt	180
actcaaaaaa	tttgggtataat	accagaaga	ttttcatcag	ataactatcc	aatgttaatgt	240
aaaccggccc	gacctacttc	aaagtatcaa	agttattatgt	atccatgtta	tttatctact	300
gatgaacaaa	aagatacatt	ttttaaaagg	attataaaat	tattttaaaag	aattaatgaa	360
agagatata	aaaaaaaatt	aataaaattat	tttagtagtt	gttcacccctt	tatgggagat	420
tcaagtacgc	ctgaagatac	attgtat	acacgcctca	cctaataat	tgcgttgaa	480
aattttgaaa	atggtagtt	gaaagtataa	aatattat	caccaagtgt	attgtatatt	540
ggaccatctc	ctaataattat	agactataca	gcataccctt	cattgcagg	acacaatca	600
aatccatcat	ttgaagggtt	ttgaacatta	tctatactaa	aagttagcacc	tgaatttttg	660
ttaacattta	gtgtatgtac	atctaata	agttcagctg	tattaggca	atctatatt	720
tgtatgtatc	cgtataatgc	tttaatgcat	gagtttacac	atttttgtcc	tcaattat	780
ggaataataa	tattaccatgt	taaaaggatt	cgtccacaag	tttagcgaggg	attttctct	840
caagatggac	ccaaatgtaca	atttgaggaa	tttatacat	ttgggaggatt	agatgttga	900
ataataccctc	aaatttggaaag	atcacaatta	agagaaaaag	cattaggtca	ctataaaagat	960

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atagcgaaaa	gacttaataa	tattaataaa	actattcctt	ctagttggat	tagtaatata	1020
gataaaatata	aaaaatattt	ttctgaaaag	tataattttt	ataaaagataa	tacaggaaat	1080
tttgggtttaa	atattgtataa	attcaatago	ttatattcag	acttgactaa	tgtttatgtca	1140
gaagttgttt	attcttcgca	ataaatgtt	aaaaacagga	ctcattattt	ttcaaggcat	1200
tatctacctg	tatttgc当地	tatatttagat	gataatattt	atactataag	agatggttt	1260
aatttaacaa	ataaaaggttt	taatataaga	aattcgggtc	agaatataga	aaggaatctt	1320
gcactacaaa	agcttagttc	agaaaagtta	gtagatttt	ttacaaaagt	atgtttaaga	1380
ttcacaaaac	tcgacccac	ccaccaccac	cactga			1416

SEQ ID NO: 28	moltype = DNA	length = 1356				
FEATURE	Location/Qualifiers					
source	1..1356					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 28						
atgggcacga	gccatcatca	tcatcatcac	agcagcggcc	ttgtgcccgc	cgccagccat	60
atgatgcca	caattaatag	ttttaattat	aatgatcctg	ttaataatag	aacaatttta	120
tatattaaac	caggcggtt	tcaacaaattt	tataaatcat	ttaattttat	aaaaaatattt	180
tggataattc	cagagagaaa	tgtatgggt	acaattcccc	aagattttct	tccgctact	240
tcatgtaaaa	atggagatag	tagttttat	gaccctaattt	atttacaag	tgatcaagaa	300
aaggataat	ttttaaaaat	agtccacaaa	atatttaataa	gaataatata	taatcttca	360
ggaaggattt	tatttataaga	actgtccaaa	gtaatccat	attttagaaa	tgataatact	420
ccagatggtt	atccattat	taatgtatc	tcagcgttcc	caatttcaattt	ctcaatgtt	480
agccaaagca	tacttattc	taatgtttt	ataatgggg	cagagcttga	tttatttggaa	540
actaacatgt	ccaatatttc	tctaaagaaat	aatttatatgc	caagcaatca	cggttttgg	600
taatactgtt	tagtaacatt	ctcacctgaa	tattctttt	gatttaaaaga	taatagtatg	660
aatgaattt	ttcaagatcc	tgcttttata	ttaatgcatt	atttttttttt	tttatttttt	720
ggactatatt	gggctaaagg	gattactaca	aaagtatata	taacacaaa	acaaaatccc	780
cttataacaa	atataaagg	tacaaatattt	gaagaattct	taacttttt	aggtactgtat	840
ttaacacata	ttactatgtc	tcagtc当地	gatattcttata	ctaatcttct	agctgtatt	900
aaaaaatat	cgcttact	tagccaaatgt	caagttatcat	atccactact	taatctttat	960
aaagatgtt	tttgc当地	gtatggata	gataaaatgt	ctagcggat	ttttcggtt	1020
aatataaaaca	aatttataat	tattttttaa	aaatttataca	gttttacgg	atttgtat	1080
gcaactaaat	ttcaagttt	atgttggca	actttatgg	gacagtataa	atacttcaaa	1140
cttcaacaa	ttttttat	ttcttatttt	aatatatatcg	aaggcttataa	tataataat	1200
ttaaaaggtaa	attttagagg	acagaatgc	aattttatc	ctgaaattat	tacaccaatt	1260
acaggtagag	gacttagttaa	aaaaatcatt	agattttgtt	aaaatattgt	ttctgtaaaa	1320
ggcataaggc	tcgacccac	ccaccaccac	cactga			1356

SEQ ID NO: 29	moltype = DNA	length = 1398				
FEATURE	Location/Qualifiers					
source	1..1398					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 29						
atgggcacga	gccatcatca	tcatcatcac	agcagcggcc	ttgtgcccgc	cgccagccat	60
atgatgccc	atggcaataaa	tagttttat	tataatgacc	ctgttaatgt	tgatataattt	120
ttatacatatc	agatattttat	tgaagaaaaaa	agttttttat	atttttttttt	tttttttttt	180
atgcgtatgt	tttggataat	tcctggagaga	aaataatag	gaacgaaatcc	tagtgc当地	240
gatccacccg	cttcattttaa	gaacggaa	agtgcttatt	atgtatctt	tttatttttt	300
actgtatgt	aaaaatgtat	attttttttt	acaacgtataa	aattttttaa	gagaattttat	360
agtaatctt	cggggaaatgt	tttgc当地	gaaatattat	atgc当地	atattttat	420
aatgaccaca	cgccaaatgt	tgaatttctt	ccagttacta	gaacttacaa	tgttatata	480
aaatttatca	ctaatgttga	aaatttcaat	ttattttat	tttttttttt	tttttttttt	540
ccttgatata	tttgc当地	tttttttttt	tttttttttt	tttttttttt	tttttttttt	600
ttatgtatca	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	660
gaatataactt	ttatgtatgt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	720
gatccctgca	tttcttactt	tcatgtatgt	tttttttttt	tttttttttt	tttttttttt	780
agggggatgtt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	840
aaacccatata	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	900
atgtctatgt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	960
agacttagtg	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1020
tttcaatgtt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1080
aaattttat	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1140
ttttaaggtaa	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1200
tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1260
aacaatcgcc	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1320
ggtcttagtag	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1380
caccaccacc	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1398

SEQ ID NO: 30	moltype = DNA	length = 1416
FEATURE	Location/Qualifiers	
source	1..1416	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 30		

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atgggcagca	gccatcatca	tcatcatcac	agcagcggcc	tggtgcgcgcg	cggcagccat	60
atgtatcccg	ttaataataaa	aanccttaat	tataatgacc	ctattaataa	tgatgacatt	120
attatgtatgg	aaccattcaa	tgaccaggc	ccaggaacat	attataaagg	ttttaggatt	180
atagatcgta	tttggatagt	accagaaaagg	tttacttatg	gattcaacc	tgaccaattt	240
aatgccagta	caggagtttt	tagtaaagat	gtctacgaat	attacgatcc	aacttattta	300
aaaacccatg	ctgaaaaaga	taaaatttta	aaaacaatga	ttaaatttta	taatagaatt	360
aattcaaaac	catcaggaca	gagattactg	gatatgatag	tagatgtat	accttatttt	420
ggaatatcgat	ctacaccggc	cgacaaattt	gcagcaaatg	ttgcaaatgt	atcttattat	480
aaaaaaaaata	tccaacctgg	agctgaagat	caaataaaag	gtttaatgac	aaatttaata	540
atatttgac	caggaggact	tctaagtat	aattttactg	atagatgtat	tatgaatggc	600
catcccccaa	tatcagaagg	atttggcga	agaatgtat	tttttttttgc	tcctagtgt	660
ttaaatgtat	ttaataatgt	tcaggaaat	aaagatcat	ctatattttat	tagacgcgcg	720
tattttgcg	atccagctct	aacgttaatg	catgaactta	tacatgtgtt	acatggatta	780
atatggatata	agataagtaat	tttaccaattt	actccaaatata	caaagaattt	tttcatgcaaa	840
catagcgatc	ctgtacaaagc	agaagaacta	tatacattcg	gaggacatga	tcctagtgtt	900
ataaagtctt	ctacggatata	gaatatttat	aataaagcgt	tacaaattt	tcaagatata	960
gctaataatggc	ttaatattgt	ttcaagtgc	caagggagt	gaattgtat	ttccttat	1020
aaacaaatata	ataaaaataa	atatgatattt	gttgaagatc	ctaatggaaa	atatagtgtt	1080
gataaggatata	atgttgatata	attatataag	gccttaatgt	ttggctttac	tgaaactaat	1140
ctagctgtt	aatatggatata	aaaaactagg	tattttttat	tttagtataa	tttgcacccg	1200
ataaaaaactg	aaaaattgtt	agacaatata	atttataactt	aaaatgtt	cttacatata	1260
gtctgttttttt	atctcaaaac	ggaatttata	ggtcagaata	aggcggtaaa	taaagaggct	1320
tatgtatata	ttagccatgt	acatctcgat	atataatggaa	tagcaatgt	caagctgtt	1380
atgtacaaac	tcgagccaca	ccaccaccac	cactga			1416

SEQ ID NO: 31	moltype = AA	length = 461				
FEATURE	Location/Qualifiers					
source	1..461					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 31						
MKAMININKF	LNQCPFPVNQK	FNYKDPVNGV	DIAYIKIPNA	GQMOPVKAFK	IHNKIWVIE	60
RDTFTNPEEG	DLNPPPEAKQ	VPVSYVDSTY	LSTDNEKDNY	LKGVTKLFER	IYSTDGLRML	120
LTSIVVRGIPF	WGGSTIDTEL	KVIDTNCINV	IQPDGSRSE	ELNLVIIGPS	ADIIQFECKS	180
FGHEVNLNTR	WTGYSTQYIR	FSPDFTGFGE	ESLEVDTNPL	LGAGKFATDP	AVTLAHELIH	240
AGHRFLYGIAI	NPNRVPFKNT	NAYYEMSGLE	VSFEEELRTFG	GHDAKFIDS	QENEFRLYYY	300
NKFKDIASTL	NKAKSIVGTT	ASLQYMKNVF	KEKYLLSEDT	SGKFSVDKLK	FDKLYKMLTE	360
IYTEDNFVKF	FKVLRKTYL	NFDKAVFKIN	IVPKVNYTIY	DGFNLRNTNL	AANFNGQNT	420
INNMNFTKLK	NFTGLFEFYK	LLCVRGIITS	KTKSLDKGYN	K		461

SEQ ID NO: 32	moltype = AA	length = 454				
FEATURE	Location/Qualifiers					
source	1..454					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 32						
MKAMININKF	LNQCPVTIINN	FNYNDPIDNN	NIIMMEPPFA	RGTGRYYKAF	KITDRIWIIP	60
ERYTFGYKPF	DFNKSSGIFN	RDVCHEYD	YLNTNDKKNI	FLQTMKLFN	RIKSPLGEK	120
LLEMIINGIP	YLGDRRVPLE	EFTNTNIASVT	VNKLISNPGE	VERKKGIFAN	LIIFGPGPV	180
NENETIDIGI	QNHFASREGF	GGIMQMFKCP	EYVSVFNNVQ	ENKGASIFNR	RGYFSDPALI	240
LMHELHVLH	GLYGIKVDDL	PIVPMEEKKFF	MOSTDAIQAE	ELEYTFGGQDP	SIITPSTDKS	300
IYDKVQLQNF	GIVDRLNKVL	VCISDPMINI	NIYKNKFKDK	YKFVDESEGK	YSIDVESFDK	360
LYKSLMFGFT	ETNIAEYK	KTRASYFSDS	LPPVKIKNL	DNEIYTIEEG	FNISDKDMEK	420
YERGQNKAIN	KQAYEEISKE	HLAVYKIQMC	KSVK			454

SEQ ID NO: 33	moltype = AA	length = 462
FEATURE	Location/Qualifiers	
source	1..462	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 33		

MKAMININKF	LNQCPITINN	FNYSDPVDNK	NILYLDTHLN	TLANEPEKAF	RITGNIWVIP	60
DRFSRNSNPN	LNKPPRVTSP	KSGYYPDNYL	STDSDKDPFL	KEIIKLFKRI	NSREIGEELI	120
YRLSTDIPFP	GNNNTPINTF	DFDVDFNSVD	VKTROGNNWV	KTGSINPSVI	ITGPRENIID	180
PETSTFKLTN	NTFAAQEGFG	ALSIISISPR	FMLTYSNATN	DVGEGRFSKS	EFCMDPILIL	240
MHELNHAMHN	LYGIAIPNDQ	TISSVTSNIF	YSQYNVKEY	AEIYAFCGPT	IDLIPKSARK	300
YFEEKALDYY	RSIAKRLNSI	TTANPSSFNK	YIGEYKQKLI	RKYRFVVESS	GEVTVNRNKF	360
VELYNELTQI	ETEFNYAKIY	NVQNRKYL	NVYTPVTANI	LDDNVYDIQN	GFNIPKSNLN	420
VLFMGQNL	SRNPALRKVNPE	NMLYLFTKFC	HKAIDGRSLY	NK		462

SEQ ID NO: 34	moltype = AA	length = 455
FEATURE	Location/Qualifiers	
source	1..455	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 34		

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MKAMININKF	LNCQCTWPVKD	FNYSDPVNDN	DILYLRIPQN	KLITTPVKAF	MITQNIWVIP	60
ERFSSDTNPS	LSKPPRPTSE	YQSYYDPSPYL	STDEQKDFTL	KGIKLFKRI	NERDIGKLLI	120
NYLVVGSPFM	GDSSTPDTF	DFTRHTTNIA	VEKFENGWSWK	VTNIITPSVL	IFGPLPNILD	180
YTASLTQGQ	QSNPSPEGFG	TLSILKVAPE	FLLTFSVDTS	NQSSAVLGKS	IFCMBPVIAL	240
MHELTSHSLHQ	LYGINIPSDK	RIRPQVSEGF	FSQDGPNVQF	EELYTFGGLD	VEIIPQIERS	300
QLREKALGHY	KDIAKRLNNI	NKTIPSSWIS	NIDKYKKIFS	EKYNFDKDNT	GNFVVNIDKF	360
NSLYSDLTNV	MSEVVYSSQY	NVKNRTHYS	RHYLPVFANI	LDNNIYTIRD	GFNLTNKGFN	420
IENSGQNIER	NPALQKLSSE	SVVDSLFTKVC	RLRLTK			455

SEQ ID NO: 35	moltype = AA	length = 435				
FEATURE	Location/Qualifiers					
source	1..435					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 35						
MKAMININKF	LNCQPTINSF	NYNDPVNNRT	ILYIKPGGCQ	QFYKSFNIMK	NIWIIPERNV	60
IGTIPQDFLP	PTSLKNGDSS	YYDPNQLQSD	QEKDQFLKIV	TKIFNRINDN	LSGRILLEEL	120
SKANPYLGLND	NTPDGDFIIN	DASAVPIQFS	NGSQSILLPN	VIIMGAEPDL	FETNSSNISL	180
RNNYMPNSNHG	FGSIAIVTFS	PEYSRFPKDN	SMNEFIQDPA	LTLMHELIHS	LHGLYGAKGI	240
TTKTYTITQKQ	NPLITNIRGT	NIEEFLTFGG	TDLNIITSAQ	SNDIYTNLLA	DYKKIASKLS	300
KVQVSNPLLN	PYKDVFEAKY	GLDKDASGY	SVNINKFNDI	FKKLYSFTEF	DLATKFQVCK	360
RQTYIGQYKY	PKLSNLLNDS	IYNISEGYNI	NNLKVNFRQQ	NANLNPRIT	PITGRGLVKK	420
IIRFCKNIVS	VKGIR					435

SEQ ID NO: 36	moltype = AA	length = 449				
FEATURE	Location/Qualifiers					
source	1..449					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 36						
MKAMININKF	LNCQCPVAINS	FNYNDPVNDN	TILYMQIPYE	EKSKKYYKAF	EIMRNWVIIIP	60
ERNTIGTGNPS	DFDPPASLKN	GSSAYDPNV	LTTDAEKDRY	LKTTIKLFKR	INSNPAGKVL	120
LQEISYAKPY	LGNDHPTIDE	FSPVTRTTSV	NIKLSTNVES	SMLLNLLVLG	AGPDFESCC	180
YPVRKLIDPD	VVYDPSNYGF	GSINIVTFSP	EYEYTFNDIS	GGHNSSTESF	IADPAISLAH	240
ELIHALHGLY	GARGVTYEE	IEVKQAPLMI	AEKPIRLEEF	LTFGGQDLNI	ITSAMKEKIY	300
NNLLANYKEI	ATRLSEVNSA	PPEYDLINEYK	DYFQWKYGLD	KNADGSYTVN	ENKFNEIYKK	360
LYSFTESDLA	NKFKVKCRNT	YFIKYEFLKV	PNLDDDIYI	VSEGPNIGNL	AVNNRGQSIK	420
LNPKIIDSI	DKGLVEKIVK	PNLDDDIYI				449

SEQ ID NO: 37	moltype = AA	length = 454				
FEATURE	Location/Qualifiers					
source	1..454					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 37						
MKAMININKF	LNCQCPVNIKF	NYNDPINNDD	IIMMEPFNDP	GPGTYYKA	IIDRIWIVPE	60
RFTYGFQDQ	FNASTGVFSK	DVYFYDPTY	LKTDAAEKDFT	LKTMKLFNR	INSKPSGQRL	120
LDMDIVDAIPY	LGNASTPPDK	PAANAVNSI	NKKLIQPGAE	DQIKGLMTNL	IIFGPGPVLS	180
DNFTDSMIMN	GHSPISEGFC	ARMMIRFCPS	CLNVFNNVQEE	NKDTTSIFSR	AYFADPALT	240
MHELIHLVHG	LYGKISNLP	ITPNTEKEFFM	QHSDPVQAEE	LYTFGGHDPS	VISPSTDMMI	300
YKQALQNFQD	IANRLNIVS	AQGSGCIDSL	YKQIYKNEYD	FVEDPNGKYS	VDKDKFDKLY	360
KALMFGFTET	NLAGEYGIKT	RYSYFSELYP	PIKTEKLLDN	TIYTQNEGPN	IASKNLKTEF	420
NGONKAVNKE	AYEEISLEHI	VIYRIAMCK	VMYK			454

SEQ ID NO: 38	moltype = AA	length = 461				
FEATURE	Location/Qualifiers					
source	1..461					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 38						
MPFVNQKQFNY	KDPVNGVDIA	YIKIPNAGQM	QPVKAFKIH	KIWVIPERDT	FTNPPEEGDLN	60
PPPEAKQVPV	SYYDSTYLST	DNEKDNYLKG	VTKLFERIYS	TDLGRMLLTS	IVRGIPFWGG	120
STIDTELKVI	DTNCINVIQP	DGSYRSEELN	LVIIGPSADI	IQFECKSFGH	EVLNLTRNGY	180
GSTQYIRFSP	DFTFGFEELS	EVDTNPLLG	GKFATDPAVT	LAHELIHAGH	RLYGIAINPN	240
RVFKVNTNAY	EMSGLEVSF	EELRFTGGHH	AKFIDSLQEN	EPRFLYYNNK	KDIASTLNKA	300
KSTIVGTTASL	QYMKNVFKEI	YLLSEDTSGK	FSVDKLLKFDK	LYKMLTEIYT	EDNFVKFFKV	360
LNRKTYLNFD	KAVFKINIVP	KVNYTIYDGF	NLRNTNLAA	FNGQNTIEINN	MNFTKLKNFT	420
GLPEFYKLLC	VRGIITSKTK	SLDKGYNKQ	NLFKNINIMA	K		461

SEQ ID NO: 39	moltype = AA	length = 454				
FEATURE	Location/Qualifiers					
source	1..454					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 39						
MPVTINNFNY	NDPIDNNNII	MMEPPFARGT	GRYYKAFKIT	DRIWIIPERY	TFGYKPEDFN	60

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KSSGIFNRDV	CEYYDPDYLN	TNDKKNIFLQ	TMKLFNRK	SKPLGEKLLE	MIINGIPYLG	120
DRRVPLEEFN	TNIASVTVNK	LISNPGEVER	KKGIFANLII	FGPGPVLNEN	ETIDIGIQNH	180
FASREGFGGI	MQMFKCPEVY	SFNNVQENK	GASIFNRRGY	FSDPALILMH	ELIHVLHGLY	240
GIKVDDLPV	PNEKKFPMQS	TDAIQAEELY	TFGGQDPSII	TPSTDKSIYD	KVLQNFRGIV	300
DRLNKVLVCI	SDPNININIIY	KNKFKDKYKF	VEDSEGKYSI	DVESFDKLYK	SLMPGFTETN	360
IAENYKIKTR	ASYFSDSLPP	VKIKNLLDNE	IYTIEEGFNI	SDKDMEKEYR	GQNKAINQKA	420
YEEISKEHLA	VYKIQMCKSV	KCQNLFKNN	IMAK			454

SEQ ID NO: 40	moltype = AA	length = 462				
FEATURE	Location/Qualifiers					
source	1..462					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 40						
MPITINNFY	SDPVDNKNIL	YLDTHLNTLA	NEPEKAFRIT	GNIWVIPDRF	SRNSNPNLNK	60
PPRVTSPKSG	YYDPNVLSTD	SDKDPFLKBI	IKLFKRINSR	EIGEELIYRL	STDIPFPGN	120
NTPIINTFD	VDFNSVDVKT	RQGNNVVKTG	SINPSVIITG	PRENIIDPET	STFKLTNTF	180
AQAEQFGALS	IIISIPRFML	TYSNATNDVG	EGRFSKSEFC	MDPILILMHE	LNHAMHNLYG	240
IAIPNDQTIS	SVTSNIFYSQ	YNVKLEYABI	YAFGGPTIDL	IPKSARKYFE	EKALDYYRSI	300
AKRLLNSITTA	NPSSFNKYIG	EYKQLKIRKY	RFVVESSGEV	TVNRNKFVEL	YNELTQIFTE	360
FNYAKIYNVQ	NRKYLNSVY	TPVTANILDD	NVYDIQNGFN	IPKSNLNVLF	MGQNLRSRNP	420
LRKVNPENML	YLFTKPCCHKA	IDGRSLYNKC	QNLFKNINIM	AK		462

SEQ ID NO: 41	moltype = AA	length = 455				
FEATURE	Location/Qualifiers					
source	1..455					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 41						
MTWPVKDFNY	SDPVNDNDIL	YLRIPKQNL	TTPKVAKFMIT	QNIWVIPERF	SSDTNPSLSK	60
PPRPTSPKYSQ	YYDPSYLSTD	EQKDTFLKG	IKLFKRINER	DIGKKLINYL	VVGSPFMGDS	120
STPEDTFDFD	RHTTNIAVEK	FENGWSKVTN	IIITPSVLIFG	PLPNILDYTA	SLTLQGQQSN	180
PSFEGFGTLS	ILKVAPEFLL	TFSVTSNQS	SAVLGKSIFC	MDPVIALLMHE	LTHSLHQLYG	240
INIPSDKRIR	PQVSEGFFSQ	DGPNVQFEEL	YTFGGLDVEI	IPQIERSQLR	EKALGHYKDI	300
AKRLLNNINKT	IPSSWISNID	KYKKIFSEKY	NFDKDNTGNF	VVNIDKFN	YSDLTNVMSE	360
VVYSSQYNVK	NRTHYFSRH	LPVFANILDD	NIYTIRDGFN	LTNKGFNIEN	SGQNIERNPA	420
LQKLSSESVV	DLFTKVCRL	TKCQNLFKNI	NIMAK			455

SEQ ID NO: 42	moltype = AA	length = 435				
FEATURE	Location/Qualifiers					
source	1..435					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 42						
MPTINSFNY	DPVNNRTILY	IKPGGCQQFY	KSFNIMKNI	IIPERNVIGT	IPQDFLPPTS	60
LKNGDSSYYD	PNYLQSDQEK	DKFLKIVTKI	FNRINDNLG	RILLEELS	KA NPYLGNDNT	120
DGDFIINDAS	AVPIQFSNGS	QSILLPNVII	MGAEPDLFET	NSSNISLRNN	YMPSNHGFGS	180
IAIVTFSPEY	SPRFKDMSMN	EFIQDPALT	MHELIHSWL	LYGAKGITTK	YTITQKQNP	240
ITNIRGNTNIE	EFLTFGGTDL	NIITSAQNSD	IYTNLADYK	KIASKLKVQ	VSNPLLNPYK	300
DVFEAKYGLD	KDASGIYSVN	INKFNDIFKK	LYSFTEFDIA	TKFQVKCRQT	YIGQYKFKL	360
SNLLNDSIYN	ISEGYNINNL	KVNFRGQAN	LNPRIITPIT	GRGLVKKIIR	FCKNIVSVKG	420
IRCQNLFKNI	NIMAK					435

SEQ ID NO: 43	moltype = AA	length = 449				
FEATURE	Location/Qualifiers					
source	1..449					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 43						
MPVAINSFNY	NDPVNDDTIL	YMQIPYEKS	KKYYKAFEIM	RNVWIIPERN	TIGTNPSDF	60
PPASLKNONGSS	AYDPNVLTT	DAEKDRYLT	TIKLFKRINS	NPAGKVLLQE	ISYAKPYLGN	120
DHTPIDEFSP	VRTRTSVNIK	LSTNVESSML	LNLLVLGAGP	DIFESCCYPV	RKLIDPDVVY	180
DPSNYGFSSI	NIVTFSPEYE	YTFNDISGGH	NSSTESFIAD	PAISLAHELI	HALHGLYGR	240
GVTYEETIEV	KQAPLMAIEK	PIRLEFLTF	GGQDLNIIITS	AMKEKIYNNL	LANYEKIATR	300
LSEVNSDAPPE	YDNEYKDYF	QWKYLDKNA	DGSYTVNENK	FNEIYKKLYS	FTESDLANKF	360
KVKCRNTYFI	KYEFLKVPNL	LDDDIYTVE	GFnIGNLAVN	NRGQSIKLN	PKIIDSIPDK	420
LVEKIVKFCK	SVIPRKCQNL	FKNINIMAK				449

SEQ ID NO: 44	moltype = AA	length = 454				
FEATURE	Location/Qualifiers					
source	1..454					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 44						
MPVNIKFNYN	DPINNDDIIM	MEPFNDPGPG	TYYKAFRII	RIWIVPERFT	YGFQPDQFNA	60
STGVFSKDVY	EYYDPTYLKT	DAEKDKFLKT	MIKLFNRINS	KPSGQRLLDM	IVDAIPYLG	120

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ASTPPDKFAA	NVANVSINKK	IIQPGAEDQI	KGLMTNLIIIF	GPGPVLSDNF	TDSMIMNGHS	180
PISEGFGARM	MIRFCPSCLN	VFNNVQENKD	TSIFSRRAYF	ADPAITLMHE	LIHVLHGLYG	240
IKISNLNPTP	NTKEFFPMQS	DPVQAEELYT	FGGHDPVSIS	PSTDMNIYNK	ALQNFQDIAN	300
RLNIVSSAQG	SGIDISLYKQ	IYKNKYDFVE	DPMGKYSVDK	DKFDKLYKAL	MFGFTETNLA	360
GEYGIKTRYS	YFSEYLPIK	TEKLLDNTIY	TQNEGFnIAS	KNLKTefNGQ	NKAVNKEAYE	420
EISLEHLVIY	RIAMCKPVMY	KCQNLFKNN	IMAK			454

SEQ ID NO: 45	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 45						
MKAMININF	LNQCPFVNQK	FNYKDPVNGV	DIAYIKIPNA	GQMOPVKAF	IHNKIWIPIE	60
RDTFTNPEEG	DLNPPPEAKQ	VPVSYDDSTY	LSTDNEKDNY	LKGVTKLFER	IYSTDLGRML	120
LTSIVRGIPF	WGGSTIDTEL	KVIDTNCINV	IOPDGSYRSE	ELNLVIIIGPS	ADIIQFECKS	180
FGHEVNLNTR	NGYGSTQYIR	FSPDFTFGFE	ESLEVDTNP	LGAGKFATDP	AVTLAHELIH	240
AGHRILYGIAI	NPNRVRVKVN	NAYYEMSGLE	VSFEELRTFG	GHDAKFDSL	QENEFRLYYY	300
NKFKDIASTL	NKAKSIVGTT	ASLQYMKNVF	KEKYLLED	SGKFSVDKLK	FDKLYKMLTE	360
IYTEDNPFVFK	PKVLRKTYL	NFDKAVFKIN	IVPKVNYTIY	DGFNLRTN	AANFNGQNT	420
INNMNFTKLK	NFTGLFEFYK	LLCVRIIITS	KTKSLDKGYN	KLEHHHHHH		469

SEQ ID NO: 46	moltype = AA	length = 462				
FEATURE	Location/Qualifiers					
source	1..462					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 46						
MKAMININF	LNQCPVTINN	FNYNDPIDNN	NIIMMMEPPFA	RGTGRYYKAF	KITDRIWIIP	60
ERYTFTGYKPE	DFNKSSGIFN	RDVCEYYDPD	YLNNTNDKKNI	FLQTMIKLFN	RIKSKEPLGEK	120
LLEMIINGIP	YLGDRRVPL	EFNTNIASVT	VNKLISNPGE	VERKKGIFAN	LIIFGPGPV	180
NENETIDIGI	QNHFAREGF	GGIMQMFKCP	EYVSFVNQ	ENKGASIFNR	RGYFSDPALI	240
LMHELIHVHL	GLYGIKVDDL	PIVPNEKKFF	MQSTDAIQAE	ELEYTFGGQDP	SIITPSTDKS	300
IYDKVLNQFNR	GIVDRLNQKVL	VCISDPNINI	NIYKNKFSDK	YKFVEDSEGK	YSIDVESFDK	360
LYKSLMFGFT	ETNIAENYKI	KTRASYFSDS	LPPVKIKNL	DNEIYTIEEG	FNISDKDMEK	420
EYRGQNKAIN	KQAYEEISKE	HLAVYKIQMC	KSVKLEHHHH	HH		462

SEQ ID NO: 47	moltype = AA	length = 470				
FEATURE	Location/Qualifiers					
source	1..470					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 47						
MKAMININF	LNQCPITINN	FNYSDPVDNK	NILYLDTHLN	TLANEPEKAF	RITGNIWIP	60
DRFSRNSNPN	LNKPPRVTSP	KSGYYDPNYL	STDSDKDPFL	KEIIKLFKRI	NSREIGEELI	120
YRLSTDIPFP	GNNNTPINTF	DFDVDFNSVD	VKTROGNNNW	KTGSINPSVI	ITGPRENIID	180
PETSTFKLNT	NTFAAQEGFG	ALSIISISPR	FMLTYSNATN	DVGEGRFSKS	EFCMDPILIL	240
MHELNHAMHN	LYGIAIPNDQ	TISSVTSNIF	YSQYNVKLEY	AEIYAFGGPT	IDLIPKSARK	300
YFEEKALDYY	RSIAKRLNSI	TIANPSSFNK	YIGEYKQKLI	RKYRFVVESS	GEVTVNRNKF	360
VELYNELTQI	FTEFNYAKIY	NVQNRKIYLS	NVYTPVTANI	LDDNVYDIQN	GFNIPKSNLN	420
VLFMGQNLQR	NPALRKVNPE	NMLYLTFTKFC	HKAIDGRSLY	NKLEHHHHHH		470

SEQ ID NO: 48	moltype = AA	length = 463				
FEATURE	Location/Qualifiers					
source	1..463					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 48						
MKAMININF	LNQCTWPVKD	FNYSDPVNDN	DILYLRIPON	KLITTPVKAF	MITQNIWIP	60
ERFSSDTNPS	LSKPPRPTSK	YQSYYDPSYL	STDEQKDTFL	KGIIKLFKRI	NERDIGKKLI	120
NYLVVGSPFM	GDSSTPDTF	DFTRHTTNIA	VEKPENGWSK	VTNIITPSVL	IFGPLPNILD	180
YTASLTLQGQ	QSNPSFEGFG	TLSILKVAPE	FLLTFSVDTS	NQSSAVLGKS	IFCMDPVIAL	240
MHELTHSLHQ	LYGINIPSDK	RIRPQVSEGF	FSQDGPNVQF	EELYTFGGLD	VEIIPQIERS	300
QLREKALGHY	KDIACKRLNNI	NKTIPSSWIS	NIDKYKKIFS	EKYNFDKDNT	GNFVVNIDKF	360
NSLYSDLTVN	MSEVVYSSQY	NVKNRTHYFS	RHYLPVFANI	LDDNIYTIRD	GFNLTNKGFN	420
IENSGQNIER	NPALQKLSSE	SVVDSLFTKVC	LRLTKLEHHHH	HHH		463

SEQ ID NO: 49	moltype = AA	length = 443				
FEATURE	Location/Qualifiers					
source	1..443					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 49						
MKAMININF	LNQCPТИNSF	NYNDPVNNRT	ILYIKPGCCQ	QFYKSFNIMK	NIWIIPERNV	60
IGTIPQDFLP	PTSLKNGDSS	YYDPNLYQSD	QEKDKEFLKIV	TKIFNRINDN	LSGRILLEEL	120
SKANPYLGND	NTPDGDFIIN	DASAVPIQFS	NGSQSILLPN	VIIMGAEPDL	FETNSSNISL	180

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RNNYMPNSNHG	PGSIAIVTFS	PEYSFRFKDN	SMNEFIQDPA	LTLMHELIHS	LHGLYAKGI	240
TTKYTITQKQ	NPLITMIRGT	NIEEFLTFGG	TDLNIITSAQ	SNDIYTNLLA	DYKKIASKLS	300
KVQVSNPLLN	PYKDVFPEAKY	GLDKDASGY	SVNINKFNDI	FKKLYSFTEF	DLATKFQVKC	360
RQTYIGQKY	FKLSNLNLDS	IYNISEGYNI	NNLKVNFRGQ	NANLNPRIT	PITGRGLVKK	420
IIRFCKNIVS	VKGIRLEHHH	HHH				443
 SEQ ID NO: 50		moltype = AA	length = 457			
FEATURE		Location/Qualifiers				
source		1..457				
		mol_type = protein				
		organism = synthetic construct				
SEQUENCE: 50						
MKAMININF	LNQCPVAINS	FNYNDPVNDD	TILYMQIPYE	EKSKKYYKAF	EIMRNVWIIP	60
ERNTIGTNPS	DFDPASPLN	GSSAYDPNY	LTTDAEKDRY	LKTTIKLFR	INSNPAGKVL	120
LQEISYAKP	LGNDHTPIDE	FSPVTRTTSV	NIKLSTNVES	SMMLNLLVLG	AGPDIFESCC	180
YPVRKLIDPD	VVYDPSNYGF	GSINIVTFSP	EYEYTFNDIS	GGHNSSTESF	IADPAISLAH	240
ELIHALHGLY	GARGVTYEET	IEVKQAPLMI	AEPKIRLEEF	LTFGGQDLNI	ITSAMKEKIY	300
NNLLANYEKI	ATRLSEVNSA	PPEYDINEYK	DYFQWKYGLD	KNADGSYTVN	ENKFNEIYKK	360
LYSFTESDLA	NKFKVKCRNT	YFKYEFKLK	PNLLDDDIY	VSEGFNIGNL	AVNNRGQSIIK	420
LNPKIIDSIP	DKGLVEKIVK	FCKSVIPRKL	EHHHHHHH			457
 SEQ ID NO: 51		moltype = AA	length = 462			
FEATURE		Location/Qualifiers				
source		1..462				
		mol_type = protein				
		organism = synthetic construct				
SEQUENCE: 51						
MKAMININF	LNQCPVNIKF	NYNDPINND	IIMMEPFNNDP	GPGTYYKAFR	IIDRIWIVPE	60
RFTYGFQPDQ	PNASTGVFSK	DVYEYDPTY	LKTDAEKDFK	LKTMKLFNR	INSKPSGQRL	120
LDMIVDAIPY	LGNASTPPDK	FAANVANSI	NKKIIQPGAE	DQIKGMLMTNL	IIFGPGPVLS	180
DNFTDSMMN	GHSPISEKPG	ARMMIRFSRR	CLNVFNNVQE	NKDTSFRR	AYFADPALTL	240
MHELIHLVHG	LYGIKISNLP	ITPNTEKEFFM	QHSDPVQAEE	LYTFGGHDPS	VISPSTDMMI	300
YNKALQNQFDQ	IANRLNIVSS	AQGSGIDISL	YKQIYKNKYD	FVEDPNGKYS	VDKDKFDKLY	360
KALMFGFTET	NLAGEYGIKT	RYSYSEYLP	PIKTEKLLDN	TIYTQNEGPN	IASKNLKTEF	420
NGQNKAVNKE	AYEEISLEHL	VIYRIAMCKP	VMYKLEHHHH	HH		462
 SEQ ID NO: 52		moltype = AA	length = 481			
FEATURE		Location/Qualifiers				
source		1..481				
		mol_type = protein				
		organism = synthetic construct				
SEQUENCE: 52						
MGSSHHHHHH	SSGLVPRGSH	MPFVNQFNY	KDPVNGVDIA	YIKIPNAGQM	QPVKAFKIH	60
KIWVIPERDT	FTNPEEGDNL	PPPEAKQPV	SYYDSTYLST	DNEKDNYLKG	VTKLFERIYS	120
TDLGRMLLTS	IVRGIPFWGG	STIDTELKV	DTNCINVIOQ	DGSYRSEELN	LVIIGPSADI	180
IQFECKSFGH	EVNLNLRNGY	GSTQYIRFSP	DFTFGFEESL	EVDTNPLLGA	GKFATDPAVT	240
LAHELIHAGH	RLYGIAINPN	RVFVKVNTNA	YEMSGGLEVSF	EELRTFGGHD	AKFIDSLQEN	300
EFLRYYYNKF	KDIASLNLKA	KSIVGTTASL	QYMKNVFKEK	YLLSEDTSGK	FSDKLLKFDK	360
LYKMLTEIYT	EDNFVKFFKV	LNRKTYLNF	KAVFKINIVP	KVNYTIYDGF	NLRNTNLAA	420
FNGQNTTEINN	MNFTKLKNFT	GLFEFYKLLC	VRGIITSKTK	SLDKGYNKCQ	NLFKNINIMA	480
K						481
 SEQ ID NO: 53		moltype = AA	length = 474			
FEATURE		Location/Qualifiers				
source		1..474				
		mol_type = protein				
		organism = synthetic construct				
SEQUENCE: 53						
MGSSHHHHHH	SSGLVPRGSH	MPVITINNFNY	NDPIDNNNNI	MMEPPFARGT	GRYYKAFKIT	60
DRIWIPIERY	TFGYKPDFN	KSSGIPNRDV	CSEYYDPDYLN	TNDKKNIFLQ	TMKLFNRIK	120
SKPLGEKLLE	MIINGIPYLG	DRRVPLLEEFN	TNIASVTVNK	LISNPGEVER	KKGIFANLII	180
FGPGPVLNEN	ETIDIGIQNH	FASREGFGGI	MQMKFCPEYV	SVFNNVQENK	GASIFNRG	240
FSDPALILMH	ELIHVLHGLY	GIKVDDLPV	PNEKKFFFQ	TDALQAEELY	TFGGODPSII	300
TPSTDKSIYD	KVLQNFRGIV	DRLNKVLVCI	SDPNININII	KNKFKDKEYKF	VEDSEGKYSI	360
DVESEFDKLYK	SLMFGFTETN	IAENYKIKTR	ASYFSDLPLP	VKIKNLNDNE	IYTIEEGFNI	420
SDKDMEKEYR	QONKAINQKA	YEEISKEHLA	VYKIQMCKSV	KCQNLFKNIN	IMAK	474
 SEQ ID NO: 54		moltype = AA	length = 482			
FEATURE		Location/Qualifiers				
source		1..482				
		mol_type = protein				
		organism = synthetic construct				
SEQUENCE: 54						
MGSSHHHHHH	SSGLVPRGSH	MPITINNFNY	SDPVDNKNIL	YLDTHLNTLA	NEPEKAFRIT	60
GNIWVIPDRF	SRNSNPNLNK	PPRVTSPKSG	YYDPNVLSTD	SDKPFLKEI	IKLFKRINSR	120
EIGEELIYRL	STDIPPPGNN	NTPINTFDPD	VDPNSVVDVKT	RQGNNWWVKTG	SINPSVIITG	180

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PRENIIDPET STFKLTNNTF AAQEGFGALS IISISPRFML TYSNATNDVG EGRFSKSEFC	240
MDPILILMHE LNHAMHNLHYG IAIPINDQTIS SVTSNIFYSS YNVKLEYAEI YAFCGGPTIDL	300
IPKSARKYFE EKALDYRSI AKRRLNSITTA NPSSFNKYIG EYKQKLIRKY RFVVESSGEV	360
TVMRNKFVEL YNELTOIFTE FNYAKIYNVQ NRKIYLSMVY TPVTANILDD NVYDIQNNGFN	420
IPKSNLNVLF MGQNLSRNPA LRKVNPENML YLFTKFCHKA IDGRSLYNKC QNLFKNINIM	480
AK	482
SEQ ID NO: 55 moltype = AA length = 475	
FEATURE Location/Qualifiers	
source 1..475	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 55	
MGSSHHHHHH SSSLVPRGSH MTWPVKDFNY SDPVNDNDYL YLRIPQNKLI TPPVKAFMIT	60
QNIWVIPERF SSDTNPLSK PPRPTSKYQS YYDPSYLSSTD EQKDTFLKGII KLFKRINER	120
DIGKKLINYL VVGSPFMGDS STPEDTFDFT RHTTNTIAVEK FENGSWKVTN IITPSVLIFG	180
PLPNILDYTA SLTLQGQOSN PSFEGFGTLS ILKVAPEFFL TFSDVTSNQS SAVLGKSIIC	240
MDPVIALMHE LTHSLHOLYG INIPISDKRIR POVSEGFFSQ DGPNVQFEEL YTFGGLDVEI	300
IPQIERSQLR EKALGHYKDI AKRLLNNINKT IPSSWISNID KYKKIFSEKY NFDKDNTGNF	360
VVNIDKFNLSL YSDLTNVMSE VVYSSQYNVK NRTHYFSRHY LPVFANILDD NIYTIRDGFN	420
LTNKGFIENI SGQNIERNPA LQKLSSESVV DLFTKVCLRL TKCQNLFKNI NIMAK	475
SEQ ID NO: 56 moltype = AA length = 455	
FEATURE Location/Qualifiers	
source 1..455	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 56	
MGSSHHHHHH SSSLVPRGSH MPTINSFNY DPVNNRTILY IKPGGCQQFY KSFNIMKNIW	60
IIPERNVIWT IPQDFLPPTS LKNGDSSYYD PNLYLQSDQEKF DKFLKIVTKI FNRINDNLSG	120
RILLEELSKA NPYLGNDNTP DGDFIINDAS AVPIQFSNNGS QSILLPNVII MGAEPDLFET	180
NSSNISLRNN YMPSNHGFGS IAIVTFSPPEY SFERPKDNSMN EFIGQDPAITL MHELIHSLG	240
LYGAKGITT K YTITQKQPL I TNIIRGTNIE EFLTFGGTDL NIITSQAQND IYTNLLADYK	300
KIASKLKVQ VSNPLLNPYK DVFEAKYGLD KDASGIYSVN INKFNDIFKK LYSFTEFDLA	360
TKFQVKCRQTY QIGQYKYFKL SNLLNDSIYN ISEGYNINNL KVNFQGQAN LNPRIITPIT	420
GRGLVKKII R PCKNIVSVKG IRCQNLFKNI NIMAK	455
SEQ ID NO: 57 moltype = AA length = 469	
FEATURE Location/Qualifiers	
source 1..469	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 57	
MGSSHHHHHH SSSLVPRGSH MPVAINSFNY NDPVNDDTIL YMQIPYEeks KKYYKAFEIM	60
RNWIIPERN TIGTNPSDFD PPASLKNGSS AYYDPNLYLT DAEKDRYLT TIKLFKRINS	120
NPAGKVLLQE ISYAKPYLGN DHTPIDEFSP VTRRTTSVNIK LSTNVESSML LNLLVLGAGP	180
DIFESCCYPV RKLIDPDDVY DPSNYGFGSI NIVTFSPPEY YTFNDISGHH NSSTESFIAD	240
PAISLAHELI HALHGHLGYAR GVTYEETIEV KQAPLMAIEK PIRLEEFPLTF GGQDLDNITS	300
AMKEKIYNNL LANYEKIATR LSEVNSAPPE YDINEYKDYF QWKYGLDKNA DGSYTVNENK	360
FNEIYKKLYS FTESDLANKF KVVKCRNTYFI KYEFLKVPNL LDDDIYTVSE GFNIGNLAVN	420
NRQOSIKLNP KIIDSPDKG LVEKIVKFCK SVIPRKCQNL FKNIINIMAK	469
SEQ ID NO: 58 moltype = AA length = 474	
FEATURE Location/Qualifiers	
source 1..474	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 58	
MGSSHHHHHH SSSLVPRGSH MPVAINSFNY DPINNDDIIM MEPFNDPGPG TYYKAFRIID	60
RIWIVPERL TYGFQPDQFNA STGVFSKDVY EYYDPTYLKT DAEKDKFLKT MIKLFNRINS	120
KPSGQRLLDM IVDAIPYLGK ASTPDKFAA NVANVSINKK IIQPGAEDQI KGLMTNLIIIF	180
GPPVPLSDNF TDSMIMNGHS PISEGFGARM MIRFCPSCLN VFNNVQENKD TSIFSRAYF	240
ADPALTLMHE LIHVVLHGLYK IKISNLPIPT NTKEFFMHOHS DPVQAEELYT FGGHDPSVIS	300
PSTDMNIYNNK ALQNFQDIAN RLNVSSAQG SGIDISLYKQ IYKNKYDFVE DPNGKYSVDK	360
DKFDKLYKAL MFGFTETNL A GEYGIKTRYS YFSEYLPPPIK TEKLLDNTIY TQNEGFNIAS	420
KNLKTTEFNGQ NKAVNKEAYE EISLEHLVIY RIAMCKPVY KCQNLFKNI IMAK	474
SEQ ID NO: 59 moltype = DNA length = 1386	
FEATURE Location/Qualifiers	
source 1..1386	
mol_type = other DNA	
organism = synthetic construct	
SEQUENCE: 59	
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ttcaactaca aggaccgagt taatggat gacatcgcat atatcaagat tcccaacgct	120
ggccagatgc aaccgcgttaa ggcatataaa atccataaca aaatctgggt tatcccagag	180

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cgggataacct tcaccaaccc cgaggagggc gatctgaacc ccccgcggga ggcgaagcag 240
gtccccagtga gotactacga tagcacccatc cttagcacccg acaacgagaa ggacaactac 300
ctcaaaaggag tcacgaagtt gttcgagaga atctactcca cagacctgg ccgcattgtt 360
ctaaccacga ttgtgcgtgg cattccctt tggggcggctt ctaccatcga cacagagctg 420
aagggtgatag acaccaactg catcaacgt aatccagcctg acggcagctg ccgaagcag 480
gagcttaacc ttgtgtatcat cggecccttc gccgatatac tccaaattcga gtgcagagc 540
ttcggccacg aggttcgttga cctcaceccgg aacggctatg gaagcacca gtacataaga 600
tttagccctt acttcacccctt cgggttttag gagagcttgg aggttcacac aaacccctg 660
ctggggagccg ggaagttgcg cactgaccca gccgtgactc tggcacacga gctgtccac 720
gcgggtcacc gcgttgcacgg catacgtata aacccaaacaa gggtgttcaa agtgaacacc 780
aacgttacta aatggatagtg cggcctggag gtgagcttcg aggagctgaa aacgttcggg 840
ggacatgtatc taaaatttat ctagacccctg caggagaacg agttcaggct gtactactac 900
aataagttaa aggtatagc gagcactctg aacaaggccca agtccatctg aggcactact 960
gcattcccttcc agtatgtatggaa gaatgttgc 3aaagagaat acctgttgcg cgaggatacc 1020
ageggtaatgt tcagcgttga taatgtttaga ttgcacaagg tttgtataatg gtcacccgaa 1080
atctacaccg aggataattt cgttaagtcc ttcaaggctt tgaacccggaa gaccatctg 1140
aacttcgaca aggcgtgtt caagatcaac atcgtgccta aagtgaacta caccatctac 1200
gacgggttta accttgcggaa cacaacccctg gccgctaaat tcaacggccaa gaacacagag 1260
atcaacaaca tgaatttcac gaagttgaag aacttcacccg gactgttga gtttacaaa 1320
ttgctgtgtg tgcgcgggat catactagc aagaccaaga gccttgacaa aggctacaac 1380
aagtga

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SEQ ID NO: 60      moltype = DNA length = 1362
FEATURE          Location/Qualifiers
source           1..1362
mol_type = other DNA
organism = synthetic construct

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SEQUENCE: 60
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tttaatttata atgatccatc tgataataat aatatttata tgatggagcc tccatttgcg 120
agagggtacgg ggagatatta taaagctttt 3aaatcacag atcgttattt gataataccg 180
gaaagatata cttttggata taaaatcttag gattttataa aagatccgg tattttat 240
agagatgttt gtgaatattt tgatccatg tacttaataa ctaatgatataa aaagaatata 300
tttttacaaa caatgtatcaaa gtttattttatc agaatcaat caaaaccatt gggtgaaaag 360
tttatttgcggaa tgattttatc ttgttacatc tatcttggag atagacgtgt tccactcgaa 420
gagtttaaca aacacatgtc tagtgtactt gtaatataat taatctgtaa tccaggagaa 480
gttgagccaa aaaaaggat tttcgcaat ttaataatataat ttggacccgg gccagttt 540
aatgaaaatg agactataga tataggatata caaaatcattt ttgcacatcaag ggaaggctt 600
gggggtataa tgcaatgtaa gttttggccca gaatatgtaa gctgtttaa taatgttca 660
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ttatgtcatc aacttataca ttttttacatc gtttattatg gcttataatg agatgtat 780
ccaaatgtac caaatgaaaaaaa aaaaatttttt atgcaatctt cagatgtat acaggcagaa 840
gaactatata cattttgggg acaatgtcc agcatatataa ctccttcatac ggataaaatg 900
atctatgtatc aagttttgc aatatttttgc gggatagtgg atagactttaa aaaatgtttt 960
gtttgcataat cagatcttca cattaatataa aatattatataa aaaatataat taaagatataa 1020
tataaatttcg ttgaagatcc tgaggggaaa tataatgtatag atgttagaaag ttttgataaa 1080
ttatataaaa gtttataatgtt tttttttttttt gaaactatataa tagcggaaaa ttataaataa 1140
aaaacttagag ttctttttttt tagtgttcc ttaccaccaag taaaatataaa aaatttataa 1200
gataatgaaa ttatataatc agggaaaggg ttaatataat cttttttttttt tttttttttt 1260
gaatatagag gtcagaatataa agcttataat aacaaatgtt atgaaatgtt tagcaaggag 1320
cattttgggttcc tatataatgtt acaaattgtt aatgtttaaa 1362

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SEQ ID NO: 61      moltype = DNA length = 1386
FEATURE          Location/Qualifiers
source           1..1386
mol_type = other DNA
organism = synthetic construct

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SEQUENCE: 61
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acactagcttca atgacccatc aaaaacccctt cgcatttacag gaaatataatg ggttaccc 180
gatagatttt caagaaatttca taatccaaat ttaaataaaac ctcctcgatc tacaaggcc 240
aaaagggtttt attatgtatcc taattttttt agtactgtt ctgacaaaga tacattttt 300
aaagaaatata taaaggatata taaaatgtatc aatattttttt aatattttttt aatattttttt 360
tatagactttt cgcacatgtt acatccctt gggatataac atactccat taatactttt 420
gatgttgcataat cttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 480
aaaactgttca gttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 540
ccagaaacttcc tttttttttttt attatgtatcc taatccaaat aatattttttt gttttttttttt 600
gtttttttttttt attatgtatcc taatccaaat aatattttttt gttttttttttt gttttttttttt 660
gatgttgcataat cttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 720
atgtcatc aatattttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 780
acaattttttcaat cttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 840
gcagaaatataa atgacccatc aatattttttt gttttttttttt gttttttttttt gttttttttttt 900
tattttttttttt gttttttttttt gttttttttttt gttttttttttt gttttttttttt gttttttttttt 960
actactgttcaat cttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 1020
agaatgttcaat cttttttttttt tagtgttgc gttttttttttt gttttttttttt gttttttttttt 1080

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gttgagttat	ataatgaact	tacacaaata	tttacagaat	ttaactacgc	taaaaatat	1140
aatgtacaaa	ataggaaaat	atatcttca	aatgtatata	ctccggcac	ggcgaatata	1200
tttagacgata	atgtttatga	tataaaaaat	ggattnata	tacctaaaag	taatttaat	1260
gttactatata	tgggtcaaaa	tttatctcg	aatccagcat	taagaaaagt	caatcctgaa	1320
aatatgtttt	atttattttac	aaaattttgt	cataaaagcaa	tagatggtag	atcattat	1380
aaaaaaa						1386

SEQ ID NO: 62 moltype = DNA length = 1365
 FEATURE Location/Qualifiers
 source 1..1365
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 62

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aatgttaat	cttacacctgt	aaaagctttt	atgattactc	aaaatattt	ggtaatacca	180
gaaagagttt	catcagatac	taatccaagt	ttaagtaaac	cgccccagacc	tacttcaag	240
tatccaaatgt	attatgtatcc	tagtttata	tctactgtat	aacaaaaaaga	tacatttt	300
aaaggggatta	ttaaaaattt	taaaatggatt	aatgaaaagag	atatggaaa	aaaatttaata	360
aatttatttag	tagttgttc	acccttttag	ggagattca	gtacgcttgc	agatacattt	420
gattttcac	gtcatactac	taatattgc	gttggaaaatgt	ttggaaaatgg	tagttggaaa	480
gttaacaaaata	ttataacacc	aagtgttattt	atatttggac	cacttccaa	tatatttagac	540
tatatacagat	cccttacat	gcaatggacaa	caatccaaatc	catcatttgc	agggttttgc	600
acattatctt	tacttcaat	aaaagctttt	agcaccctgaa	tttttgcata	cattttgcata	660
aatcaaagt	cagctgtatt	aggcaaatct	atattttgtt	tggatccagt	aatagcttta	720
atgcatagt	taacacatc	tttgcataat	ttatatggaa	taatataacc	atctgataaa	780
aggatttgtc	cacaagttt	cgagggttt	ttttctcaag	atggacccaa	cgtacaattt	840
gaggaatttat	atacattttgg	aggatttagt	gttggaaataa	tacctcaat	tggaaagatca	900
caattaagag	aaaaagcatt	aggtcaactt	aaaagatata	cgaaaaagact	taataatatt	960
aataaaaacta	ttcccttctag	ttggattatgt	aatatagata	aatataaaaa	aatattttct	1020
gaaaatgtata	attttgatata	agataatata	ggaaattttg	ttgtttaat	tgataaaattt	1080
aatagcttta	atttgcactt	gactaatgtt	atgtcagaa	ttgtttat	ttcgcaat	1140
aatgtttaaa	acaggactca	tttattttca	aggcattttc	tacctgtatt	tgcaatata	1200
tttagatgata	atattttatac	tataagagat	ggttttaat	taacaaat	aggtttaat	1260
atagaaaattt	cggggtcagaa	tataaaaaag	aatccctgcac	tacaaaatgt	tagttcagaa	1320
agtgttagtag	atttattttac	aaaatgtatgt	ttaagattaa	caaaa		1365

SEQ ID NO: 63 moltype = DNA length = 1305
 FEATURE Location/Qualifiers
 source 1..1305
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 63

atgaaggcca	tgatcaatat	taacaagttc	ttaaatcaat	gtccaaacaat	taatagttt	60
aattataatg	atccgtttaa	taatagaaca	attttata	ttaaaccagg	cggttgcata	120
caattttata	aatcattttaa	tattatggaa	aatatttgg	taattccaga	gagaaatgt	180
atttgtacaa	ttccccaaga	ttttttcccg	cttacttcat	tggaaaaatgg	agatagtat	240
tattatgacc	ctaattttat	aaaatgtat	caagaaaaag	ataaattttt	aaaaatagt	300
acaaaaatata	taatagaat	aatgtata	ctttcaggaa	ggatttttt	agaagaactg	360
tcaaaagcta	atccatattt	aggaaatgt	aatactccg	atggtgactt	cattattaat	420
gtatgcattc	cagtttcaat	tcaatttctca	aatggtagcc	aaagcatact	atttcttaat	480
gttattataa	ttggggcaga	gcctgat	tttggaaacta	acagttccaa	tatttctcta	540
agaaataat	atatgcctaa	caatcacgg	ttttggatca	tagctat	aacattctca	600
cctgaatatt	cttttagatt	taaagataat	agttgtat	tttttttca	agatcctgct	660
tttacattaa	ttgtatgtt	aataccat	tttacatggac	tatatggggc	taaagggtt	720
actacaaatgt	atactataac	acaaaaacaa	aatcccctaa	taacaaat	aagggatca	780
aatatttgc	atttgcataac	ttttggatgt	actgttata	acattttac	tagtgcctag	840
tccaaatgata	tctatactaa	tcttctatgt	gattataaa	aaatagcg	ttaacttgc	900
aaagtacaa	tatctat	actacttta	ctttttaaag	atgttttgc	agcggaaatgt	960
ggatttagata	aatatgtat	cggtttat	tcggtaataa	taaacaatt	taatgtat	1020
ttttaaaaaat	atactatgtt	tacggat	tttttttttca	tttttttttca	tttttttttca	1080
aggccaaatct	atatttgcata	gttataat	tttttttttca	tttttttttca	tttttttttca	1140
atttataata	tatcagaagg	ctataatata	aataatttta	agtttttttca	tttttttttca	1200
aatgcataat	taaattcctat	aattttata	ccaaatttgc	tttttttttca	tttttttttca	1260
atcatttagat	ttttgtttat	tatttttttca	tttttttttca	tttttttttca	tttttttttca	1305

SEQ ID NO: 64 moltype = DNA length = 1347
 FEATURE Location/Qualifiers
 source 1..1347
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 64

atgaaggcca	tgatcaatat	taacaagttc	ttaaatcaat	gtccagttgc	aataaatagt	60
ttaatttata	atgaccctgt	taatgtat	acaattttat	acatgcagat	accatatgaa	120
gaaaaaaatgt	aaaaatatttta	taaagctttt	gagattatgc	gtatgttgc	gataatttct	180
gagagaaaata	caatggaaac	gaatccatgt	tttttttgcata	caccggcttc	attaaagaaac	240

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SEQ ID NO: 65          moltype = DNA  length = 1365
FEATURE                 Location/Qualifiers
source                  1..1365
                        mol_type = other DNA
                        organism = synthetic construct
```

SEQ ID NO: 66 moltype = DNA length = 1386
FEATURE Location/Qualifiers
source 1..1386
mol_type = other DNA
organism = synthetic construct

-continued

ttcaacgggc agaacacaga gatcaacaac atgaattca cgaagttgaa gaactcacc 1260
ggactgttg agttctacaa attgtgtgt gtgcgcggga tcatacttag caagaccaag 1320
gccttgaca aaggctacaa caagtgtatg caaaatttat tcaagaacat taatatcatg 1380
gccaag 1386
SEQ ID NO: 67 moltype = DNA length = 1362
FEATURE Location/Qualifiers
source 1..1362
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 67
atgccagta caataaataa tttaattat aatgatccta ttgataataa taatattatt 60
atgatggcgc ctccatttgc gagaggtac gggagatatt ataaagctt taaaatcaca 120
gatcgattt ggataatacc ggaaagat acctttggat ataaacctga ggattttaat 180
aaaagttccg gtattttaa tagagatgt tggatattt atgatccaga ttacttaat 240
actaatgata aaagaataat attttacaa acaatgtac agtttttaa tagaatcaa 300
tcaaaaccat tgggtaaaa gttatttagag atgattataa atggatacc ttatcttgg 360
gatagacgtg ttccactcga agagtttaa acaaaccattt ctatgttac ttgttataaa 420
ttaatcgtat atccaggaga agtggagcga aaaaaggta ttttcgcaaa ttttataata 480
tttggacctg ggccaggat ttatggaaa gagaactatag atatggat acaaaatcat 540
tttgcataa gggaaaggctt cgggggtata atgcaatgaa agttttggcc agaatatgt 600
agcgttata ataatgttca agaaaaacaaa ggcgcagaatg tattttatag acgtggat 660
ttttcagatc cagccttgat attatcgtat gaaatattac atgttttaca tggattat 720
ggcattaaatg tagatgtt accaatgttca ccaatgaaa aaaaattttt tatgtcaatct 780
acagatgcta tacaggcaga agaactatata acatgttggag gacaagatcc cagcatcata 840
actcccttca cggataaaaag tatctatgt aaagttttgc aaaaattttt agggatagtt 900
gatagactta acaagggtttt agtttgcata tcagatcata acatataat taatataat 960
aaaatataat ttaaagatata atataatttcc gtttgcata ctgaggaaaa atatagtata 1020
gatgtgaaa gttttgtata attatataaa agttaatgtt ttggtttac agaaaactat 1080
atagcagaaaa attatataaa aaaaactaga gcttcttattt ttagtgcattt cttaccacca 1140
gtaaaaataa attatataaa agataatgtt atctataacta tagaggaaat gtttataata 1200
tctgtataaag atatggaaaa agaatatgtt ggtcagaata aagttataaa taaaacaaat 1260
tatgaagaaa ttagcaagga gcattttggcgt gtatataaga tacaatgtg taaaatgtt 1320
aatatgtcaaa atttattcaaa gaacattaat atcatggcca ag 1362
SEQ ID NO: 68 moltype = DNA length = 1386
FEATURE Location/Qualifiers
source 1..1386
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 68
atgccaataa caattaacaa tttaattat tcaagatcctg ttgataataa aaatatttt 60
tatatttataat ctcattttaa tacatctgtt aatgagccctt aaaaagccctt tcgcatttaca 120
ggaaatataat ggttataacc ttatgtatgat aatggatattt tcaagaaat ttttataataa 180
cctccctcgat ttacaaggccc taaaatgttca tattatgttca ttttataataa 240
tctgacaaatg atacattttt aaaaatgttca ttttataataa 300
gaataatgggg aagaatataat atatagactt tccgacagata taccctttcc ttggaaataac 360
aataactccaa ttaataactt ttatgttgc ttttataataa 420
agacaaggta acaactgggt taaaactgtt aatggatattt ttttataataa 480
ccttagagaaa acattataga tccagaaact ttttataataa 540
ggcgcacaaatg aaggatgggt ttgtttatca atatgttca ttttataataa 600
acatataatgtt atcaactaa ttttataataa 660
atggatccaa tactatttt aatgttgc ttttataataa 720
atagctatac caaatgttca aacaatttca ttttataataa 780
tataatgttca aatggatgtt ttttataataa 840
atttccatggaa atggatgtt ttttataataa 900
gtctaaaatggaa atggatgtt ttttataataa 960
gaatataaaac agaaaacttta ttttataataa 1020
acagttttttt ttttataataa 1080
ttaactatcg ttttataataa 1140
actcccttgc ttttataataa 1200
atacctaaaa gtaattttttt ttttataataa 1260
ttaagaaaatggaa atggatgtt ttttataataa 1320
atagatgttca gtttataataa 1380
gccaag 1386
SEQ ID NO: 69 moltype = DNA length = 1365
FEATURE Location/Qualifiers
source 1..1365
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 69
atgacatggc cgttaaaaaga tttaattat agtgcatttgc ttttataataa 60
tatatttataat ttttataataa 120
caaaatattttt ggttataacc agaaaatgtt ttttataataa 180
ccggcccgacat ttttataataa 240

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gaacaaaag	atacatttt	aaaagggatt	ataaaattat	ttaaaaagaat	taatggaaaga	300
gatataggaa	aaaaattaat	aaatttatta	gtagtttgtt	caccttttat	ggggattca	360
agtacgcctg	aagatatact	tgattttaca	cgtcactata	ctaataattgc	agtgttaaaag	420
tttggaaaat	gtagttggaa	agtaacaaaat	attataaacac	caagtgtt	gatattttgg	480
ccacttcctt	atataatgg	ctatacagaca	tcccttcat	tgcggggaca	acatacaata	540
ccatcattt	aagggtttgg	aacattatct	atactaaaag	tagccctga	atttttgtta	600
acattnatgt	atgttaacatc	taatcaaaat	tcagctgtat	taggcaaaatc	tatattttgt	660
atggatccca	taatagett	aatgcatag	ttaacacatt	cttgcatcat	attatattgg	720
ataataatatac	catctgtat	aaaggattctgt	ccacaagtt	gcggggatt	ttttctctaa	780
gtggggccca	acgtacaaatt	tgaggatata	tatataatttgc	gaggatttaga	tgttggaaata	840
ataaccttcaa	ttgaaagatc	acaattaaga	aaaaaaagcat	taggtcaacta	taaagatata	900
gcggaaaagac	ttaataatat	taataaaact	attcccttca	gttggatttag	taatataatgt	960
aaataataaaa	aaatattttt	ttggaaaatgt	aattttgata	aagataataac	aggaaatttt	1020
gtttggaaaata	ttgtataaaat	caataggtt	tattcagact	tgactaatgt	tatgttgcagaa	1080
gtttgtttat	cttcgcata	taatgtttaaa	aacaggactc	attatttttc	aaggcattat	1140
ctacctgtat	ttgcaaaat	attagatgtat	aatattttata	ctataagaga	tgggttttaat	1200
ttaacaaaata	aagggttttaa	tagataaaat	tcgggttcaga	atataaaaag	gaatctctgc	1260
ctacaaaagc	ttagttcaga	aagtgtatgt	gattttat	caaaaatgt	ttaaagattt	1320
acaaaatgtc	aaaattttat	caaaacat	aatatcatq	ccaaad		1365

SEQ ID NO: 70 moltype = DNA length = 1305
FEATURE Location/Qualifiers
source 1..1305
mol_type = other DNA
organism = synthetic constru

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SEQ ID NO: 71          moltype = DNA    length = 1347
FEATURE              Location/Qualifiers
source               1..1347
                     mol_type = other DNA
                     organism = synthetic construct
```

SEQUENCE: 71

atgcgcgttg	caataaatag	ttttaatttat	aatgaccctg	ttaatgatga	tacaattttt	60
tacatgcaga	taccatatga	agaaaaaaagt	aaaaaaatatt	ataaagctt	tgagattatg	120
cgtatgttt	ggataattcc	tgagagaaaat	acaataggaa	cgaatccatg	tgatgttgt	180
cccccgctt	cattaaaggaa	cggagacgtt	gcttattatg	atccattaattt	ttAACCTT	240
gatgctgaaa	aagatagata	ttttaaaaaca	acgataaaaat	tatttaagag	aattaatagt	300
aatccctgcag	ggaaagtttt	gttacaagaa	atatcatatg	cttaaccata	tttagggaaaat	360
gaccacacgc	caattgtatg	attcttcctca	gttactagaa	ctacaagtgt	taatataaaa	420
ttatcaacta	atgttggaaag	tttcaatgtt	ttgaatctt	ttgttattttt	agcaggacct	480
qatataattt	aaagtgtgtt	ttaccctgtt	agaaaaactaa	tagatccaga	ttgtatTTTT	540
gatccaagta	attatggttt	tggatcaatt	aatatcgtga	cattttcacc	tgagttatgaa	600
tatacttttta	atgatatttt	tggagggcat	aatagtagta	cagaatcatt	tattgcagat	660
cctgcaattt	cactgtctca	tgaattgtata	catgcactgc	atggattata	cggggctatgg	720
ggagttactt	atgaagagac	tatagaagta	aagcaagcac	ctctttatgt	agccggaaaaa	780
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gctatgaagg	aaaaaaatata	taacaatctt	tttagctact	atgaaaaaaat	agttacttaga	900
cttagtgaag	ttaatatgtc	tcctcctgttt	tatgatattt	atgaatataaa	agattatTTT	960
caatggaaatg	atgggtctaa	taaaaaatgt	gatggaaatgt	atactgtaaa	tggaaaataaa	1020
tttaatgaaa	tttataaaaa	attatatagt	tttacagaga	gtgacttgc	aaataatTTT	1080
aaagtaaaaat	gtgaaatata	tttattttttt	aaatataatgt	tttttttttt	tccaaattttt	1140
tttagatgtat	atatttatac	tgtatcagag	gggttttataa	taggttaattt	agcgttaaaac	1200
aatccgcggac	aaagtataaa	gtttaatctt	aaaattttt	attccattcc	agataaaagg	1260

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tatttagaga tgattataaaa tggtataacct tatcttggag atagacgtgt tccactcgaa	420
gagtttaca caaacattgc tagtgtaact gtaataaaa taatcagttt cccaggagaa	480
gttggagccaaa aaaagggtt ttgcgaat ttaataat ttgcacccgtt gccagtttt	540
aatggaaaatg agactataga tataggtaa caaaatcatt ttgcatacg ggaaggcttc	600
gggggtataa tgcaaatggaa gttttgccta gaatatgtaa gcgtatTTAA taatgttcaa	660
aaaaacaaag gcgcagtat atttaataga cgtggatatt ttccagatcc agccttgata	720
ttaatgcatt aacttataca tggtttacat ggattatgtg gcattaaatg agatgatttt	780
ccaatgttgc caaatggaaa aaaaattttt atgcatactt cagatgtat acaggcagaa	840
gaactatata catgggggg acaagatccc agcatcataa ctctttctac ggataaaatg	900
atctatgata aagtttgca aaattttaga gggatagttt atagacttaa caaggtttt	960
gtttgcattt cagatcctaa cattaaattt aatatatataaaaataaaattttaaagataaaa	1020
tataaaattcg ttgaaatgtc tgaggggaaa tatagtatag atgttggaaa ttgttggataa	1080
ttatataaaa gcttaatgtt tggttttaca gaaactataa tagcggaaa ttataaaaataa	1140
aaaacttagag cttctttttt tagtgatcc ttaccacccag taaaataaaa aaatttttata	1200
gataatgaaa tctatactat agaggaaaggg ttaatataat ctgataaaaga tatggaaaaa	1260
gaatatagag gtcagaataaa agctataat aaacaagctt atgaagaaaat tagcaaggag	1320
cattttggct tataataagat acaaattgtgt aaaatgttta aactcgagca ccaccaccc	1380
caccactgaa	1389

SEQ ID NO: 75 moltype = DNA length = 1413
FEATURE Location/Qualifiers
source 1..1413
mol_type = other DNA
organism = synthetic constru

SEQUENCE: 75

SEQUENCE: 73

atgaag

ttaattttag cagatccctgt tgataaaaa aatattttat atttagatag tcattaaat 120
acactagcta atggcccttaaaa aaaaaggccctt cgcattacag gaaatataatg ggtaatcc 180
gatagattt caagaaaatc taatcccaat ttaaaaataac ctccctcgagt tacaaggccc 240
aaaagggtt attatgatcc taatttattt agtactgatt ctgacaaga tacatttta 300
aaagaaatta taaaagtatt taaaagaaattt aatttcctag aatattggaga agaatataa 360
tatagactt cgacagatcc accctttcc gggaaataaca atactccat taatcttt 420
gatgggtatg tagattttaa cagtgttgat gttaaaacta gacaaggtaa caactgggtt 480
aaaactggta gcataaattcc tagtgttata ataactggac cttagaaaaa cattatagat 540
ccagaaactt ctacgtttaa attaactaac aataactttt cggcacaaga aggatttggt 600
gctttatcaa taatttcaat acacccat tttatgtcaa catatagtaa tgcaactaa 660
gtatgttaggaa agggtagatt ttcaatgtt gaaattttgc tgatggccaat actattttt 720
atgcatgaac ttaatcatgc aatgcataat ttatatggaa tagctatacc aaatgatcaa 780
acaatttcat ctgtaaatctg taatattttt tattttcaat ataatgtgaa atttagatgt 840
gcagaaaaat atgcattttgg aggttccaaat atagacccat ttccctaaaag tgcaaggaaa 900
tattttgggg aaaaggccattt ggattttat agatctatag ctaaaaagact taatagtata 960
actactgcaa atcccttcaag cttaataaa tatatagggg aatataaaaca gaaactttt 1020
agaaaatgtt gattcgtagt agaatcttca ggtgaatgtt cagtaatccg taataatgtt 1080
gttgaggattt atataatgttact tacacaaataa tttagacaaat tttaatctcgc taaaatataat 1140
aatgttacaaa attagggaaaat atatcttca aatgtatata ctcccggttac ggggatata 1200
ttagacgata atgtttatga tatacaaaaat ggatttaata tacctaaaag taattttaat 1260
gtactattha tggggccaaa ttatctcga aatccgcatt taagaaaatg caatccctgaa 1320
aatatgtttt attttttatc aaaattttgtt ctaaaagccaa tagatggtag atcattatata 1380
ataaaactcg agcaccacca ccaccacccac tga 1413

SEQ ID NO: 76 moltype = DNA length = 1392
FEATURE Location/Qualifiers
source 1..1392
mol_type = other DNA
organism = synthetic constru

SEQUENCE : 76

SEQUENCE: 78
atggccggatc ttgttgtttt tggggatttt ttccatgtttt atcgatggaa

atgaa

tttaattata gtgatcctgt taatgacaat gatatattat atttaagaat

aagttaatta c

```

gaaaggatttt catcagatac taatccaagt ttaagtaaac cggccagacc tacttcaaag 240
tatcaagaatg attatgtatcc tagttatatta tctactgtatg aacaaaaaga tacatttta 300
aaaggggatta taaaattatt taaaagaatt aatgaagag atataggaaa aaaattaata 360
aatttttag tagtgtgttc acctttatgg gtagatccaa gtacgcctga agatacattt 420
gattttcacac gtcatactac taatattgc tagtggaaaatgt ttgaaatgg tagtggaaa 480
gtaacaataa ttataacacc aagtgtatgg atatttggac cacttcttaa tatattagac 540
tatacagcat cccttacattt gcaaggacaa caatcaaatc catcatttga aggggttggaa 600
acattttttacta tactaaaagt agcactgtaa ttttttttaa cattttgtatg tgtaacatcc 660
aatcaagaatg cagctgtat aggcaatctt atatTTTGTa tggatccatg aatagcttt 720
atgcatgatgtaa acatccatc ttgcatcatc ttatattggaa taaaatatacc atctgatataa 780
aggatttcgtc cacaagtttg cgagggtttt ttcttccaag atggacccaa cgtacaattt 840
gaggaatttat atacattttgg aggatttagat gttgaaataa tacctcaaat tgaaagatca 900
caattaagag aaaaaggattt aggtcactat aaagatatacg cgaaaagact taataatatt 960
aataaaaaactt ttcccttctatg ttggattagt aatataatgaa aataaaaaaa aatattttt 1020
ggaaaatgtata attttgatata agataatataa gggaaattttggatataat tgataaaatcc 1080
aatacgatattt attcgacactt gactaaatgtt atgtcagaag ttgttttattc ttgcacat 1140
aatgtttaaaa acaggactca ttatTTTCA aggcattatc tacctgtatt tgcaaatata 1200

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tttttaaaaa	caatgattaa	attatTTTaa	agaattaatt	caaaaccatc	aggacagaga	360
ttactggata	tgatagtaga	tgctatcac	tatcttggaa	atgcatccac	accgccccac	420
aaatttgcag	caaATGTTGc	aatatgtatc	attaataaaa	aaattatccca	acctggagct	480
gaagatcaa	taaaAGGTT	aatgacaaat	ttaataatat	ttggaccagg	accagtctta	540
agtgataatt	ttactgatag	tatgattatg	aatggccatt	ccccatatac	agaaggattt	600
ggTGcaagaa	tgatgataag	atTTTGTCT	agtTgtttaa	atgtttaaa	taatgtttcg	660
gaaaataaaag	atACATCTAT	atTTGTTAGA	cgcgcgtt	ttgcagatcc	agctctaCG	720
ttaatgcatg	aacttataca	tgtgttat	ggattatATG	gaattaaGAT	aagtaatttA	780
ccaattactc	caaatacAAA	agaatTTTC	atgcaacata	gcgatectgt	acaAGCAGAA	840
gaactataat	cattcggagg	acatgatcT	agtgttataa	gtcCTTCAc	ggatATGAAT	900
atttataata	aaggcgttacA	aaatTTCAA	gatagatGTA	ataggcttaa	tattgttca	960
agtGCCAAg	ggagtggaat	tgatatttc	ttatataAC	aaatataAA	aaataatAT	1020
gattttgttG	aaAGATCCTAA	tggaaaatAT	agtgttagata	aggataAGT	tgataAAATA	1080
tataaggcCT	taATGTTGG	cTTTACTGAA	actaatCTG	ctggTGAATA	TGGAATAAAA	1140
actaggTATT	cTTTATTTAG	tgatataATG	ccaccGAA	aaACTGAA	attGTTAGAC	1200
aatacaATT	atACtAAAGA	tGAAGGCTT	aacatGCTA	gtaaaaATCT	caAAACGGA	1260
ttaatggcT	agaATAAGGC	ggtaataAAA	gaggctATG	aagaATCAG	cCTAGAACAT	1320
ctcgTTATAT	atAGATAGC	aatgtGCAAG	cCTGTAATG	acAAACTCGA	gcACCACAC	1380
caccaccACT	ga					1392

SEQ ID NO: 80 moltype = DNA length = 1446
 FEATURE Location/Qualifiers
 source 1..1446
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 80

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atGCCCTTG	tcaacAAACA	gttcaactac	aaggacCCAG	ttaatggagt	agacatcgca	120
tatatacaaga	ttcccAACGc	tggccagatG	caaccGTTA	aggcatttaa	aatccataac	180
aaaatctggg	ttatcccAGA	gccccatacc	ttcaccaACC	ccgaggaggG	cgatctgAAC	240
ccccccGCCC	aggcGAAGCA	ggTCCAGTg	agetaCTACG	atagcaccta	cCTCAGCAC	300
gacaacGAGA	aggacAACTA	ccttAAAGGA	gtcAcGAAGT	tgttgcAGAG	aatCTACTCC	360
acagacCTCG	gcccGATGCT	tcttaaccGAG	attgtgcGtG	gcattccCTT	ttggggCCGc	420
tcttACCATCG	acACAGAGCT	gaaggTGTATA	gacaccaACT	gcatcaACGT	aatCCAGCCT	480
gacggcAGCT	acccAGGcGA	ggagGTTAAC	ctggTGTATC	tcggCCCTC	cgccqGATATC	540
atccAACTCG	agtGCAAGAG	cttgcGGCac	gaggTCCGTA	accttACCCG	gaACGGCT	600
ggaAGCACC	AGTACATAAG	attcAGCCt	atttcACCT	tcgggttGA	ggAGAGCTT	660
gaggTCGACA	caaACCCCT	gctgggAGGC	gggaAGTTC	ccactgACCC	agCCGTGACT	720
ctggcACACG	ACGTGATCCA	cgcggGTCAC	cgCCTGTACG	gcatAGTAT	AAACCCAAAC	780
aggGTGTTCA	AAGTGAACAC	caacGCTAC	tatGAAATGA	gccccGTTG	GGTGAACCT	840
gaggAGCTGA	GAACGTTGCG	gggACATGAT	gtcaAAATTtA	tcgACACCT	gcAGGAGAAC	900
gagttcAGGC	TGTACTACTA	caataAGTTC	aaggatATAg	cgAGCActCT	gaACAAGGCC	960
aaGTCCATCG	TAGGCACTAC	tgcAtCCCTC	caGtATATGA	AGAATGTTGTT	CAAAGAGAAA	1020
tacCTGTGTA	TGCGAGGATAC	cAGCGGTAG	ttcAGCGTGG	AtAAGTtAA	gttGACAAAG	1080
ctgtATAAGA	TGCTCACCGA	aatCTACACD	gaggATAAT	tcgttAAAGTT	cttcaAGGTC	1140
ctgAACCGGA	AGACCTACCT	GAACTTCGAC	AGGCGCTGT	TCAAGATCAA	CATCGTCC	1200
aaAGTGAACt	ACACCTACTA	cGACGGGTT	AACCTGAGGA	ACACCAACt	GGCCGCTAAC	1260
ttaaACCGGG	AGAACACAGA	GATAACAAc	AtGAATTTCA	cGAAGTTGA	GAACtTCAc	1320
ggACTGTGTT	AGTTCTACAA	attGtGtG	gtGCGCGGGA	tcatcactAG	caAGACCAAG	1380
AGCCTTGACa	AGGCTACAA	caAGTGTATG	CAAATTTAT	TCAAGAACAT	TAATATCATG	1440
gccaAG						1446

SEQ ID NO: 81 moltype = DNA length = 1422
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 source 1..1422
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 81

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atGATGAGC	CTCCATTGc	gagAGGTACG	ggggAGATAT	AtAAAGCTT	taaaATCACA	180
gatcgtATT	GGATAATAcc	ggAAAGATAT	actTTTGGAT	AtAAACCTGA	ggATTTAAT	240
aaaAGTTCCG	GTATTTTAA	tagAGATTT	tGTGAATAT	AtGATCCAGA	ttacttAAAT	300
actaaTgATA	AAAAGAAAT	AtTTTACAA	ACAATGATGA	AGTTTAA	TAGAATCAA	360
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ggcAtAAAG	TAGATGATT	ACCAATGTA	CCAAATGAA	AAAATTTT	TATGCAATCT	840
acAGATGCTA	TACAGGCGA	AGAACTATAT	ACATTGAG	GACAAGATCC	CAGCATATA	900
actcCTTCTA	CGGATAAAAG	TATCTATGAT	AAAGTTTGC	AAAATTTAG	AGGGATAGTT	960
gatAGACTTA	ACAAGGTTT	AGTTGCTA	TCAgATCCTA	ACATTAATAT	TAATATATAT	1020
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gtaaaaataa	aaaattttat	agataatgaa	atctatacta	tagggagg	gttataataa	1260
tctgtatataa	atatggaaaa	aaatataataga	ggtcagaata	aagctataaa	taacaaggt	1320
atgtatggaaa	tttagcaagga	gcattttgg	gttatataaga	taacaaatgt	tttaaaagtgtt	1380
aaaatgtcaaa	atttattccaa	gaacatttaat	atcatggcca	ag		1422

SEQ ID NO: 82 moltype = DNA length = 1446
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mol_type = other DNA
organism = synthetic constru

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SEQ ID NO: 83          moltype = DNA    length = 1425
FEATURE                Location/Qualifiers
source                 1..1425
                        mol_type = other DNA
                        organism = synthetic construct
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SEQUENCE:	83	organism = Synechococcus elongatus				
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tatthaaga	taccacaaaa	taatgttaatt	actacacctg	taaaaagctt	tgatgttact	180
caaaatattt	gggtataacc	agaaaagattt	tcatcagata	ctaattccaag	ttaagtaaa	240
ccgcggcagac	ctacttcaaa	gtatcaagaat	tattatgtatc	ctagtattt	atctactgtat	300
gaacaaaaaa	aatcattttt	aaaagggattt	ataaaaatatt	ttaaaaagaat	taatgaaaaaa	360
gatataggaa	aaaatttaat	aaatattat	gtatgttgtt	cacctttat	gggagatttca	420
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tttggaaaatg	gtatgtggaa	agtaacaat	attataaacm	caagtgtt	gatatttgg	540
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ccatcatgtt	aaagggtttgg	aacattat	atataaaag	tagcactgt	atttttgttta	660
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gtatggccca	acgtcaattt	tgaggatata	tatataattt	gaggattata	tgttgttataa	900
atacctcaaa	ttgaaagatc	acaattaaga	aaaaaaagcat	taggtcacta	taaagatata	960
gcgaaaaagac	ttaataat	taataaaact	attcccttca	gttggatttt	taatataat	1020
aaatataaaa	aaatattttt	tgaaaatgtt	aattttgata	aagataaatac	agggaaatttt	1080
gttgttataa	ttgtataaaat	caatagttt	tatttcagact	tgactaatgt	tatgttcagaa	1140
gttgttattt	cttcgcata	taatgttaaa	aacaggactc	attatttttc	aaaggcattat	1200
ctacctgtat	ttgcaaatat	attagatgtat	aatattttata	ctataagaga	tggttttat	1260
tttacaaaata	aagggttttaa	tatagaaaat	tcgggtccaga	atataaaaaag	gaatctctgca	1320
ctacaaaaggc	ttagttcaga	aagtgttagt	gattttat	caaaaatgtat	ttaagattt	1380
acaaaatgtc	aaaatttttatt	caaaacat	aatatcatq	ccaaad		1425

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SEQ ID NO: 84          moltype = DNA    length = 1365
FEATURE
source           Location/Qualifiers
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mol_type = other DNA
organism = synthetic construct
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SEQUENCE: 84

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SEQ ID NO: 85 moltype = DNA length = 1407
FEATURE Location/Qualifiers
source 1..1407
mol_type = other DNA
organism = synthetic construc

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SEQ ID NO: 86          moltype = DNA    length = 1425
FEATURE                Location/Qualifiers
source                 1..1425
                        mol_type = other DNA
                        organism = synthetic construct
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SEQUENCE: 86
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atatggaaac cattcaatga ccacaggccca ggaaacatattt aaataaggctt taggattata 180
gatcgatattt ggatagtacc aqaaaggttt actttatggat ttcaacttga ccaatataat 240
ggcagttacag gagtttttag taaagatgtc tacgaatattt acgatccaaat ttatataaaa 300
accggatgcty aaaaagataa atttttaaaa acaatgatta aattatttaa tagaattaaat 360
tcaaaaaccat caggacacag attactgtat atgatgtat agtgcatacc ttatcttgg 420
aatgcatactt caccggccga caaatttgtca gcaaaatgttgc caaatgtatc tattataaaa 480
aaaaattatcc aaccgtggcgt tgaagatcaa aaaaaagggtt taatgacaaa ttatataata 540
tttggaccag gaccaggatc aagtgtataat tttaactgtata gtatgtattt gaatggccat 600
tcccccaatatt cagaaggattt tggtgcagaagaa atgatgtataa gattttgatcc tagttgttta 660
aatgtatattt atataatgttca ggaaaatataa gatacatctt tattttatgttgc acggcgttat 720
tttgcagatc cagctcttaatc gttatgtatc gaatcttatac atgtgttaca tggattat 780
ggaaatgttca taatgtatattt accaaatattt ccaaaatataa aagaatgttataatc catgttgcacat 840
agcgtatctgttacaaggcaga agaacttatat acatcggttgc gacatgtatcc tagtgttta 900

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agtcccttcta	cggatatgaa	tatttataat	aaagcggtac	aaaatttca	agatatagct	960
aataggctta	atattgtttc	aagtgcggaa	gggagtgaa	tttatatttc	cttatataaa	1020
caaatatata	aaaataaaata	tgatTTGTT	gaagatccta	atggaaaata	tagttagat	1080
aaggataagt	ttgataaatt	ataaaggcc	ttaatgttt	gctttactga	aactaatcta	1140
gctggtaat	atggaataaa	aacttaggtat	tcttatttta	gtgaatattt	gccaccgata	1200
aaaactgaaa	aattgttga	caatacaatt	tatactcaa	atgaaggctt	taacatagct	1260
agtaaaaatc	tcaaaacgga	atthaatggt	cagaataagg	cggtaaataa	agaggcttat	1320
gaagaaatca	gctcagaaca	tctcggtata	tatagaatag	caatgtcga	gcctgtatg	1380
tacaaatgtc	aaaatttatt	caagaacatt	aatatcatgg	ccaag		1425

1. An alopecia prevention or treatment method, comprising administering a therapeutically effective amount of a composition comprising a botulinum toxin recombinant protein as an active ingredient to a subject in need thereof, wherein in the botulinum toxin recombinant protein, a cell-penetrating peptide consisting of an amino acid sequence of SEQ ID NO: 1 is fused to one end or both ends of a botulinum toxin light chain.
 2. The method according to claim 1, wherein the botulinum toxin recombinant protein consists of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 31 to SEQ ID NO: 58.
 3. The method according to claim 1, wherein the botulinum toxin light chain consists of one or more amino acid sequences selected from the group consisting of SEQ ID NO: 3 to SEQ ID NO: 9.
 4. The method according to claim 1, wherein the botulinum toxin light chain further includes a hexahistidine tag at one end.
 5. The method according to claim 1, wherein the botulinum toxin light chain is selected from the group consisting of botulinum toxin serotypes A, B, C, D, E, F, and G.
 6. The method according to claim 1, wherein the cell-penetrating peptide is fused to a carboxyl terminus, an amino terminus, or both of the botulinum toxin light chain.
 7. The method according to claim 1, wherein the fusion is achieved by a peptide bond or a covalent bond.
 8. The method according to claim 1, wherein the composition promotes the proliferation of dermal papilla cells.
 9. The method according to claim 1, wherein the composition promotes prostaglandin F_{2α} expression.
 10. The method according to claim 1, wherein the composition promotes hair growth and reduces alopecia.
 11. The method according to claim 1, wherein the composition is for transdermal administration.
- 12-17. (canceled)**
18. The method according to claim 1, wherein the composition is a pharmaceutical composition, a quasi-drug composition, a composition for external skin application, or a cosmetic composition.

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